Neuroanatomical Correlates of Happiness, Sadness, and Disgust

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Objective: Happiness, sadness, and disgust are three emotions that differ in their valence (positive or negative) and associated action tendencies (approach or withdrawal). This study was designed to investigate the neuroanatomical correlates of these discrete emotions. Method: Twelve healthy female subjects were studied. Positron emission tomography and [^{15}O]H_2O were used to measure regional brain activity. There were 12 conditions per subject: happiness, sadness, and disgust and three control conditions, each induced by film and recall. Emotion and control tasks were alternated throughout. Condition order was pseudorandomized and counterbalanced across subjects. Analyses focused on brain activity patterns for each emotion when combining film and recall data. Results: Happiness, sadness, and disgust were each associated with increases in activity in the thalamus and medial prefrontal cortex (Brodmann's area 9). These three emotions were also associated with activation of anterior and posterior temporal structures, primarily when induced by film. Recalled sadness was associated with increased activation in the anterior insula. Happiness was distinguished from sadness by greater activity in the vicinity of ventral mesial frontal cortex. Conclusions: While this study should be considered preliminary, it identifies regions of the brain that participate in happiness, sadness, and disgust, regions that distinguish between positive and negative emotions, and regions that depend on both the elicitor and valence of emotion or their interaction.

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The concept of basic or primary emotions originated with Charles Darwin (1) in his classic study in 1872 titled *The Expression of Emotion in Man and Animals.* Darwin believed that certain patterns of behavior such as displays of emotion were genetically based biological mechanisms that evolved to serve the survival needs of the individual and the species. The concept of primary emotions was further elaborated in this century by Tomkins (2), Izard (3), Plutchik (4), and others. The universality of certain basic emotions was supported by the work of Ekman and Friesen (5), who found that facial expressions for certain emotions were universally displayed and recognized in all cultures studied, suggesting that they were not the result of learning. More recent developmental studies reveal that human infants display the facial expressions of anger, fear, happiness, sadness, surprise, and disgust during the first year of life (6). These observations support the hypothesis that a distinct neurological network may exist for certain primary emotions in humans.

Positron emission tomography (PET) studies of emotion in normal individuals have to date been few in number (7–11). For example, Pardo and colleagues (7) induced sadness by asking seven normal men and women to think sad thoughts and observed increased brain activity in bilateral inferior and orbitofrontal cortex. George and colleagues (9) studied happiness and sadness in 11 normal women by combining recall of a personal experience and viewing a picture displaying the corresponding facial affect. Sadness was associated with increased activity bilaterally in anterior cingulate, medial prefrontal, and mesial temporal cortex, as well as in brainstem, thalamus, and caudate/putamen. Happiness was associated with decreased activity in right

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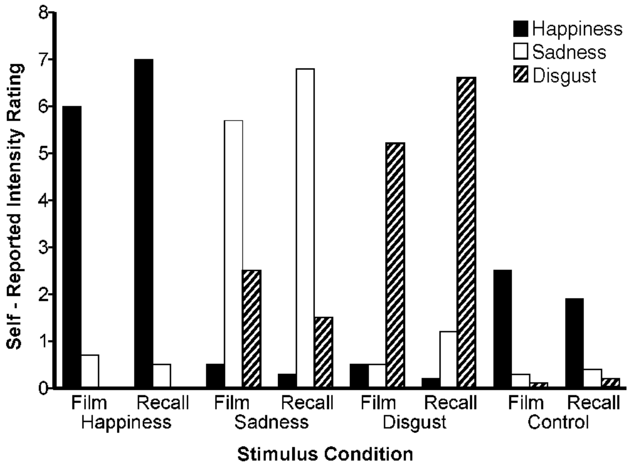
prefrontal and temporal-parietal regions but not with activity increases. One of the major conclusions from that study was that happiness and sadness are mediated by different neural networks. Paradiso and colleagues (11) recently reported induction of happiness, fear, and disgust in eight normal elderly subjects through use of film clips and also observed brain activation patterns specific to each emotion.

