



Neuroanatomical correlates of pleasant and unpleasant emotion

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Abstract—Substantial evidence suggests that a key distinction in the classification of human emotion is that between an appetitive motivational system associated with positive or pleasant emotion and an aversive motivational system associated with negative or unpleasant emotion. To explore the neural substrates of these two systems, 12 healthy women viewed sets of pictures previously demonstrated to elicit pleasant, unpleasant and neutral emotion, while positron emission tomographic (PET) measurements of regional cerebral blood flow were obtained. Pleasant and unpleasant emotions were each distinguished from neutral emotion conditions by significantly increased cerebral blood flow in the vicinity of the medial prefrontal cortex (Brodmann's area 9), thalamus, hypothalamus and midbrain ($P < 0.005$). Unpleasant was distinguished from neutral or pleasant emotion by activation of the bilateral occipito-temporal cortex and cerebellum, and left parahippocampal gyrus, hippocampus and amygdala ($P < 0.005$). Pleasant was also distinguished from neutral but not unpleasant emotion by activation of the head of the left caudate nucleus ($P < 0.005$). These findings are consistent with those from other recent PET studies of human emotion and demonstrate that there are both common and unique components of the neural networks mediating pleasant and unpleasant emotion in healthy women. © 1997 Elsevier Science Ltd

Key Words: emotion; PET; cerebral blood flow; thalamus; prefrontal cortex; amygdala.

Introduction

The neural substrates of human emotion have received considerable attention recently. Major theoretical treatises on the brain and emotion by Damasio [9] and LeDoux [31] have recently been published. These integrative theses have been possible largely due to recent experimental findings in animals and observations in patients with brain lesions. An important next step, which has already begun, is to determine how these findings relate to functioning in the intact human brain using functional brain imaging techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (MRI) in healthy volunteers. Indeed,

until such work is done the applicability of findings in animals and patients to intact humans will be uncertain.

Fundamental work in laboratory animals including non-human primates has significantly advanced our understanding of the neural substrates of facial emotion perception [41], visceral sensation associated with emotion [3], fear [11, 31], reward [14], the influence of reward and punishment in biasing future behavior [46], and the integration of somatomotor and visceromotor output associated with emotional arousal [12]. These functions have been related in particular to the ventral visual processing stream, insula, amygdala, ventral striatum including nucleus accumbens and ventral tegmental area, orbitofrontal cortex and anterior cingulate cortex, respectively. Studies of patients with lesions affecting face perception [53], fear [1] and use of emotional states to guide behavior [9] have demonstrated important correspondences with the animal findings. Functional imaging studies involving emotion have also generated

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important findings involving visual processing areas [15, 30, 45, 52], the insula [23, 43–45], the amygdala [6, 20, 36], the orbitofrontal cortex [19, 23, 40] and the anterior cingulate cortex [19, 21, 24, 32, 42]. Although several studies [19, 23, 40, 45, 48] have been conducted to address the issue, a key question which has not been resolved is how different types or classes of emotion are mediated in healthy humans.

A fundamental distinction which is potentially pertinent to any classification of emotion is that emotion is subserved by an appetitive motivational system associated with positive or pleasant emotion and an aversive motivational system associated with negative or unpleasant emotion [13, 22]. Consistent with this view, recent studies of psychophysiological responses to pictures [26, 27, 29] have provided evidence that two motive systems underlie affective reactions to these emotionally evocative materials. These studies have demonstrated, for example, that the defensive startle reflex is potentiated in the context of aversive stimulation in humans as well as laboratory animals [11].

The relationship between pleasant and unpleasant emotions has been conceptualized in several different ways. One view is that pleasant and unpleasant emotions represent opposite ends of a pleasure continuum [38]. This view would suggest that the neural substrates of the appetitive and aversive motivational systems share much in common or are closely interconnected [39]. It has been suggested, for example, that the various types of emotion can be defined by their location on a two-dimensional plot, the so-called circumplex model, consisting of a pleasure continuum (as above) on one axis and arousal on the other [47]. An alternative view is that the two motivational systems are independent of one another [51], possibly suggesting that their neural substrates are also independent or more loosely interconnected. Indeed, LeDoux [31] holds that different types of emotion are mediated by different neural systems. This perspective leads to a different way of relating various emotions to one another, e.g., sadness would be characterized by low appetitive and disgust by high aversive motivation in this scheme [10], whereas they would both be considered unpleasant or aversive in the former approach. To the extent that different neural structures subserve the appetitive and aversive systems, one might expect very different areas of activation in response to pictures that evoke pleasant and unpleasant emotion.

