Subcortical and cortical brain activity during the feeling of self-generated emotions

Antonio R. Damasio, Thomas J. Grabowski, Antoine Bechara, Hanna Damasio, Laura L.B. Ponto, Josef Parvizi and Richard D. Hichwa

Department of Neurology (Division of Cognitive Neuroscience) and PET Imaging Center, University of Iowa College of Medicine, 200 Hawkins Drive, Iowa City, Iowa 52242, USA

Correspondence should be addressed to A.R.D. (antonio-damasio@uiowa.edu)

In a series of [^{15}O]PET experiments aimed at investigating the neural basis of emotion and feeling, 41 normal subjects recalled and re-experienced personal life episodes marked by sadness, happiness, anger or fear. We tested the hypothesis that the process of feeling emotions requires the participation of brain regions, such as the somatosensory cortices and the upper brainstem nuclei, that are involved in the mapping and/or regulation of internal organism states. Such areas were indeed engaged, underscoring the close relationship between emotion and homeostasis. The findings also lend support to the idea that the subjective process of feeling emotions is partly grounded in dynamic neural maps, which represent several aspects of the organism's continuously changing internal state.

Both the recognition of emotions, as expressed in the human face, and actual states of emotion have been studied by neuroimaging[1–13]. Correlates of sadness are relatively clear, but the correlates of happiness and anger, for example, remain elusive. Thus, our understanding of the neural correlates of emotional experience is incomplete, and the range of currently identified neuroanatomical regions whose activity correlates with emotion and feeling is very limited[1].

The hypothesis we tested in this study was guided by a theoretical framework that proposes that emotions are part of a multitiered and evolutionarily set neural mechanism aimed at maintaining organism homeostasis. This mechanism is based on structures that regulate the organism's current state by executing specific actions via the musculoskeletal system, ranging from facial and postural expressions to complex behaviors, and by producing chemical and neural responses aimed at the internal milieu, viscera and telencephalic neural circuits. The consequences of such responses are represented both in subcortical regulatory structures (for example, in hypothalamus and brainstem tegmentum) and in cerebral cortex (for example, insula, SII and cingulate regions), and those representations constitute a critical aspect of the neural basis of feelings. The physiological programs of each emotion-feeling cycle engage brain regions in distinctive patterns. Preliminary evidence in both human and nonhuman animals indicates that these proposed representational and/or regulatory sites are involved in emotion[1,14–19].

We used functional imaging and a task in which four primary emotions were induced by the recall of personal emotional episodes to test the following hypothesis: in addition to already-identified neural sites in amygdala and orbitofrontal cortex, emotions would engage (activate or deactivate) cortical and subcortical regions concerned with representing and/or regulating organism state, namely in the insular cortex, secondary somatosensory cortex (SII), anterior and posterior cingulate cortex, hypothalamus and nuclei in the brainstem tegmentum (upper pons and midbrain). All of these regions were engaged by our task, and the patterns of activation/deactivation varied with each emotion-feeling cycle. The subjective process of feeling an emotion is thus correlated with activity patterns in brain regions that map the continuously changing internal states of the organism.

Results

We used PET to compare each of four target emotions—produced by the recall of an emotionally powerful, personal episode—with recall of a neutral personal episode. Subtraction of activity in the neutral state from that of the emotional state was assumed to reveal the patterns related to the feeling state for two reasons. First, the process of the mental imagery associated with neutral states should cancel that of the mental imagery associated with feeling states. Second, PET data were collected only after the subjects began feeling the emotion.

All subjects attained the target emotion during the PET session. The area under the skin-conductance response curve during scanning averaged 1.88 ± 0.51 μs (s.e.m.) for sadness, 1.67 ± 0.51 μs for happiness, 2.61 ± 0.70 μs for anger and 2.61 ± 0.63 μs for fear; all were significantly different from the neutral state of 0.63 ± 0.10 μs ($p < 0.01$). Heart rate averaged 81.71 ± 1.86 beats per minute (bpm) for sadness, 79.47 ± 1.97 bpm for happiness, 79.65 ± 1.27 bpm for anger and 80.52 ± 1.69 bpm for fear; all were significantly different from the neutral state of 74.25 ± 1.08 bpm ($p < 0.01$). Intensity ratings (on a scale of 0–4) averaged 3.20 ± 0.15 for sadness, 3.00 ± 0.14 for happiness, 3.09 ± 0.12 for anger and 3.27 ± 0.13 for fear; all were significantly different from the average neutral state rating of 0.38 ± 0.09 ($p < 0.01$). These values were not significantly different from those obtained in the screening session, and all the subjects reported being better able to evoke the emotions during the actual scan. In all cases, rises in psychophysiological activity preced-