The present investigation further elaborates on previous studies by examining three emotions: happiness, sadness, and disgust. These three emotions differ in their valence (positive or negative) and associated action tendencies (approach or withdrawal) and thus permit exploration of how different kinds of emotion are organized in the brain (12–14). Furthermore, each emotion was induced in two ways (by film and recall) and was then averaged with the goal of identifying changes attributable to each emotion independent of the method of emotion induction. In a separate report (15), we used the same data set to investigate the association between the method of emotion induction and the neuroanatomical correlates of emotion independent of the type and valence of emotion.

FIGURE 1. Mean Ratings (N=12) of Happiness, Sadness, and Disgust for Each Type of Film and Recall Stimulus[a]



[a]Ratings on a 0–8 visual analog scale were obtained on multiple emotions immediately after each scan. The values for film and recall controls each represent the mean values for three scans.

METHOD

Subjects

A screening procedure was used to identify 12 right-handed, neurologically and psychiatrically well, unmedicated female volunteers who were likely to have intense emotional responses in the PET laboratory. The study group was restricted to women to maximize the homogeneity of emotion-dependent activity changes and the likelihood of intense self-reported emotional experiences (16). An advertisement was used to recruit female volunteers between the ages of 18 and 30 who were "able to accurately describe [their] emotional reactions to daily events." Psychiatric and medical histories, the Structured Clinical Interview for DSM-III-R—Non-Patient Edition (17), the Edinburgh Handedness Inventory (18), and a complete neurological examination were used to identify prospective subjects for further evaluation. Prospective subjects were included in the PET study if they reported separate experiences of happiness, sadness, and disgust during the previous 6 months; rated each of these experiences at least 6 on a 0–8 visual analog scale (in which 8 represented the most intense experience of the particular emotion in their lives); and rated each of an alternate screening set of three films targeting happiness, sadness, and disgust, respectively, at least 5 on an 8-point scale. After complete description of the study to the subjects, written informed consent was obtained. Subjects received compensation for their participation in the PET study. One subject withdrew from the PET study before its completion because of back discomfort; her data are not included in this report. The 12 subjects who completed the PET protocol had a mean age of 23.3 years (SD=3.2), above average scores on the Vividness of Visual Imagery Questionnaire (19), a measure of imagery ability, and average scores compared to those of women of the same age on the Affect Intensity Measure (20), an estimate of the tendency to experience emotions intensely.

Experimental Design

During the PET session, three empirically validated film clips from a silent color feature film (21) were used to generate three subjectively, facially, and electrophysiologically well-characterized target emotions: happiness, sadness, and disgust. The clips included a joyous romantic reconciliation (happy), grieving a friend who committed suicide by hanging (sad), and a scene depicting a rat crawling on a sleeping man (disgust). Three additional emotionally "neutral" film clips from a silent nature film (e.g., scenes of a beach or woods) were used to control for potentially confounding features of the emotion-generating film task, such as emotionally irrelevant visual stimulation and eye movement. Each emotion-generating and control film clip was approximately 2 minutes long, began before radiotracer administration, and continued throughout each PET scan. The 1-minute segment of each emotion-generating film clip that had been found to elicit the most intense emotional responses in the investigators was synchronized to the 1-minute scan.

During the PET session, autobiographical scripts of three recent experiences were used for the internal generation of the same three target emotions. These scripts were used to identify a time within the past 6 months in which the target emotion was experienced intensely and other emotions were experienced much less intensely. Three additional emotionally "neutral" autobiographical scripts of recent experiences were used to control for potentially confounding features of the emotion-generating recall task, such as emotionally irrelevant visual imagery, recall memory, and the recency of the recalled scene.

Immediately before each PET scan, the subject listened to either a brief synopsis of the film clip or the autobiographical script. For the emotion-generating film and recall tasks, subjects were asked to feel the relevant target emotion. For the control film and recall tasks, subjects were asked to feel emotionally "neutral." During the film task, the subjects' eyes were open and fixed on the center of a ceiling-mounted 27-inch television monitor. During the recall tasks, the subjects' eyes were closed and directed forward.