In a previous PET study of normal women in our laboratory, we observed that the thalamus and medial prefrontal cortex [Brodmann's area (BA) 9] were activated when viewing films or recalling personal experiences that evoked happiness, sadness or disgust [23, 45]. The similarities between the neural substrates of the different types of emotion appeared to be greater than their differences, supporting the former model. To our knowledge, no studies involving cerebral blood flow (CBF) measurement have specifically examined the neural correlates of emotion conditions indicative of the two motive systems.

This study therefore provided a unique opportunity to determine the extent to which there are common and/or unique components of the neural substrates of pleasant and unpleasant emotion. Based on our previous results, we predicted that pleasant and unpleasant emotions would each be associated with increased activity in the thalamus and medial prefrontal cortex. We also predicted greater activity in the hypothalamus [4], orbitofrontal cortex, anterior cingulate cortex and ventral visual processing stream during both emotion conditions relative to the neutral conditions. Based on previous findings, we also predicted that the amygdala [6, 36], insula [23, 43–45] and extrastriate visual cortex [15, 36, 52] would show greater activity during unpleasant compared to pleasant emotion. Finally, we predicted greater activity in the ventral striatum, including the nucleus accumbens and ventral tegmental area [14], during pleasant compared to unpleasant emotion.

Methods

Subjects

Twelve right-handed, neurologically, medically and psychiatrically well female volunteers aged 18–45 years were recruited through posted announcements. Subjects provided information about their menstrual and contraceptive history and were excluded if birth control measures were not adequate. The sample was restricted to females to maximize the homogeneity of emotion-dependent changes in CBF and the likelihood of intense self-reported emotional experiences [49]. Potential subjects were asked directly about their sexual preference. Only heterosexual women were studied to ensure that pictures depicting heterosexual encounters were viewed positively. The study was approved by the Human Subject Committees at the University of Arizona in Tucson and the Good Samaritan Regional Medical Center in Phoenix. Subjects provided informed consent and received compensation for their participation.

Experimental design

Pictures were selected from the International Affective Picture System [28] based on normative pleasure ratings to produce three 20-item sets each of pleasant, neutral and unpleasant pictures. Pleasant pictures included themes such as erotica, babies, sports events, etc. Unpleasant pictures included themes such as frightening animals, mutilated bodies, human violence, etc. Neutral pictures consisted of inanimate objects, people with neutral facial expressions and complex visual stimuli (e.g., scenes, patterns, etc.). A visual fixation set, consisting of repeated presentations of a small white cross-hair at the center of a black background, was also created. All stimuli were presented on videotape using a 27-inch color TV monitor positioned 48 inches above the subject's face.

Pictures were presented for 6 sec each. The screen was blank for 1 sec between pictures. Bolus injection of radiotracer occurred at the onset of the ninth picture. Scans began 16 sec after the start of bolus injection during the eleventh picture. Pictures were never repeated during scans.

The 12 conditions for each subject consisted of three blocks of four scans each (pleasant, unpleasant, neutral and visual

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fixation). The visual fixation condition was always first in each block. The three picture conditions were counterbalanced to control order effects.

Following each scan, subjects made a single rating of the pleasure and arousal of the entire picture sequence. Each picture was then presented again (approximately 2 min after initial viewing) and rated for the pleasure and arousal of that picture as experienced at the time of the initial presentation. The Self-Assessment Manikin (SAM) rating scales for pleasure and arousal were used to make these ratings [5, 28] and were on display for the rating period only. Valence ratings ranged from 1 (very unhappy) to 9 (very happy) and arousal ratings ranged from 1 (very calm) to 9 (very excited).