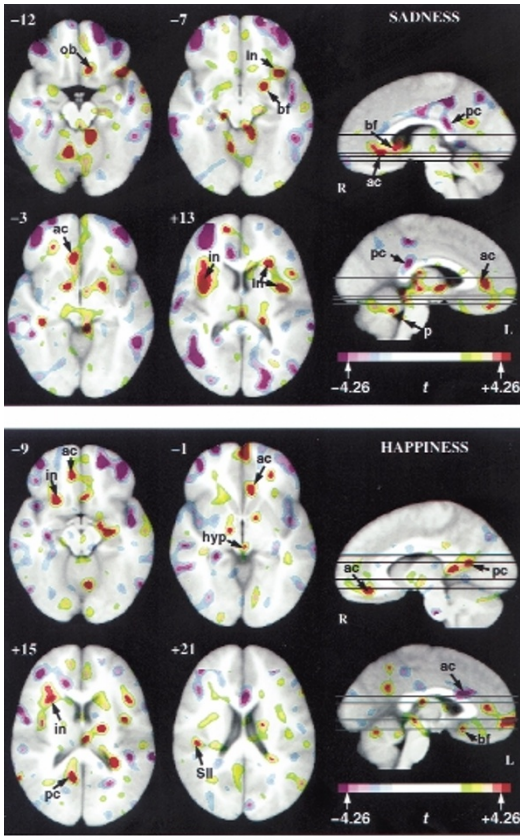

Fig. 1. Neural correlates of feeling sadness and happiness. Representative axial slices and paramedial brain views of the three-dimensional reconstructed brain of the 39 subjects in this study corendered with the PET results. The level of the axial slices has been marked by black lines on the paramedial images. Each axial slice is also identified by its Talairach coordinate (upper left corner). Deep red areas denote significant activation peaks (*t* statistic value of +4.26 or greater), purple areas denote significant deactivations (*t* statistic value of –4.26); the bottom bar provides a color code for the significance value of the activation. Top, sadness. Note the bilateral, but asymmetric, activations of the insula (in) and the mixed activation–deactivation pattern in cingulate cortex (activations anterior, deactivations posterior). Note also the activation in dorsal pons. Bottom, happiness, whose activation pattern is remarkably distinct from that of sadness. Note the positive peak in right posterior cingulate, the negative peak in the anterior third of the left cingulate, the positive peak in left insula, and the positive peak in right SII. For details, see text and Tables 1 and 2. ob, orbitofrontal; in, insula; bf, basal forebrain; ac, anterior cingulate; p, pons; hyp, hypothalamus; pc, posterior cingulate; SII, secondary somatosensory cortex.

ed the subject's signal that the target emotion was felt, which supports the notion that the enactment of emotion precedes the feeling state.

We subtracted the neutral condition from each emotion condition using a 6 mm Gaussian filter (**Figs. 1** and **2**). Maxima and minima are reported first for the search volume pertinent to the hypothesis (critical $t = \pm 4.26$; **Table 1**) and then for the whole brain *post-hoc* search (critical $t = \pm 4.87$; **Table 2**). The anatomical labels in the left column of the tables were derived from direct neuroanatomical analysis of the data in PET-Brainvox.

Overall, activation and deactivation patterns varied qualitatively among emotions (**Table 1**). For example, happiness increased activation in right posterior cingulate and right SII, and sadness decreased activation in these regions. Activation of certain regions, such as the orbitofrontal cortex, right insula and right SII, increased or decreased during feeling of all four emotions, although some conditions affected different subregions. Moreover, both increases and decreases were observed within certain single regions, such as in the right insula for fear, in the right anterior cingulate for happiness and anger, and in the posterior cingulate for sadness and anger.

Specifically, the dorsal pons was active in sadness and anger but not in happiness or fear. The dorsal midbrain was active in anger and fear, showed an activation trend in happiness, and was not active in sadness. The hypothalamus was active in happiness and anger, showed an activation trend in sadness, and showed a negative peak in fear. The insula was bilaterally active in sadness and anger, and active on the right in happiness and fear; all these activations occurred mainly in anterior insula, although the posterior insula showed a significant negative peak for fear. The cingulate cortex showed anterior and posterior activation in sadness and happiness, although in anger there was activation in most of the anterior sector but no posterior activation. Fear, on the other hand, only showed a single negative peaks in the posterior region. The secondary somatosensory cortex (SII) was active on the right in happiness and fear, and showed negative peaks bilaterally in sadness and anger. The orbitofrontal region showed active peaks in sadness only; in happiness, anger and fear, there were negativities. The basal forebrain region showed activation in sadness and happiness. There was no significant activation of the amygdala on either side for any of the emotion/feeling states.

Most of the positive and negative peaks identified within the search volume met the significance level set for whole brain search ($t = 4.87$). *Post hoc* analysis at the whole-brain level revealed additional maxima and minima (**Table 2**). Another set of significant positive peaks was noted in anterior pons for both sadness and anger, although we noted deactivation trends that did not reach significance in this same region for happiness and fear (**Fig. 3**). Both sides of the midline cerebellum were significantly activated for sadness, anger and fear. The left midline cerebellum was activated for happiness, the right lateral cerebellum for anger and fear, the caudate nucleus for sadness and happiness, the lenticular nucleus for sadness, happiness, and anger, the left thalamus for sadness and anger, and the right thalamus for fear. Bilateral activation was seen in the the motor cortex for anger and fear (only the inferior third was included in the field of view), and in the left hippocampus and parahippocampal region for happiness and fear.

The most visually salient result in the whole-brain search was the finding of major negativites in neocortical areas of both hemispheres (**Table 2**; **Figs. 1** and **2**). These decreases were prominent in the left frontal pole for sadness and happiness, in the right frontal pole for sadness, anger and fear, in the right and left dorsolateral prefrontal cortices for sadness, happiness and fear, in the right dorsolateral prefrontal cortex for anger, and in the right premotor/prefrontal dorsolateral regions for sadness and happiness. The inferior parietal lobule showed bilateral and significant decreases for sadness and anger, but not for happiness or fear. The parieto-occipital region showed significant bilateral decreases for sadness and fear, right significant decreases for happiness, and left significant decreases for anger. Both inferotemporal (IT) and temporal polar (TP) regions showed significant decreases for sadness, anger and fear, and a significant left decrease for happiness. The occipital lobe showed bilateral and significant decreases for sadness and anger but none for happiness or fear.