The 12 scans were performed in blocks of six for film and recall, respectively. The order of the blocks was counterbalanced; within each block, emotion-generating and control tasks were performed in an alternating sequence and counterbalanced for which came first. Within these constraints, the order of the three elicitors and three control tasks in each block were presented in random order. Subjective ratings of seven emotions (interest, amusement, happiness, sadness, fear, disgust, and anger) were recorded immediately after each scan on an 8-point visual analog scale.

Imaging Procedures

Magnetic resonance images (MRIs) of the head were acquired before the PET session to ensure structural normality of the brain, facilitate head positioning in the PET scanner, and permit co-registra-

TABLE 1. Location and Magnitude of Significant Changes in Regional Brain Activity in 12 Healthy Women During Viewing of Emotion-Generating and

	Film + Recall					Film				
	Coordinate				Mean Change (%)	Coordinate				Mean Change %
Emotion and Structure	x	y	z	z		x	y	z	z	
Happiness										
Prefrontal (BA 9)	8	46	24	2.33*	1.5	2	52	20	2.69**	2.4
	-4	48	24	3.29**	2.5	-4	46	24	2.82**	2.6
Thalamus	-10	-8	4	2.89**	1.5	-8	0	8	2.99**	2.9
Middle and posterior tempo-	48	-40	8	4.00***	2.8	46	-42	4	5.77***	5.5
ral (BA 21, 22, 37, 39)	-40	-52	16	3.97***	2.1	-44	-54	12	4.52***	3.8
Anterior temporal (BA 38)	40	18	-28	3.88***	9.3	44	8	-20	7.40***	9.2
	-34	8	-20	4.66***	3.3	-36	10	-24	4.78***	7.7
Hypothalamus	-6	-4	0	3.36***	1.6					
Sadness										
Prefrontal (BA 9)	-2	44	28	2.60**	1.9	10	48	28	1.94*	1.5
						-10	54	28	1.94*	2.1
Thalamus	12	-28	4	2.95**	1.8					
	-10	-26	4	3.60***	2.3	-8	-22	12	2.99**	2.9
Middle and posterior tempo-	-50	-58	4	3.29**	2.1	50	-46	8	4.30***	3.8
ral (BA 21, 22, 37, 39)						-50	-56	8	4.88***	4.6
Anterior temporal (BA 38,	36	10	-20	3.64***	2.2	36	2	-20	5.07***	5.0
28)	-32	6	-24	3.00**	2.4	-34	4	-20	4.00***	3.7
Hypothalamus	6	-12	-8	3.74***	2.1	4	-6	-8	4.28***	3.7
Lateral cerebellum	22	-52	-24	3.44***	2.4	28	-52	-24	3.66***	4.5
						-34	-68	-20	3.74***	4.6
Cerebellar vermis	2	-54	-20	3.39***	2.0	0	-28	-20	2.42*	1.6
Midbrain	12	-10	-4	4.15***	2.1	10	-12	-4	3.42***	2.6
	-10	-20	-4	3.74***	2.1	-12	-14	-4	3.10**	2.5
Putamen	22	4	-4	2.66**	1.2	20	4	-8	3.32***	2.0
	-22	4	-4	3.19**	1.2	-14	2	-8	2.63**	2.1
Caudate	-10	2	4	3.25**	1.9	0	4	0	3.10**	2.4
Disgust										
Prefrontal (BA 9)	-4	46	32	1.67*	1.0					
Thalamus	8	-16	0	3.01**	1.8	8	-20	0	1.67*	1.4
	-4	-20	4	2.19*	1.7					
Anterior temporal (BA 38)	44	18	-24	4.22***	6.8	44	8	-24	2.66**	4.5
	-34	10	-24	3.63***	3.9	-32	6	-24	1.97*	2.8
Midbrain	10	-12	-4	3.42***	1.5	14	-10	-8	1.91*	1.0