Skin conductance was transduced using Biopac standard electrodes to the hypothenar eminence of the left palm. A Biopac skin conductance coupler provided a constant 0.5 V across electrodes. The data were sampled at 1000 Hz and reduced off-line into 12 half-second bins (in μ Siemens). Skin conductance responses (SCRs) were scored as the largest half-second value during the 6-sec picture viewing period. A log transformation [$\log(\text{SCR} + 1)$] was used to normalize the distribution of these responses.

Imaging procedures

A T1-weighted, three-dimensional Volume Spoiled Gradient Recalled Acquisition in the Steady State pulse sequence (SPGR, TE=5 msec, TR=33 msec, angle=30°, NEX=1, FOV=24 cm, imaging matrix=256 × 198) was used to acquire 128 contiguous, 1.5-mm-thick horizontal slices of the brain. These MRI images were acquired prior to the PET session to ensure structural normality of the brain, facilitate head positioning in the PET scanner (to include as much of the cerebral cortex and temporal lobes as possible and to correct for lateral tilt), and permit co-registration between the PET and MRI images when this technique is incorporated into our image analysis software.

Subject preparation for PET included: the insertion of a catheter in the left antecubital vein to permit tracer administration; head immobilization using a fast-hardening foam mold; and the performance of a transmission scan using a $^{68}\text{Ge}/^{68}\text{Ga}$ ring source to correct subsequent emission images for radiation attenuation. During each scan, subjects rested quietly in the supine position without movement.

Twelve 31-slice PET images of regional CBF were obtained in each subject using the ECAT 951/31 scanner (Siemens, Knoxville, TN, U.S.A.), 40 mCi intravenous bolus injections of ^{15}O -water, 60-sec scans and an interval of 10–15 min between scans [18, 43, 44]. PET images were reconstructed with an in-plane resolution of 10 mm full width half maximum (FWHM) and a slice thickness of 5 mm FWHM. For data analysis, a Gaussian blur yields an in-plane resolution of 20 mm FWHM and a slice thickness of 10 mm FWHM.

Data were analysed using Statistical Parametric Mapping (SPM). Automated algorithms were used to align each subject's sequential PET images [34], transform her PET images into the standard spatial coordinates of a brain atlas [17, 50], investigate regional CBF changes independent of variations in whole brain measurements [16, 17], and generate separate normalized *t* score (i.e. Z score) maps of CBF increases during pleasant, unpleasant and neutral emotion.

Image analysis

Significant CBF differences were identified using a one-tailed threshold of $P < 0.005$. In a previous (unpublished) study of a

well-characterized behavioral task (hand movement), this threshold provided the best balance between Type I and Type II errors. Data were analysed both with and without a threshold (the exclusion of all pixels external to those with at least 40% of the maximal count rate in the control CBF image). Non-thresholded images were used *post-hoc* to detect any blood flow changes originating outside the brain. Automated algorithms were used to transform each subject's brain MRI into standard atlas coordinates [8], compute an average of the 12 subjects' MRI images and superimpose each Z-score map onto the averaged MRI (Fig. 1) to permit visual inspection of the composite images.

The principal analyses consisted of subtracting the three neutral scans from the three pleasant scans and the three neutral scans from the three unpleasant scans. Structures are listed below if they exceed the $P < 0.005$ threshold, represent the point of maximum activation in an SPM-defined region of interest on a given slice, and represent the point of maximum activation for that structure across slices. Other points are also reported below if they exceed the $P < 0.005$ threshold and either (i) represent a structure of *a priori* interest (as defined in the introduction) or (ii) represent a replication within this study and across studies. Significant right-left asymmetries in activity were determined by direct comparisons between CBF increases during emotion (pleasant or unpleasant emotion minus neutral) in one hemisphere compared to CBF increases in homologous regions in the opposite hemisphere on a pixel-by-pixel basis which exceeded the $P < 0.005$ threshold.