Because we studied subjects of both genders, we also analyzed data from a subset of 32 subjects (16 men, 16 women) for an interaction of neural activity associated with emotion state and gender. We found one significant difference (–31, +18, +11, $t = 4.29$)

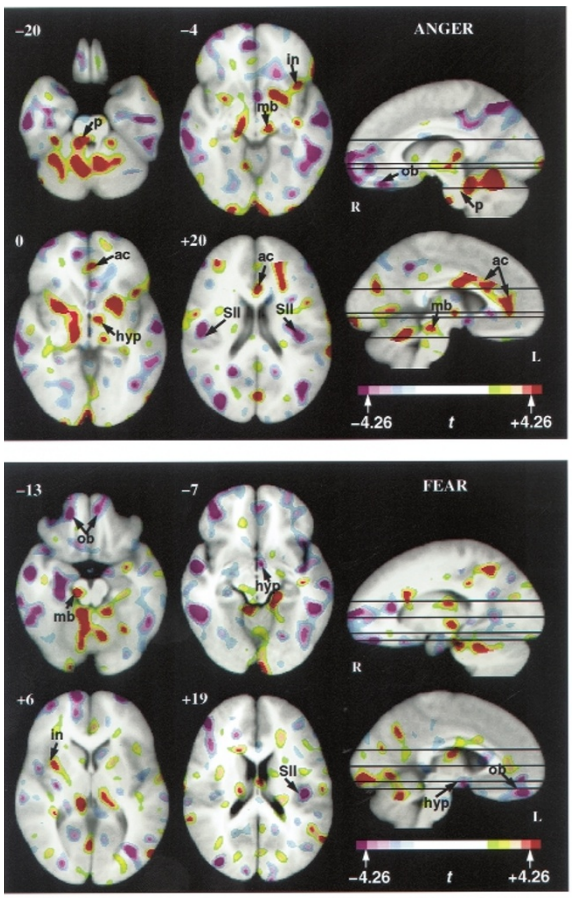

Fig. 2. Neural correlates of feeling anger and fear. Conventions and color coding same as in Fig. 1. Anger activates midbrain and pons, along with the anterior half of the left cingulate, and bilaterally deactivates SII. Fear activates midbrain and deactivates left SII, hypothalamus and orbitofrontal cortex. For details, see text and Tables 1 and 2. p, pons; in, insula; mb, midbrain; ac, anterior cingulate; hyp, hypothalamus; ob, orbitofrontal; SII, secondary somatosensory cortex.

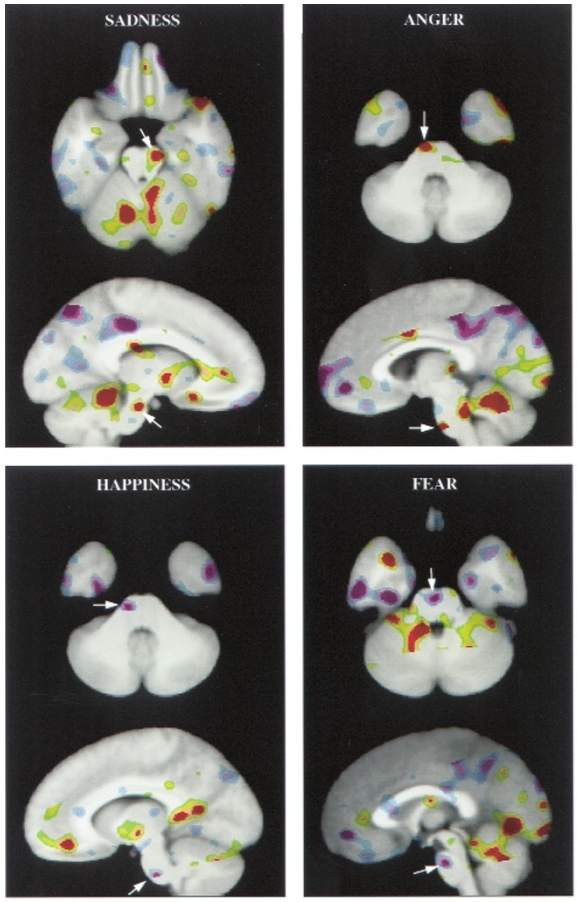

Fig. 3. Emotion-related activity in anterior pontine nuclei. Sadness and anger increase activity in anterior pons, whereas happiness and fear decrease activity (white arrows). There are also notable activations in cerebellum, largely in midline structures. The *t* values for the activations in sadness and anger are, respectively, +5.48 and +7.77 (critical *t* is ±4.70). The *t* values for the negativities in happiness and fear are, respectively, –4.48 and –4.60, not reaching significance at whole-brain search level.

in the left anterior insula, which was engaged more prominently in women than men. No differences were found outside the search volume.

Discussion

In general, the results supported the hypothesis. All emotions engaged structures related to the representation and/or regulation of organism state, for example, the insular cortex, secondary somatosensory cortex, cingulate cortex, and nuclei in brainstem tegmentum and hypothalamus. These regions share a major feature in that they are all direct and indirect recipients of signals from the internal milieu, viscera and musculoskeletal frame. In addition, some of these regions, namely, some brainstem nuclei, the hypothalamus, and subsectors of the insula and cingulate, also generate regulatory signals necessary to maintain homeostasis[1,14,19]. At the very least, the results underscore the close anatomical and physiological connection between emotion and homeostasis, and between emotion and mapping of the ongoing state of the organism. The findings, however, speak to another issue: the neural patterns depicted in all of these structures constitute multidimensional maps of the organism's internal state, and we believe that they form the basis for an important aspect of the mental states known as feelings. Some of these maps, such as those in brainstem and hypothalamus, are coarse, and their information is perhaps not directly accessible to consciousness. In contrast, the maps in insula, SII and cingulate, regions that receive regulatory signals from brainstem and hypothalamus in addition to direct sensory signals from the organism, are more refined, and their information is probably accessible to consciousness, thus providing integrated perceptual maps of the organism state. These results support the idea that part of the feeling-state of emotions might be grounded in emotion-specific neural patterns in the regions identified here. Those neural patterns are different for each emotion, as shown by comparing the foci of activation and deactivation noted in subregions of the insula, SII and cingulate (**Table 1**; **Fig. 1**). We believe that these varied patterns provide distinctive 'perceptual landscapes' of the organism's internal state, and that the differences among those landscapes constitute the critical reason why each emotion feels different. The varied neural patterns are generated by inputs from varied aspects of the organism's state, but can be modified by top-down signaling from regions such as orbitofrontal cortex and amygdala, by means of an 'as-if-body loop' mechanism[14,19] (a mechanism that drives activity in somatosensory maps from within the brain, independently of actual body signaling). The

Table 1. Maxima and minima in the search volume defined *a priori* (critical *t* value ± 4.26).