[a]The principal comparisons (film + recall) involved subtracting the six control scans from the two scans (appropriately weighted) targeting a particular emotion. Regions are identified by name of structure, Brodmann's area (BA), and stereotactic coordinates in the brain atlas of Talairach and Tournoux (27). x=distance (in millimeters) to the right (+) or left (–) of midline; y=distance anterior (+) or posterior (–) to the anterior commissure; z=distance superior (+) or inferior (–) to a horizontal plane through the anterior and posterior commissures. The z scores are normalized t statistics that reflect the significance of the activation effect generated by the appropriate comparison using Statistical Parametric Mapping. For the principal comparisons involving film + recall, a one-tailed threshold of $p<0.005$, was used. Mean change refers to brain activity in a given area during a given emotion compared to the neutral control conditions. Areas of significant change that replicate the film + recall

tion between the PET and MRI images when this technique is incorporated into our image analysis software.

Preparation of subjects for PET included the insertion of a catheter in the left antecubital vein to permit tracer administration, head immobilization through use of tape rather than a fast-hardening foam mold to permit quantitative EEG measurement during the PET session, and the performance of a transmission scan in which a germanium-68/gallium-68 ring source was used to correct subsequent emission images for radiation attenuation. During each scan, the subjects rested quietly in the supine position without movement.

Twelve 31-slice PET images of regional brain activity (counts per pixel per minute) were obtained from each subject by using an ECAT 951/31 scanner (Siemens, Knoxville, Tenn.), 40 mCi intravenous bolus injections of $[^{15}O]H_2O$, 60-second scans, and an interval of 10–15 minutes between scans (22–24). The radiotracer was administered at predetermined times shortly after the film and recall tasks began. PET images were reconstructed with an in-plane resolution of 10 mm full width at half maximum and a slice thickness of 5 mm full width at half maximum. For data analysis, a Gaussian blur yielded an in-plane resolution of 20 mm full width at half maximum and a slice thickness of 10 mm full width at half maximum (24).

Image Analysis

Automated algorithms were used to align each subject's sequential PET images (25), to transform her PET images into the standard spatial coordinates of a brain atlas (26, 27), to investigate changes in regional brain activity independent of variations in whole brain measurements with the use of analysis of covariance (26, 28), and to generate separate normalized t score (i.e., z score) maps of brain activity increases during happiness, sadness, and disgust. The brain activity patterns associated with each emotion were determined by combining results across the film and recall conditions: the six control scans were subtracted from the two scans (appropriately weighted) targeting a particular emotion. Significant differences in activity were identified through use of a threshold of $z=2.58$, $p<0.005$, one-tailed. These difference images were then superimposed on the brain MRIs obtained in this study for visual inspection of significant regional brain activity changes. Procedures to ensure that changes in temporal lobe structures were not due to artifacts from the muscles of mastication or ascending arteries were then applied to these data, as described in the accompanying article (15).

A lower significance threshold of $p<0.05$ was used in subsequent analyses for brain activity increases that represented a replication

Control Film Clips and During Emotion-Generating and Control Recall[a]

Recall				
Coordinate				Mean Change (%)
x	y	z	z	
14	58	32	1.74*	1.5
14	-16	4	1.98*	1.7
-40	-62	12	1.65*	1.7
38	12	-28	1.81*	5.1
10	54	28	1.69*	1.5
8	-20	0	2.26*	2.2
-6	-20	0	2.87**	2.7
0	-12	-4	1.85*	1.9
42	-60	-28	2.36*	9.6
2	-50	-20	2.25*	1.7
-6	-34	-4	2.29*	1.9
26	4	-4	2.16*	1.5
-26	4	-4	3.69***	2.4
-6	4	4	1.70*	1.8
-16	44	24	1.66*	1.4
14	-20	0	2.54*	2.1
–10	-12	0	2.97**	2.1
48	10	-20	4.01***	5.6
-40	10	-24	3.45***	5.5
14	-6	-4	2.94**	2.1
-12	-10	-4	2.75**	2.1

findings in the film or recall condition are also shown if they exceed the threshold of p<0.05. These secondary comparisons (film or recall) involved subtracting the average of the three control scans from the one scan (appropriately weighted) targeting a particular emotion.