Results

The ratings data confirmed that the pictures varied as intended in both pleasure [$F(2,22) = 198.8$, $P < 0.001$] and arousal [$F(2,22) = 25.62$, $P < 0.001$]. Unpleasant pictures were rated lower in pleasantness (mean = 2.43) compared to neutral pictures (mean = 5.11) [$F(1,11) = 108.9$, $P < 0.001$], and pleasant pictures were rated higher in pleasantness (mean = 7.46) [$F(1,11) = 152.0$, $P < 0.001$]. Both pleasant [$F(1,11) = 45.57$, $P < 0.001$] and unpleasant [$F(1,11) = 49.28$, $P < 0.001$] pictures were also rated significantly higher in arousal (mean = 4.91 and 5.45, respectively) than neutral pictures (mean = 2.66).

Differences in arousal among the picture contents were also indicated in the electrodermal responses [$F(2,22) = 7.88$, $P < 0.003$], which are primarily an index of sympathetic nervous system activity. Skin conductance magnitude was larger when viewing unpleasant (0.06 μ Siemens) or pleasant (0.04 μ Siemens) materials, compared to neutral pictures (0.02 μ Siemens) [$F(1,11) = 13.59$, $P < 0.004$]. Responses elicited by unpleasant pictures were also marginally larger than those elicited by pleasant stimuli [$F(1,11) = 4.04$, $P = 0.07$].

The CBF increases during pleasant and unpleasant emotion are presented in Tables 1 and 2. These tables reveal activation during pleasant and unpleasant emotion in the thalamus, hypothalamus, midbrain and medial prefrontal cortex (BA 9). There were no significant CBF differences between pleasant and unpleasant emotions in these structures. Compared to neutral, pleasant emotion was also associated with activation of the head of the