Region	Side	Sadness T_{88} coordinates *x*	*y*	*z*	Sadness Threshold *t* (dof)	Happiness T_{88} coordinates *x*	*y*	*z*	Happiness Threshold *t* (dof)	Anger T_{88} coordinates *x*	*y*	*z*	Anger Threshold *t* (dof)	Fear T_{88} coordinates *x*	*y*	*z*	Fear Threshold *t* (dof)
Pons	R	*1	–41	–26	+5.16					*10	–36	–20	+5.81				
	L									–2	–29	–12	+4.57				
Midbrain	R	16	–26	–8	+4.82					14	–21	–1	+6.28				
	L	–4	–38	–3	+5.03	*–1*	*–28*	*–2*	*+4.04*	–10	–25	–4	+4.85	13	–24	–13	+5.67
Hypothalamus	R					12	–13	–1	+4.52								
	L	*0*	*–21*	*0*	*+4.15*					–6	–9	0	+5.10	–3	–4	–9	–4.42
Amygdala	R																
	L					–16	–10	–9	+4.42					*15*	*–7*	*–15*	*–4.11*
Insula	R	42	21	0	+5.85	23	14	–71	+5.18	36	11	2	+4.37	33	3	6	+4.60
		36	0	13	+5.11	29	17	16	+4.59					46	1	0	–4.67
		35	10	15	+5.03												
	L	–35	12	–9	+5.49					–37	13	–4	+5.07				
		–36	–1	13	+5.13					–41	–3	12	+5.10				
Cingulate																	
Anterior	R	8	26	–3	+5.00	9	36	–10	+5.01	1	4	–32	+6.58				
						4	39	7	+4.42	11	44	12	–4.40				
						0	15	22	–5.27								
	L	–5	36	6	+6.17	–7	23	1	+5.19	–5	35	9	+5.84				
						–1	38	10	+4.38	–12	–2	34	+5.39				
										–8	–34	32	+4.55				
Posterior	R	7	–56	24	+4.40	9	–41	9	+4.91	8	–29	43	–5.75	7	–32	44	–4.79
		9	–34	42	–7.28	10	–55	14	+4.84	6	–33	38	–4.62				
		2	–32	24	–5.81	0	–52	28	+4.36								
		14	–28	31	–5.04												
	L	–9	–29	38	–6.08					–8	–34	32	+4.55				
										–2	–47	40	–5.19				
SII	R	*58	–14	11	–4.46	43	–26	21	+4.42	48	–16	20	–6.24	37	–13	29	+4.64
	L									–36	–23	18	–5.27	–40	–22	19	–5.27
Orbitofrontal	R					21	39	–14	–4.26	12	38	–17	–4.84	18	44	–14	–5.49
		–7	17	–12	+4.93									–4	48	–17	–5.89
	L	–1	41	–16	+4.17												
Basal forebrain	R	13	0	–3	+5.06												
	L	–20	0	–7	+5.34	–12	–1	–4	+4.79								

Maxima marked by * fall between two adjacent structures and may reflect activity in both regions. Values in thin and italic font represent trends that fall short of significance threshold.

activations in the upper brainstem tegmentum occur in a region that encompasses the periaqueductal gray, the parabrachial nucleus, the monoaminergic nuclei in the raphe and the locus coeruleus, the cholinergic nuclei, the substantia nigra and the classical reticular nuclei. In one way or another, these nuclei work in concert to promote homeostasis, and some do so directly. For example, the periaqueductal gray generates specific action programs that involve chemical, visceral and musculoskeletal responses[20], and, along with structures such as the parabrachial nucleus, senses the ongoing state of the organism so that action programs can be properly adjusted. The brainstem has not been noted to be active in other human studies of emotion, perhaps because it has not been included in hypotheses on emotion, and because its activity has not been specifically probed (but we note that two studies[11,21] found evidence for engagement of the midbrain in recall-based sadness and disgust and provoked anxiety). However, behavioral and neuro-

physiological studies in animals indicate that these nuclei are critical for the processing of emotions[14,17,18,20]. In addition, neural correlates of pathological laughter and crying in humans suggest that brainstem nuclei and related cerebellar circuitry are involved in emotional processes, as does the acute induction of sadness with high-frequency stimulation of substantia nigra[22].

The upper brainstem activations in the emotional conditions would not be explained satisfactorily by the exclusive engagement of the reticular nuclei in the attentive process. First, there is reason to believe that the brainstem structures that participate in attention are driven by aspects of the emotional state[14]. Second, both the neutral condition and the emotional conditions required the subjects to attend to internally generated imagery, yet the subtractions yielded activation of brainstem structures in the emotion conditions. Third, although the need to attend to mental images may be presumed to be fairly comparable across conditions, brainstem activation changed with each emotion condition. This suggests that the changes may be related to the particular physiological program of each emotion, specifically to the engagement of some program subcomponents during the processing of an emotion. In support of this interpretation, even varieties of the same emotion, such as fear, engage different columns of the periacqueductal gray in animals[15].