*p<0.05. **p<0.005. ***p<0.0005.

(e.g., film) from a more inclusive comparison (e.g., film and recall). Similarly, the lower significance threshold was also applied to brain activity increases that were associated with a particular emotion if the brain activity increases were also observed in comparisons involving the combination of the three emotions in relation to their respective controls (see accompanying article [15]). The lower significance threshold was used in this context because a replicated finding is less likely to be a false positive.

Bilateral activity increases were noted when present. Significant right-left asymmetries in activity for individual emotions (film and recall) were determined by direct comparisons (normalized t score maps) of increases in regional brain activity to increases in homologous regions in the opposite hemisphere on a pixel-by-pixel basis.

RESULTS

In comparison with the average of the three control conditions, subjects reported large increases in the relevant target emotion during the emotion-generating film tasks (F=226, df=1, 11, p<0.001) and recall tasks (F=1041, df=1, 11, p<0.001) and minimal increases in nontarget emotions. These ratings are depicted in figure 1.

Happiness, sadness, and disgust were each associated with significant increases in regional brain activity (see table 1 and figure 2). Significant increases in activity were observed in the vicinity of prefrontal cortex (Brodmann's area 9) and thalamus for each of the three emotions (all p values <0.005). Significant increases in activity were also observed bilaterally in anterior temporal structures for all three emotions (all p<0.005) and were predominantly attributable to film-induced emotions. Happiness was also associated with significant activity increases bilaterally in the vicinity of middle and posterior temporal cortex and hypothalamus; sadness was also associated with bilateral activity increases in the vicinity of middle and posterior temporal cortex, lateral cerebellum, cerebellar vermis, midbrain, putamen, and caudate; and disgust was also associated with activity increases in the midbrain. These findings were typically replicated for each emotion in the comparisons involving film and recall only.

To evaluate regions that distinguished between emotions, subtractions between emotions (film and recall) were examined. Regional brain activity was greater during happiness than sadness (coordinates=8, 34, –4; z=2.87, p<0.005; mean difference=1.7%) in the vicinity of a region that encompasses both ventral anterior cingulate and ventral mesial frontal cortex.

In comparisons performed subsequent to inspection of the film plus recall analyses, each film-induced emotion was associated with bilateral activity increases in association (visual, auditory, or multimodal) areas, including middle-posterior temporal regions and occipitotemporal and temporoparietal opercular zones (tables 1 and 2). As shown in table 2, film-induced happiness was also associated with activity increases in the vicinity of left amygdala or nucleus accumbens, bilateral globus pallidus or caudate, and medial posterior cingulate; film-induced sadness was also associated with bilateral activity increases in the vicinity of the amygdala; and film-induced disgust was associated with activity increases in the vicinity of the lateral cerebellum. Changes noted in table 2 were not replicated in the recall comparisons, with the exception of lateral cerebellar activation during disgust (see following text).