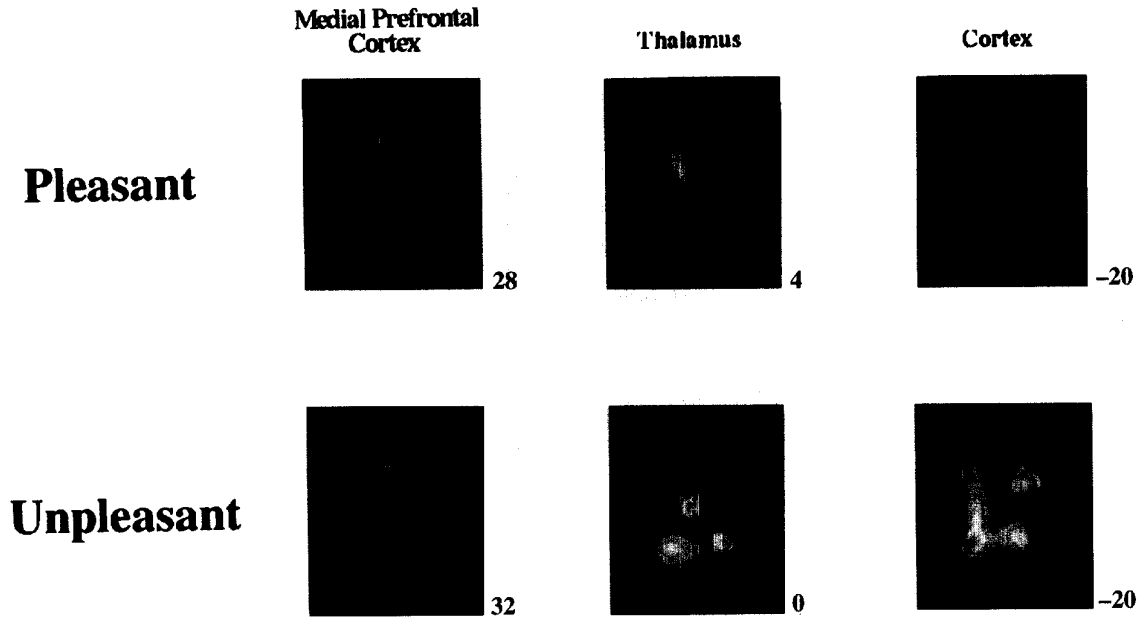


Fig. 1. Significant CBF increases in the medial prefrontal cortex (BA 9), thalamus and medial temporal lobe/bilateral cerebellum during pleasant and unpleasant emotion relative to neutral. Normalized t -value maps are superimposed onto an averaged brain MRI using PET data from 12 healthy female subjects. Images in the transverse plane were selected to depict the maximum change in each of the labelled regions for that emotion condition. The images are denoted by their distance in mm superior (+) or inferior (-) to the level of the horizontal plane between the anterior and posterior commissures. The right side of the brain is displayed on the reader's right. Lighter areas within each brain image represent loci where $Z > 2.58$. The gray scale shading varies as a function of the Z score. The activation in the medial prefrontal cortex associated with unpleasant emotion in plane 32 is located in the brain but appears to extend beyond it due to smoothing of the images and a slight misalignment in the PET and MRI data due to their differing spatial normalization algorithms. CBF increases in the occipito-temporal cortex (BA 18, 19, 37) associated with unpleasant emotion are evident in plane 0. Plane -20 depicts the CBF increase in the left parahippocampal gyrus and bilateral cerebellum associated with unpleasant emotion. The most anterior changes in that plane (which are bilateral), extend outside the brain and therefore are not reported. There are no significant CBF increases associated with pleasant emotion in plane -20.

caudate nucleus, and unpleasant emotion was also associated with activation of the left amygdala, hippocampus, parahippocampal gyrus, and bilateral occipito-temporal cortex and cerebellum. Blood flow was significantly greater in the latter areas during unpleasant compared to pleasant emotion. There were no CBF increases during

pleasant emotion which were greater than neutral and also greater than unpleasant emotion.

Images depicting common and unique changes during pleasant and unpleasant emotion are shown in Fig. 1. A significant asymmetry was observed during unpleasant compared to neutral emotion centered on the left para-

Table 1. Representative areas of significant cerebral blood flow change during pleasant emotion relative to neutral

Structure	Brodmann's area	x	y	z	Z score	P
Prefrontal cortex	9	-4	52	28	2.72	0.005
Left caudate (head)		-6	6	4	3.80	0.005
Thalamus		-4	-8	4	4.73	0.005
Hypothalamus		-6	-8	-4	3.84	0.005
Midbrain		-4	-14	-4	3.76	0.005

Regions are identified by name of structure, Brodmann's area and stereotactic coordinates in the brain atlas of Talairach and Tournoux [50]; x = distance (in mm) to the right (R) (+) or left (L) (-) 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. Z scores are normalized t statistics that reflect the significance of the activation effect generated by the appropriate comparison using SPM. A one-tailed threshold of $P < 0.005$ was used to optimize the balance between Type I and Type II errors.

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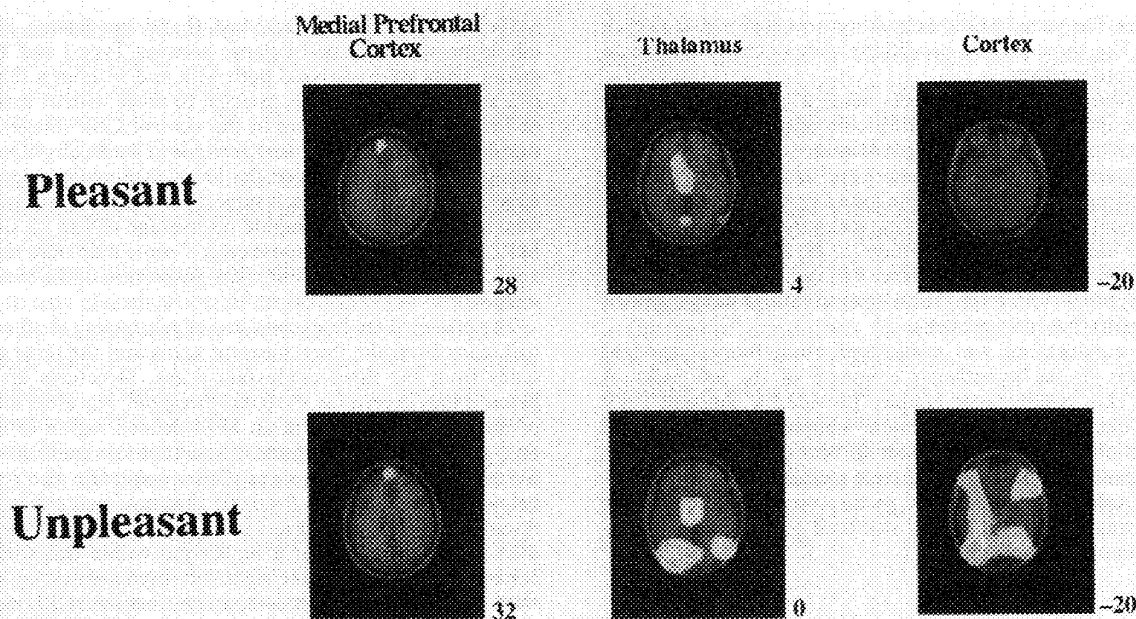