The notion of differential engagement of the brainstem during emotion-feeling states is reinforced by another finding in our study, namely the activity increases in anterior pontine nuclei noted for sadness and anger, and the decreases of activity in this same general sector for happiness and fear (**Fig. 3**). These nuclei, which are neither sensory nor motor and are unrelated to reticular nuclei, receive projections from the cerebral cortex, namely from the cingulate cortices and insula, and send projections to the cerebellum. Presumably these projections guide the cerebellum in modulating varied emotion action programs, which is likely to occur via actions on nuclei in the brainstem tegmentum. Again, the findings are distinctive for each emotion, as suggested given that the physiological programs are different. It is reasonable to speculate, for instance, that these patterns are correlated with the different distributions and intensity of muscular tone associated with varied feeling states. The region of the anterior pons deactivated in fear receives significant projections from the anterior cingulate, although the regions activated in anger and sadness, and deactivated in happiness, receive projections mostly from posterior cingulate and insula (G.W. Van Hoesen, personal communication). On a related note, although the cerebellum was not included in the hypothesis, we believe that the evolutionarily older components of the cerebellum probably are involved in the coordination of emotional responses and in the learned adjustment of those responses in a social setting. The activations found in midline cerebellum accord with this idea, and with the finding that damage to the vermis is associated with an alteration of affect[23,24]. The activation of the vermis has been noted in other functional imaging studies[10,11].

Prior studies on happiness have not identified significant activation patterns[8]. We found notable increases in right insula, right SII, left and right anterior cingulate and right posterior cingulate. Within the same region of right anterior cingulate, we observed both activation and deactivation. There were also increases in right orbitofrontal cortex, left basal forebrain, right hypothalamus and left midbrain. The finding of right dorsolateral prefrontal decrease is consistent with previous work[8]. The patterns for happiness and sadness do not appear to be mere variations of each other. There seems to be a qualitative distinction between these patterns, notably in the different locations of significant increases and decreases in regions such as cingulate and orbitofrontal cortex.

The results support prior observations that sadness involves the ventral and medial frontal cortices and the insula. Lesion studies and structural and functional imaging of depressed patients suggest involvement of the subgenual prefrontal sector in emotional processing[13,25]. Activity increases in the ventral and medial prefrontal sector during sadness have been noted previously[8,9,12], and so have the increases in insula activity and the decreases in right dorsolateral prefrontal cortex activity[12,26]. However, we also found decreases in the left dorsolateral prefrontal cortices and bilateral decreases in parietal cortices. There was an activation trend in the hypothalamus, consistent with the finding that hormonal changes controlled from hypothalamic nuclei are an integral part of depression, a pathological mood state in which sustained sadness is a dominant factor. Also consistent with prior studies was the engagement of the orbitofrontal and cingulate regions in anger and fear[27,28]. In addition, however, we found notable deactivation in SII, which was bilateral in anger and left lateralized in fear.

The lack of activation in the amygdala violated the hypothesis and at first glance seems to run counter to studies that reveal the amygdala to be involved in fear and anger[4,6,7,29]. However, most of the results on the amygdala pertain to recognition or induction of an emotion from a visual stimulus. It is possible that the amygdala is less engaged by recalled stimulus images[10,30]. Also, our data collection was skewed toward the feeling phase of the emotion-feeling cycle, rather than to its induction. The amygdala is more likely to be active during the induction of emotion and may habituate during the feeling phase of processing[1,2,31,32]. The amygdala was not activated in other functional imaging studies of recall-based sadness, happiness or disgust[8,9,11,12]. As for the activities in the basal ganglia and basal forebrain, we assume that their significant peaks are related to the induction and/or execution of emotion; however, it is premature to comment on the meaning of the significant activations in thalamic nuclei.

The investigation of the neural basis of feelings has lagged because of a lack of testable hypotheses in humans, and because, given their subjective status, feelings cannot be studied in animals. In spite of the limitations of our study, we regard the findings presented here as a first step toward a theory-driven, systematic investigation of the neurobiology of feelings.

Methods

The study, which was approved by the University of Iowa's Institutional Review Board and Radiation Protection Committee, involved normal adult volunteers who participated in an $[^{15}O]H_2O$ PET experiment. We screened 53 potential subjects. All were right-handed (Geschwind-Oldfield score of +85 or higher), had 12 years of education or more, and ranged in age from 24 to 42. None had a history of neurological or psychiatric disorder or were taking any medication. All gave informed consent in compliance with federal and institutional guidelines.

During a screening session that mimicked the actual scanning environment, the subjects were asked to recall and attempt to re-experience and re-enact intense personal emotional episodes involving sadness, happiness, anger or fear, and to recall an equally specific but emotionally neutral episode. For both conditions, the subjects were encouraged to produce detailed images of the events being recalled and to concentrate on those images attentively; they were told they might have to produce detailed accounts of the contents of their imagery in the debriefing period. Although the themes of the episodes turned out to be similar across subjects (for example, the death of a close relative or friend was used universally for sadness), there was no attempt to constrain the themes artificially by limiting the recall to episodes involving the same persons or places or a certain time span, because we wanted to gain access to the autobiographical episodes the subjects considered emotionally most

Table 2. Maxima and minima in the whole-brain *post hoc* analysis (critical *t* value ± 4.87).