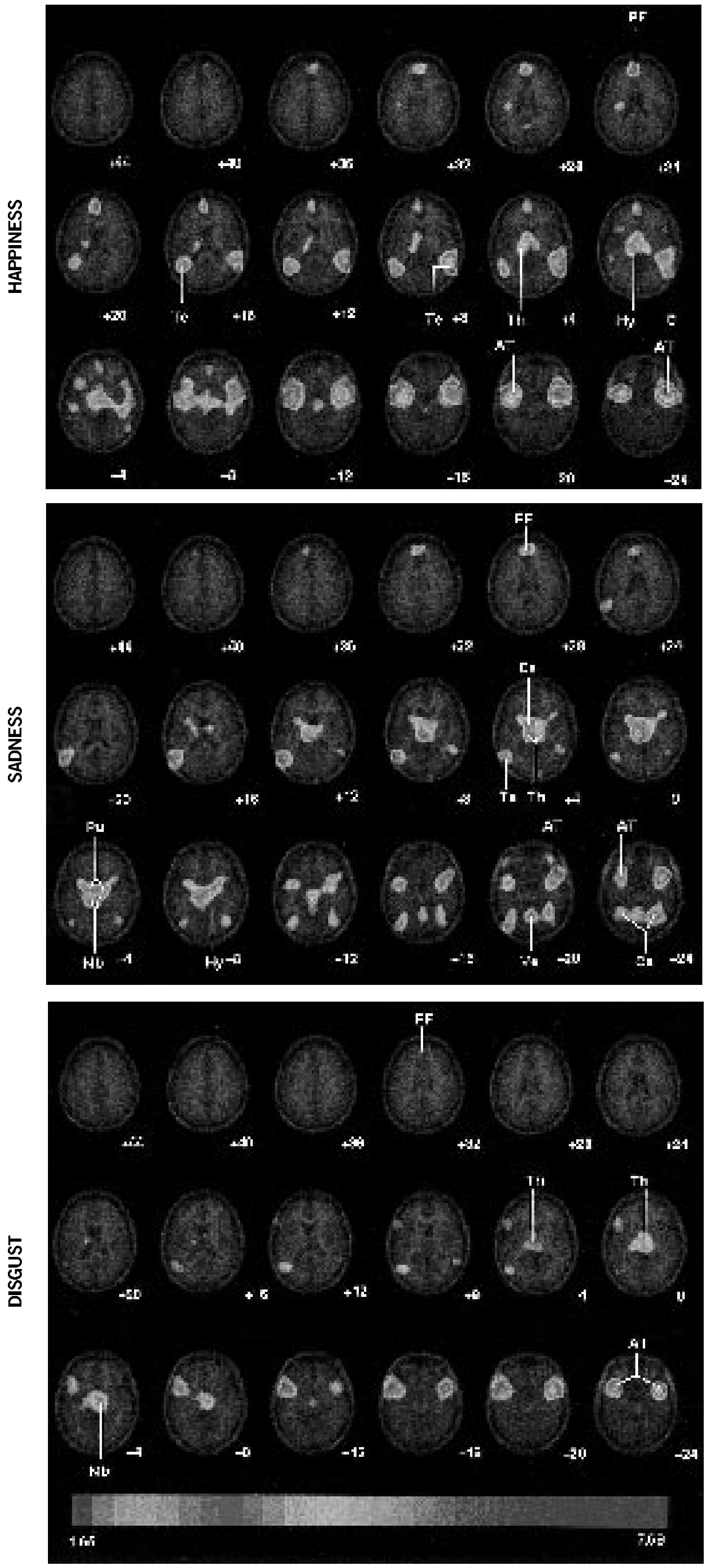
As shown in table 3, there were no unique changes during recall-induced happiness. Recall-induced sadness was associated with greater activation in the vicinity of the anterior insula. As noted earlier, recall-induced disgust was associated with lateral cerebellar activation.

Asymmetry analyses were performed for individual emotions (film and recall), as described earlier. No significant asymmetries were observed.

DISCUSSION

This study identifies neuroanatomical correlates of happiness, sadness, and disgust. The medial prefrontal cortex and thalamus appear to participate in aspects of

FIGURE 2. Images of Significant Increases in Regional Brain Activity During Happiness, Sadness, and Disgust[a]



emotion unrelated to its type, valence, or method of induction. The posterior and anterior temporal cortex appears to participate in aspects of film-generated emotion independent of its type or valence. Ventral mesial frontal cortex appears to be differentially involved in positive and negative emotions. The anterior insular cortex appears to be preferentially involved in certain aspects of negative emotions.

Together, these findings suggest that spatially distributed brain regions participate in each emotion. Emotion may be divided into evaluative, experiential, and expressive components (29), and it is likely that each region is preferentially involved in one or more of these functions. Some regions (e.g., thalamus, prefrontal cortex) are common to the three emotions, some are associated with a given emotion (e.g., caudate, putamen, and sadness), some depend on the emotional stimulus (as noted in this and the accompanying report [15]), and at least one region (the anterior insular region) appears to depend on both the type of emotion and the nature of the emotional stimulus.