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Table 2. Representative areas of significant cerebral blood flow change during unpleasant emotion relative to neutral

Structure	Brodman's area	x	y	z	Z score	P
Prefrontal cortex	9	-2	52	32	2.68	0.005
Thalamus		-4	-12	0	5.82	0.005
Hypothalamus		-2	-10	-8	4.77	0.005
Midbrain		-10	-16	-12	3.82	0.005
Amygdala		-26	-6	-16	3.67	0.005
Hippocampus		-24	-14	-16	3.46	0.005
Parahippocampal gyrus (L)	28	-30	-20	-20	4.27	0.005
Occipito-temporal cortex (L)	18, 19, 37	-34	-70	-8	5.48	0.005
Occipito-temporal cortex (R)	18, 19, 37	48	-68	-4	5.50	0.005
Cerebellum (L)		-40	-68	-16	6.25	0.005
Cerebellum (R)		34	-58	-16	5.03	0.005

See footnote to Table 1 for definitions.

hippocampal gyrus (-34, -14, -20; $Z=2.97$; $P<0.005$).

Discussion

A key question addressed in this study was the degree to which the neural substrates of pleasant and unpleasant emotions were similar or different. There was substantial but not complete overlap in the patterns of activation during these two emotion conditions. While the differences observed are consistent with the theoretical differentiation between an appetitive and an aversive motivational system, data from this study and others suggest that the neural substrates of these two systems share much in common or are closely inter-related.

The present findings replicate those from a previous study of happiness, sadness and disgust [23, 45]. The findings in that study were internally replicated using two different emotion induction methods (film and recall). The present findings extend that work by demonstrating in a very different paradigm that the thalamus, hypothalamus, midbrain and medial prefrontal cortex are also activated during the processing of pleasant and unpleasant pictures that spanned a variety of different emotions (e.g., fear, disgust, etc.). These data therefore suggest that in healthy women the neural substrates of several types of emotional states overlap. Finding that specific structures are reliably activated across a wide range of emotion-inducing tasks is among the first evidence of replicable patterns in functional brain imaging studies of normal human emotion.

The medial prefrontal region could be involved in the conscious experience of emotion [45], inhibition in the expression of emotion [35] or emotion-related decision making [9]. Focused experiments are needed to determine what role or roles the medial prefrontal cortex is playing in this context.

One of the uncertainties from our previous study of film- and recall-induced emotion was whether the instructions given to subjects in that study (e.g., 'feel happy')

may have induced a self-monitoring state reflected in prefrontal activity. This can be ruled out in the current study as subjects were not told prior to each scan what they would or should feel.

Limitations in spatial resolution and anatomical localization also prevent us from identifying the specific thalamic nuclei responsible for the CBF increases in this region. Cannon [7] and Bard's [4] work on 'sham rage' suggest that the anterior thalamus participates in the integrated behavioral and autonomic expression of emotion. Visual relay functions in the lateral geniculate nucleus cannot be ruled out in the present context of emotion-eliciting photographs, nor can a role of the thalamus in the network of structures mediating consciousness [37].

We observed amygdala activation with unpleasant and not with pleasant emotion, and also found greater amygdala activity during perception of unpleasant pictures. These findings are consistent with recent data indicating that the defensive startle reflex is augmented when processing unpleasant pictures such as those used here, and inhibited during processing of pleasant pictures [26]. Animal models of startle modulation [11] clearly implicate the amygdala in mediating reflex potentiation by fear. Furthermore, patients with Urbach Wiethe disease [1] (bilateral calcification of the amygdalae) show a selective deficit in the perception of fear.