Region	Side	Sadness T_{88} coordinates			Sadness Threshold *t* (dof)	Happiness T_{88} coordinates			Happiness Threshold *t* (dof)	Anger T_{88} coordinates			Anger Threshold *t* (dof)	Fear T_{88} coordinates			Fear Threshold *t* (dof)
		x	*y*	*z*		*x*	*y*	*z*		*x*	*y*	*z*		*x*	*y*	*z*	
Anterior pons	R									5	–19	–33	+7.77				
	L	–9	–21	–18	+5.48												
Basal ganglia																	
Caudate	R	10	21	2	+5.09												
	L	–15	–22	25	+6.45	–28	–42	12	+6.04								
		–23	21	15	+5.76												
Lenticular	R	26	5	6	+6.00					26	–1	5	+7.06				
nucleus		32	–4	21	+5.16												
	L					–16	–11	16	+5.95	–21	4	2	+7.17				
										–15	5	–5	+5.87				
Thalamus	R													10	–31	7	+6.77
														15	–22	–1	+5.07
	L	–4	–4	1	+5.74					–18	–29	7	+6.35				
		–18	–31	9	+5.64												
Cerebellum																	
Mesial	R	12	–60	–16	+6.63					10	–58	–15	+7.88	11	–43	–19	+6.52
		1	–41	–26	+5.16									8	–64	–20	+6.45
														8	–43	–11	+6.39
	L	–9	–43	–12	+7.18	–5	–63	–12	+5.14	–6	–50	–17	+6.23	–2	–58	–21	+5.56
		–4	–38	–3	+5.03					0	–61	–17	+5.42	–10	–62	–17	+5.47
Lateral	R									34	–51	–22	+5.57	1	–66	–1	+5.77
Frontal																	
Pole	R	25	61	–1	–5.32					15	65	8	–5.59	15	61	9	–6.33
	L	–16	58	–10	–6.11	–1	58	–2	–5.44								
Lateral or	R	41	46	–5	–8.41	40	47	–6	–6.98	45	44	13	–6.48	43	38	16	–6.20
mesial		32	53	8	–7.53	40	40	16	–5.43	37	58	1	–5.86	41	19	21	–5.23
prefrontal		37	51	4	–7.43					7	47	–5	–5.49				
		33	44	14	–7.29					32	57	12	–5.47				
		39	38	–11	–6.62												
	L	–37	50	–5	–5.43	–1	58	–2	+5.44	*–48	24	–8	+6.38	–25	62	6	–7.28
		–35	39	–10	–5.34	–17	47	–10	–6.86								
		–29	49	4	–5.16	–36	41	–8	–5.98								
Prefrontal/	R	39	24	23	–7.27	59	6	14	–5.35								
premotor		43	5	28	–5.73												
		55	10	4	–5.16												
Motor																	
	R	29	–9	36	–4.98					50	–19	40	+9.87	34	3	32	+5.13
										53	–5	23	+5.55				
										34	–3	34	+5.52				
	L									–45	–18	32	+6.21	–47	14	12	+5.31
										–54	–9	36	+6.00				
										–60	–4	25	+5.61				

powerful. The neutral condition, on the other hand, consisted of a detailed recall of the beginning of an unemotional but specific day, from getting up in the morning to preparing breakfast, getting dressed, hearing the news, leaving for work, arriving at work and so on.

The results of the tasks were controlled with psychophysiological measures, detailed debriefings, and post-session ratings and reports. Skin conductance response (SCR) and heart rate were recorded in an Astro-Med polygraph (Warwick, Rhode Island). The recorded signals were simultaneously converted from analog to digital format and transferred to a computer using an MP100WS system (Biopak Systems, Santa Barbara, California). The recorded data were analyzed with AcqKnowledge III software (Biopak Systems). For SCR recording, electrodes were attached to the thenar and

Region	Side	Sadness T_{88} coordinates x	y	z	Sadness Threshold t (dof)	Happiness T_{88} coordinates x	y	z	Happiness Threshold t (dof)	Anger T_{88} coordinates x	y	z	Anger Threshold t (dof)	Fear T_{88} coordinates x	y	z	Fear Threshold t (dof)
Parietal	R	46	–44	–41	–6.39					52	–48	40	–5.88				
		54	–38	34	–6.28												
	L	–41	–44	43	–8.40					–57	–38	40	–7.32				
		–36	–37	31	–6.06					–42	–45	43	–5.97				
Parieto–occipital	R	50	–54	36	–6.13	3	–77	32	–4.93					54	–56	38	–4.96
														43	–70	40	–4.88
	L	–47	–49	38	–8.40					–17	–65	39	–7.22	–36	–62	40	–5.57
		–15	–70	46	–7.35									–53	–51	38	–5.13
Occipital	R	40	–66	12	–7.49					20	–93	–9	+5.07				
		45	–59	17	–6.61					32	–78	19	–7.16				
										43	–65	32	–7.09				
										22	–53	16	–6.42				
										22	–47	7	–5.88				
	L	–33	–74	35	–6.89					–6	–97	–8	+7.33				
		–18	–87	9	–6.24					–15	–53	18	–3.94				
Temporal																	
Hippocampal/ parahippocampal	R					31	–20	–21	–5.21	22	–16	–12	–5.92	31	–21	–19	–7.22
	L					–30	–20	–18	+5.02								
						–24	–15	–9	+4.95					–16	–30	–2	+8.08
Pole/IT	R	54	–13	–28	–6.14					56	–19	–20	–6.86	54	–7	–13	–8.45
		63	–35	–7	–5.79					59	–34	–4	–6.31				
		45	–49	10	–5.23					51	–53	–13	–5.47				
										39	–9	–24	–5.21				
										55	–9	–13	–5.20				
	L	–50	–51	0	–6.71	–45	–6	–10	–5.58	*–55	4	–21	+7.88	–48	–62	0	–5.40
		–40	17	–17	–6.16					*–50	8	–23	+6.61				
										*–46	12	–29	+6.59				
										–48	–39	–11	–8.12				
										–58	–16	–2	–7.12				

Maxima marked by * are interpreted as contamination from temporal muscles.

hypothenar areas on the palms of both hands. Quantitation of SCRs entailed correction for down drift and measurement of the area under the curve during the period from the subject's signal until 30 seconds later. Immediately after the session, the subjects described the experience, labeled the emotion, and rated its intensity on a scale of 0–4. Observation of the subjects revealed concordant evidence for the target emotion. (For example, all subjects cried in the sadness condition.) Although we tightly controlled the responses with psychophysiological and report measures, all of which showed good discriminations, we could not fully control for possible differences in recall across conditions and individuals. We believe, however, that the price of this limitation was compensated by using the subjects' autobiographical memory as an especially effective retriever of imagery and thus effective inducer of intense emotions. Moreover, we note that our data were collected only after the subject was feeling the emotion, and that in our theoretical framework the induction of emotions is independent of the cognitive strategy used to arrive at the images that trigger the relevant neural devices.