Several models have been proposed to explain how the brain mediates emotion in humans. One model states that all basic emotions are mediated by the right hemisphere (12). A second model states that the brain organizes emotion differently as a function of valence, with positive emotions mediated by the left hemisphere and negative emotions by the right hemisphere (13). A third model holds that emotions are lateralized on the basis of concomitant motor responses, with approach emotions (e.g., happiness) lateralized to the left and withdrawal emotions (e.g., disgust) lateralized to the right, particularly in the prefrontal cortex (14). According to the last model, sadness is associated with decreased approach (14).

The regional brain activity patterns that we observed for each emotion were typi-

[a]After color-coded z score maps were computed, they were superimposed onto an average of the subjects' brain MRIs. Brain sections in each image correspond to the coordinates of a brain atlas (27); the number next to each section reflects the distance in millimeters superior (+) or inferior (–) to a horizontal plane between the anterior and posterior commissures; the right hemisphere in each section is on the reader's right. The images showing brain activity during happiness, sadness, and disgust correspond to the data in table 1. PF=medial prefrontal cortex, Th=thalamus, Mb=midbrain, AT=anterior temporal cortex, Ca=caudate, Te=superior temporal gyrus (Happiness) or middle temporal gyrus (Sadness), Pu=putamen, Hy=hypothalamus, Ve=cerebellar vermis, Ce=lateral cerebellum.

TABLE 2. Location and Magnitude of Additional Areas of Significant Change in Regional Brain Activity in 12 Healthy Women During Viewing of Emotion-Generating Film Clips[a,b]

Emotion and Structure	Coordinate x	Coordinate y	Coordinate z	z	Mean Change (%)
Happiness					
Amygdala or nucleus accumbens	-20	-6	-8	4.29**	3.1
Globus pallidus or	8	4	-4	3.66**	2.5
caudate	-10	-4	0	4.32**	3.3
Posterior cingulate (BA 31, 23)	0	-54	28	2.63*	2.3
Sadness					
Amygdala	16	-6	-16	2.75*	2.2
	-26	-2	-12	2.94*	1.8
Occipitotemporal	42	-62	-8	3.88**	5.6
(BA 19, 37)	-38	-66	-8	4.38**	5.2
Disgust					
Lateral cerebellum	-34	-44	-20	2.60*	2.3
Occipitotemporal (BA 19, 37)	-36	-72	4	2.73*	2.7

[a]Subtraction of control scans from scan (appropriately weighted) targeting emotion. See table 1 for details.
[b]p values are one-tailed.
*p<0.005. **p<0.0005.

TABLE 3. Location and Magnitude of Additional Areas of Significant Change in Regional Brain Activity in 12 Healthy Women During Recall of Target Emotions[a,b]

Emotion and Structure	Coordinate x	Coordinate y	Coordinate z	z	Mean Change (%)
Sadness: insula	-36	6	4	3.23**	2.7
Disgust: lateral cerebellum	-14	-64	-28	2.91*	10.8
	26	-58	-28	2.72*	9.9

[a]Subtraction of control scans from scan (appropriately weighted) targeting emotion. There were no additional significant changes during recall-induced happiness. See table 1 for details.
[b]p values are one-tailed.
*p<0.005. **p<0.0005.

cally symmetrical. Significant asymmetries associated with each emotion were not observed in this study. The failure to support any of the existing models that focus on laterality could reflect limitations in statistical power in this study. An alternative explanation is that important methodological differences exist between this and previous studies. For example, previous quantitative EEG studies (14) examined shorter time frames, analyzed only those epochs associated with a particular facial emotion, and controlled more rigorously for purity of the target emotion.

In comparison to other PET studies, the present study is most similar to that of George and colleagues (9), who also used neutral emotion control tasks and elicited emotion by using a combination of visual and recall stimuli. Our film + recall sadness condition is similar to their recall of a sad event in conjunction with viewing pictures of sad faces. Both studies showed that sadness is associated with activity increases in thalamus, medial prefrontal cortex, brainstem, caudate, and putamen. The findings in the present study differed in showing activity increases during sadness in hypothalamus, insula, and cerebellum and no activity increases in inferior frontal cortex. Numerous variables need to be standardized across studies in order to consider one study a true replication of another. To date, no such replication has been conducted in the field of PET/emotion research, making it difficult to account for differences in findings across studies.

