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A neuromodulatory role for the human amygdala in processing emotional facial expressions

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Summary

Localized amygdalar lesions in humans produce deficits in the recognition of fearful facial expressions. We used functional neuroimaging to test two hypotheses: (i) that the amygdala and some of its functionally connected structures mediate specific neural responses to fearful expressions; (ii) that the early visual processing of emotional faces can be influenced by amygdalar activity. Normal subjects were scanned using PET while they performed a gender discrimination task involving static grey-scale images of faces expressing varying degrees of fear or happiness. In support of the first hypothesis, enhanced activity in the left amygdala, left pulvinar, left anterior insula and bilateral anterior cingulate gyri was observed during the processing of fearful faces. Evidence consistent with the second hypothesis was obtained by a demonstration that amygdalar responses predict expression-specific neural activity in extrastriate cortex.

Keywords: amygdala; emotion; fear; facial expression

Abbreviations: rCBF = regional cerebral blood flow; SPM = statistical parametric map

Introduction

The survival value conferred by rapid and appropriate responses to danger will result in the evolutionary selection of neural mechanisms for processing threatening or fear-provoking stimuli (Edelman, 1987; Friston *et al*., 1994; LeDoux, 1995). Converging neurobiological evidence suggests that the amygdala is a crucial component in such a phylogenetically determined neural system. Studies in rodents strongly implicate the amygdala in the acquisition of fear responses (LeDoux *et al*., 1990), while amygdalar lesions in monkeys produce a characteristic syndrome involving an absence of normal fear responses to threatening stimuli (Kluver and Bucy, 1939; Weiskrantz, 1956). In humans, amygdalar lesions can produce a general reduction of emotional responses (Aggleton, 1992) and a selective deficit in the recognition of fearful facial expressions (Adolphs *et al*., 1994; Calder *et al*., 1996). Direct electrical stimulation of the human amygdala commonly induces fear as well as other complex sensory and visceral phenomena (Halgren *et al*., 1978). Neuroimaging experiments in normal subjects and patients with anxiety disorders have reported amygdalar activation with arousing, threatening or fear-provoking stimuli (Breiter *et al*., 1996*a*; Cahill *et al*., 1996; Irwin *et al*., 1996; Rauch *et al*., 1996). All these studies are consistent, therefore, with the amygdala having a crucial role in detecting and responding to threatening situations.

The amygdala is well placed anatomically to integrate exteroceptive and interoceptive stimuli and modulate sensory, motor and autonomic processing. In terms of relevant sensory inputs, the amygdala receives direct thalamic projections from the pulvinar and medial geniculate nucleus (Jones and Burton, 1976; Otterson and Ben-Ari, 1979), and highly processed sensory information from the anterior temporal lobe (Whitlock and Nauta, 1956; Aggleton *et al*., 1980; Iwai and Yukie, 1987). It also receives olfactory, gustatory and visceral inputs via the olfactory bulb, the nucleus of solitary tract, the parabrachial nuclei and other subcortical structures (Ricardo and Koh, 1978; Turner *et al*., 1978; Amaral *et al*., 1992). These latter inputs are thought to provide information about the positive or negative reinforcing properties of stimuli, or their biological 'value' (Rolls, 1992; Friston *et al*., 1994). Consistent with this view is the observation that single unit responses in the monkey amygdala depend on the affective significance of the stimulus (Nishijo, 1988). The outputs of the amygdala include strong reciprocal projections

to temporal cortex and to earlier visual areas in the occipital lobe (Amaral and Price, 1984; Iwai and Yukie, 1987). The amygdala also projects to orbitofrontal cortex, anterior cingulate, ventral striatum, nucleus basalis and brainstem nuclei, all of which are implicated in controlling behavioural responses (Price and Amaral, 1981; Mesulam *et al*., 1983; Amaral and Price, 1984; Russchen *et al*., 1985*a*, *b*). These extensive anatomical connections, and in particular the reentrant projections to visual cortex, suggest that the amygdala may play a neuromodulatory role with regard to both sensory processing and response coordination.