Only subjects who showed behavioral and psychophysiological signs of achieving an emotion and reported feeling the intended emotion were selected for the experimental phase. Our criteria for selection were, first, a minimum SCR increase of 50% of area under the curve during the target emotion as compared to the neutral emotion, during the 30-second interval beginning when the subject was feeling the emotion and ending when the subject produced a hand signal to indicate it, second, a minimum rise in HR of 5% (about 4 bpm) in the same time window and, third, a minimum subjective rating of 3 (of 4) for the intended emotion. A subject was included if s/he met these criteria for at least two emotions. If the subject met the criteria for all four emotions, then those two for which the subject generated the strongest response were used during the PET experiment. Subjects also had a T_1-weighted MR scan, used to exclude unsuspected brain lesions, to plan slice orientation in the scanner, and to interpret data anatomically.

PET imaging was done in the 41 selected subjects with a GE 4096B tomograph (Uppsala, Sweden), yielding 15 slices covering a 10 cm axial field of view. Each subject received six injections of 50 mCi $[^{15}O]H_2O$, two for each of two target emotions and two for the neutral condition. Subjects were cued to recall and re-experience one of the scenarios generated during the screening session, and to signal with a right-hand movement when they began feeling the intended emotion. The radiotracer was injected within five seconds. Dynamic image acquisition enabled reconstruction of images based on the 40 seconds of data collection following clearance of the arterial blood pool, as judged from time–activity curves in ROIs over the major vessels. Our injection technique results in arrival of the bolus of labeled water in the brain about 15 seconds after injection[33]. The session was divided in two halves, and the order of target emotional states randomized. Four cohorts of subjects were studied, with target emotions paired as follows: sadness and happiness (6 female, 5 male), fear and anger (3 female, 6 male), sadness and anger (8 female, 6 male), and fear and happiness (4 female, 3 male). Heart rate and SCRs were monitored as during the screening session, and a rating of emotional intensity was obtained after each injection. Two subjects did not show convincing dis-

criminatory psychophysiological changes during the PET session and were therefore excluded from further analysis. We note that the limit in injections per subject led to uneven samples for each emotion, the *n* for sadness and anger being larger than that for happiness and fear. Larger samples for the latter emotions might lead to greater sensitivity and a greater number of significant peaks.

PET images of the distribution of radioactive counts were coregistered with the MR scan using AIR3.03 (ref. 34). The MR was transformed to Talairach space using the fifth-order nonlinear warping model supported by AIR3 to co-register the image with an atlas constructed by iteratively averaging 50 normal brains in Talairach space[35]. PET data were transformed to this space by proxy, using the parameters generated by the MR-to-atlas fit. The search volume corresponding to the structures in the hypotheses was delineated by manual tracing on the averaged MR and measured 121.9 cm^3, calculated to comprise 21.3 resels. The PET data were smoothed by Fourier transformation, complex multiplication with a 16 mm FWHM Gaussian kernel, and reverse Fourier transformation; data were analyzed with a pixel-wise general linear model that included cohort, subject within cohort, subject-specific global activity and target task nested within cohort as sources of variability. The neutral state was modeled as a common effect across cohorts. (To address the possibility that the neutral state varied across cohorts, for example, due to persisting effects of emotion states, we carried out a preliminary analysis to assess the interaction of the neutral state with cohort. There was no significant interaction in the search volume, allowing us to model the stable neutral state as a common effect.) Global-adjusted mean activity in each target task state was contrasted with that in the neutral state[36,37] using the *t*-statistic.

Because the responses from different subcortical sources tended to merge, especially in the brainstem, and because of the possibility that the activity we observed in the spatially filtered data might reflect 'spilling' from adjacent brain regions, we did not analyze the data obtained with the 16 mm kernel any further. Instead we proceeded to analyze the data using the same linear model with a kernel of 6 mm FWHM (calculated final resolution 10 mm) to allow separation of signals from deep structures. This non-standard scale of analysis in Talairach space is appropriate for these deep structures such as the brainstem, because anatomical variance across subjects is far smaller than for cerebral cortex. In this data set, we searched the *t*-statistic maps for significant voxels and the corresponding local maxima in the search volume, correcting for multiple comparisons according to Gaussian random field theory for *t*-fields[38], using PET-Brainvox software[39].

Acknowledgements

Supported in part by grants from the Mathers Foundation and NIH Grant 1 P50 DC 03189-01A1.