Studies on the orbitofrontal cortex in patients (30–32) and nonhuman primates (33, 34) suggest that it participates in integrating information about rewards and punishments to bias future behavior. Damasio and colleagues (30) demonstrated that ventromedial prefrontal lesions are associated with the absence of autonomic responses to positive as well as negatively charged pictures. Hornak and colleagues (32) studied 10 patients with ventral prefrontal lesions and observed that all reported changes in their ability to feel emotions compared to their premorbid state. However, the extent to which there were changes (increases or decreases) in the capacity to feel negative (e.g., sadness) or positive (e.g., happiness) emotions was quite variable across patients. It is unclear whether this variability was due to small differences in lesion location, premorbid differences in the organization and functional connections of this region across patients, or some other cause.

In this light, the observation of different associations between emotional valence and ventral mesial prefrontal activity across different PET studies is not surprising. It is possible that different subregions within the ventromedial prefrontal cortex could be associated with the elaboration of different types of emotion, consistent with its role in integrating information about rewards and punishments. The significant regional activity increases during happiness compared to sadness (coordinates=8, 34, –4) that we observed were probably more anterior than those of George et al. (9) (coordinates=–14, 18, –8) and more medial than those of Pardo et al. (7) (coordinates=–43, 33, –2), who observed greater activity increases in sadness than controls in approximately the same region. The findings of Hornak and colleagues (32) also raise the possibility that the samples in the two PET studies differed because of differences between subjects in the organization and functional connections within this region. Yet another possibility that cannot be excluded is that there were differences in the intensity of the arousal associated with happiness and sadness in this study and in other studies.

Increases in regional brain activity have been observed in the anterior insular cortex during another study of recall-induced sadness (7), lactate-induced panic (23), normal anticipatory anxiety (22), simple phobia (35), the perception of temperature and pain (36), taste (37), and the luteal phase of the menstrual cycle (38). In this study we observed activity increases in the anterior insular cortex during recall-induced sadness. The anterior insular region may preferentially participate in assigning negative emotional significance to information about the self.

As noted in the accompanying article (15), our critical z score (z=2.58, p<0.005, uncorrected for multiple comparisons) potentially permits inclusion of false positive results. This threshold for discriminating between true and false signals had been previously established for our imaging technique in the context of a well-characterized behavioral task (hand movement) (15). The bilateral nature of most findings in this study also makes it unlikely that the regions of activation that exceed this threshold are due to chance. It is also possible in this study, as in other brain imaging studies, that some true activations were not identified because they did not reach this a priori threshold.

The accompanying article (15) also noted that the film clips were not controlled for faces, facial emotions, and social interactions, and the recalled experiences were not controlled for the characters or setting in question. Furthermore, limitations in spatial resolution and the anatomical localization method used in this study prevent us from distinguishing with certainty activity in adjacent structures. Our findings should therefore be considered preliminary until they are replicated. Additional studies are also needed to determine the extent to which our findings can be generalized to male subjects, different age groups, different handedness groups, and people who vary in their ability to have intense emotions or who are not instructed to feel the target emotion. We note, however, that we recently replicated the findings of thalamic and medial prefrontal activation during pleasant and unpleasant emotion by using emotion and control stimuli that included faces (39). Subjects in that study included healthy women who were not preselected for their ability to have intense emotions and who were not told before each scan what they should feel.

In conclusion, there appear to be several regions that participate in emotion independent of its type or valence or the method used to induce it, some regions that depend on one of these factors, and some that depend on a combination of these factors. Further delineation of how emotional valence and intensity are regulated in the normal brain will be essential in the quest to understand the functional neuroanatomy of pathological emotional states and the contributions of emotion dysregulation to physical disease.

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