A preferential association with the left amygdala has been demonstrated during the viewing of sad faces compared to control conditions [48]. CBF in the left but not the right amygdala correlated positively with fear and negatively with euphoria induced by intravenous procaine [21]. Similarly, activation in the left amygdala was significantly greater during the perception of fearful compared to happy facial expressions in a recent PET study [36], and left greater than right anterior amygdala activation was observed during perception of fearful compared to neutral facial expressions in a recent functional MRI study [6]. Given the limitations in anatomical localization associated with PET, the finding in the present study of an asymmetry in the left medial temporal lobe

when viewing unpleasant pictures is consistent with these other recent findings. However, the association between amygdala and unpleasant emotion may not be exclusive as indicated by the preliminary observation by Breiter *et al.* [6] that happy relative to neutral faces activated the amygdala significantly but to a lesser degree than fearful faces.

The bilateral activations in the occipito-temporal cortex during unpleasant emotion are also consistent with CBF changes observed during the elicitation of phobic fear in snake [52] and spider [15] phobics. These changes may reflect projections of the amygdala back to all levels of the visual system to a degree that exceeds the input that it receives from these structures [2]. The amygdala may be playing some role in tuning the visual system to become more sensitive to threat cues. It is possible, however, that these changes in the extrastriate visual cortex reflect the intensity rather than the valence of emotion. In a recent PET study in men [25], significant extrastriate visual cortical activation was observed during high arousal relative to low arousal pleasant or unpleasant photos. A functional imaging study in women experimentally differentiating between different levels of arousal within each valence category is clearly indicated.

The activation in the head of the caudate nucleus during pleasant emotion is in the general vicinity of the predicted activation in the ventral striatum. This finding is also consistent with an observation in a SPECT study by Mayburg *et al.* [33], who observed decreased blood flow in the caudate nucleus in depressed patients.

Several other predicted areas of activation were not observed using our threshold of $P < 0.005$, including the insula, orbitofrontal cortex and anterior cingulate. Activations of the anterior insula have been observed previously during internally generated (e.g., recall) rather than externally generated (e.g., film) emotion [43, 44, 45], as in the present study. With regard to the orbitofrontal and anterior cingulate cortices, the present paradigm is quite different from those used in previous studies in which these structures were activated, and thus this study should not be considered an attempt at replication. In general, negative findings are less meaningful than positive findings in PET studies due to limitations in spatial resolution, statistical power, heterogeneity in the cognitive strategies used to perform the task or a change in the pattern rather than the level of neuronal activity.

The neutral stimuli used in this study controlled for the presence of complex visual stimuli, the presence of people and the presence of human faces. However, approximately one-third of the pleasant and unpleasant pictures depicted two or more people, while the neutral photos never depicted more than one person. Therefore, while the neutral photos controlled for many of the non-specific aspects of the stimuli, it is possible that the social situations independent of the emotion(s) associated with them may have contributed to the activation patterns observed during pleasant or unpleasant emotion.

In conclusion, the results of this study indicate that

there is considerable overlap in the neural correlates of pleasant and unpleasant emotion. Activation of the thalamus, hypothalamus, midbrain and medial prefrontal cortex in this study replicates findings from our previous PET study of discrete emotion [23, 45]. Activation of these structures independent of the type of emotion or method of elicitation suggests that they are fundamental components of a neural network mediating emotion in healthy women. The exact function or functions of the medial prefrontal cortex and thalamus in this context remain(s) to be determined. Activation of the left medial temporal lobe (including the left amygdala and parahippocampal gyrus) and bilateral occipito-temporal cortex and cerebellum distinguished unpleasant from neutral and pleasant emotions, but these findings do not exclude the possibility that these structures also participate in pleasant emotion. Activation of the head of the caudate nucleus was observed during pleasant relative to neutral emotion, but not relative to unpleasant emotion. This study therefore supports the view that there is a common neural substrate for emotion generally and that the neural substrates of the appetitive and aversive motivational systems are at least partially distinguishable in healthy women. Further work is needed to delineate the other components of this network and their respective functions, disentangle the specific neural correlates of the valence and arousal of emotion, and explore whether there is a specific neural basis of individual emotions.

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