Received 26 April; accepted 21 August 2000

1. Davidson, R. J. & Irwin, W. The functional neuroanatomy of emotion and affective style. *Trends Cogn. Sci.* **3**, 11–21 (1999).
2. Dolan, R. J. *et al.* Neural activation during covert processing of positive emotional facial expressions. *Neuroimage* **4**, 194–200 (1996).
3. Breiter, H. C. *et al.* Response and habituation of the human amygdala during visual processing of facial expression. *Neuron* **17**, 875–887 (1996).
4. Whalen, P. J. *et al.* Masked presentations of emotional facial expressions modulate amygdala activity without explicit knowledge. *J. Neurosci.* **18**, 411–418 (1998).
5. Morris, J. S. *et al.* A neuromodulatory role for the human amygdala in processing emotional facial expressions. *Brain* **121**, 47–57 (1998).
6. Adolphs, R., Tranel, D., Damasio, H. & Damasio, A. Impaired recognition of emotion in facial expressions following bilateral damage to the human amygdala. *Nature* **372**, 669–672 (1994).
7. Adolphs, R., Damasio, H., Tranel, D. & Damasio, A. R. Cortical systems for the recognition of emotion in facial expressions. *J. Neurosci.* **16**, 7678–7687 (1996).
8. George, M. S. *et al.* Brain activity during transient sadness and happiness in healthy women. *Am. J. Psychiatry* **152**, 341–351 (1995).
9. Pardo, J. V., Pardo, P. J. & Raichle, M. E. Neural correlates of self-induced dysphoria. *Am. J. Psychiatry* **150**, 713–719 (1993).
10. Reiman, E. M. *et al.* Neuroanatomical correlates of externally and internally generated human emotion. *Am. J. Psychiatry* **154**, 918–925 (1997).
11. Lane, R. D., Reiman, E. M., Ahern, G. L., Schwartz, G. E. & Davidson, R. J. Neuroanatomical correlates of happiness, sadness, and disgust. *Am. J. Psychiatry* **154**, 926–933 (1997).
12. Mayberg, H. S. *et al.* Reciprocal limbic-cortical function and negative mood: Converging PET findings in depression and normal sadness. *Am. J. Psychiatry* **156**, 675–682 (1999).
13. Drevets, W. C. *et al.* Subgenual prefrontal cortex abnormalities in mood disorders. *Nature* **386**, 824–827 (1997).
14. Damasio, A. R. *The Feeling of What Happens: Body and Emotion in the Making of Consciousness* (Harcourt Brace, New York, 1999).
15. Bandler, R. & Shipley, M. Columnar organization in the midbrain periaqueductal gray—modules for emotional expression? *Trends Neurosci.* **17**, 379–389 (1994).
16. Behbehani, M. M. Functional-characteristics of the midbrain periaqueductal gray. *Prog. Neurobiol.* **46**, 575–605 (1995).
17. Bernard, J. F. & Bandler, R. Parallel circuits for emotional coping behaviour: New pieces in the puzzle. *J. Comp. Neurol.* **401**, 429–436 (1998).
18. Panksepp, J., Nelson, E. & Bekkedal M. Brain systems for the mediation of social separation-distress and social-reward. Evolutionary antecedents and neuropeptide intermediaries. *Ann. NY Acad. Sci.* **807**, 78–100 (1997).
19. Damasio, A. R. *Descartes' Error: Emotion, Reason, and the Human Brain* (Grosset/Putnam, New York, 1994).
20. Panksepp, J. *Affective Neuroscience: The Foundations of Human and Emotions* (Oxford Univ. Press, New York, 1998).
21. Rauch, S. L., Savage, C. R., Alpert, N. M., Fischman, A. J. & Jenike, M. A. The functional neuroanatomy of anxiety: A study of three disorders using positron emission tomography and symptom provocation. *Biol. Psychiatry* **42**, 446–452 (1997).
22. Bejjani, B. P. *et al.* Transient acute depression induced by high-frequency deep-brain stimulation. *N. Engl. J. Med.* **340**, 1476–1480 (1999).
23. Schmahmann, J. D. & Sherman, J. C. The cerebellar cognitive affective syndrome. *Brain* **121**, 561–579 (1998).
24. Dolan, R. J. A cognitive affective role for the cerebellum. *Brain* **121**, 545–546 (1998).
25. Damasio, A. R. Towards a neuropathology of emotion and mood. *Nature* **386**, 769–770 (1997).
26. Gemar, M. C., Kapur, S., Segal, Z. V., Brown, G. M. & Houle, S. Effects of self-generated sad mood on regional cerebral activity: a PET study in normal subjects. *Depression* **4**, 81–88 (1996).
27. Dougherty, D. D. *et al.* Anger in healthy men: A PET study using script-driven imagery. *Biol. Psychiatry* **46**, 466–472 (1999).
28. Kimbrell, T. A. *et al.* Regional brain activity during transient self-induced anxiety and anger in healthy adults. *Biol. Psychiatry* **46**, 454–465 (1999).
29. LeDoux, J. *The Emotional Brain: The Mysterious Underpinnings of Emotional Life* (Simon and Schuster, New York, 1996).
30. Whalen, P. J. Fear, vigilance, and ambiguity: Initial neuroimaging studies of the human amygdala. *Curr. Directions Psychol. Sci.* **7**, 177–188 (1998).
31. Buechel, C., Morris, J., Dolan, R. J. & Friston, K. J. Brain systems mediating aversive conditioning: an event-related fMRI study. *Neuron* **20**, 947–957 (1998).
32. LaBar, K. S., Gatenby, J. C., Gore, J. C., LeDoux, J. E. & Phelps, E. A. Human amygdala activation during conditioned fear acquisition and extinction: a mixed-trial fMRI study. *Neuron* **20**, 937–945 (1998).
33. Hichwa, R. D., Ponto, L. B. & Watkins, G. L. in *Chemists' Views of Imaging Centers* (ed. Emran, A.) 401–417 (Plenum, New York, 1995).
34. Woods, R. P., Mazziotta, J. C. & Cherry, S. R. MRI-PET registration with automated algorithm. *J. Comput. Assist. Tomogr.* **17**, 536–546 (1993).
35. Woods, R. P., Dapretto, M., Sicotte, N. L., Toga, A. W. & Mazziotta, J. C. Creation and use of a Talairach-compatible atlas for accurate, automated, nonlinear intersubject registration, and analysis of functional imaging data. *Hum. Brain Mapp.* **8**, 73–79 (1999).
36. Friston, K. J., Poline, J. B., Holmes, A. P., Frith, C. D. & Frackowiak, R. J. A multivariate analysis of PET activation studies. *Hum. Brain Mapp.* **4**, 140–151 (1996).
37. Grabowski, T. J. *et al.* Reliability of PET activation across statistical methods, subject groups, and sample sizes. *Hum. Brain Mapp.* **4**, 23–46 (1996).
38. Worsley, K. J. Local maxima and the expected Euler characteristic of excursion sets of Chi(2), F and T Fields. *Adv. Appl. Prob.* **26**, 13–42 (1994).
39. Frank, R., Damasio, H. & Grabowski, T. J. Brainvox: An interactive multimodal visualization and analysis system for neuroanatomical imaging. *Neuroimage* **5**, 13–30 (1997).