Electrophysiological studies in monkeys have identified neurons in the amygdala with selective responses for faces (Rolls, 1981, 1984; Leonard *et al*., 1985), and a general face-processing role for the amygdala in the context of primate social cognition has been proposed (Rolls, 1984, 1992; Kling and Brothers, 1992). Facial expressions of emotion play an important communicative role in primates, and fearful expressions, in particular, represent potent danger signals to conspecifics (Darwin, 1872; Kling and Brothers, 1992). Since the amygdala is implicated, therefore, in both face processing and the response to threatening stimuli, a selective involvement in the processing of fearful expressions might be predicted. The deficits produced by restricted amygdalar lesions in humans are consistent with this view (Adolphs *et al*., 1994; Calder *et al*., 1996).

In the present study, normal subjects were scanned using PET while they viewed grey-scale images of faces expressing varying intensities of fear or happiness (Fig. 1). We tested two hypotheses: (i) that the amygdala has a specific neural response to fearful facial expressions; (ii) that the amygdala can modulate expression-related processing in occipito-temporal cortex. Some of the data relating to the first hypothesis have been reported elsewhere (Morris *et al*., 1996). Here, we report in detail on the brain regions responsive to facial emotion, and use regression analyses to address the question of the amygdala's neuromodulatory role in early visual processing.

Methods

Subjects

Four males and one female (mean age 42.8 years) took part in the study which was approved by the local hospital ethics committees and Administration of Radioactive Substances Advisory Committee (UK). All subjects were unmedicated, with no past history of psychiatric or neurological illness. A sixth post-menopausal female subject (age 62 years) was scanned, but she was later found to be receiving hormone replacement therapy and was therefore excluded from the final analysis.

PET scan acquisition and analysis

Scans of the distribution of $H_2{}^{15}O$ were obtained using a Siemens/CPS ECAT EXACT HR+ PET Scanner operated in high sensitivity 3D mode. Subjects received a total of 350 Mbq of $H_2{}^{15}O$ over 20 s through a forearm cannula for each of the 12 scans, and activity was measured during a 90-s time window. Stimuli were presented in the first 50 s of the scanning window; in the remaining 40 s subjects saw only a blank monitor screen. The PET images comprised $2 \times 2 \times 3$ mm voxels with a 6.4 mm transaxial and 5.7 mm axial resolution (full width at half maximum). The data were analysed with statistical parametric mapping (SPM95, Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab (Mathworks, Sherborn, Mass., USA). Structural MRIs from each subject were co-registered to the PET data following realignment of the PET time series. All the scans were then transformed into a standard stereotactic space (Talairach and Tournoux, 1988; Friston *et al*., 1995*a*, *b*). The scans were smoothed using a Gaussian filter set at 12 mm full width at half maximum. The regional cerebral blood flow (rCBF) measurements were adjusted to a global mean of 50 ml/dl/min.

A blocked (by subject) ANCOVA (analysis of covariance) model was fitted to the data at each voxel, with a condition effect for each level of emotional intensity, and global CBF as a confounding covariate. Predetermined contrasts of the condition effects at each voxel were assessed using the usual *t* statistic, giving a statistical parametric map (SPM) for each contrast. For the parametric contrasts, weights were assigned to each condition according to the proportion of fearful or happy prototype in the face stimuli. The values of the weights were centred for both the fearful and happy continua in order to ensure orthogonality of the category and intensity factors. In the regression analysis, the adjusted rCBF values at the maximal focus of activation in the amygdala ($x = -14$, $y = -8$, $z = -20$), were grouped into fearful and happy conditions. These two sets of values were then used as covariates of interest in a separate SPM95 analysis testing for pyschophysiological interactions (Friston *et al*., 1997). The condition blocks and the global rCBF values were used as confounding covariates. Differences between the regression slopes obtained for the two covariates of interest were tested directly in SPM95 to produce a $SPM_{\{t\}}$ showing voxels in which the contribution of the amygdala changed significantly as a function of emotional category. The general methods employed by SPM are described in detail by Friston *et al*. (1995*a*, *b*).

Experimental design

Subjects viewed static grey-scale images of emotionally expressive faces taken from a standard set of pictures of facial affect (Ekman and Friesen, 1975). The faces depicted either happy or fearful expressions, and for each emotional category, and each individual face, a range of six intensity levels was produced by computer graphical manipulation. The 25%, 50% and 75% faces were interpolations created using computer morphing procedures (Perrett *et al*., 1994) to shift the shape and pigmentation of the 0% (neutral) face

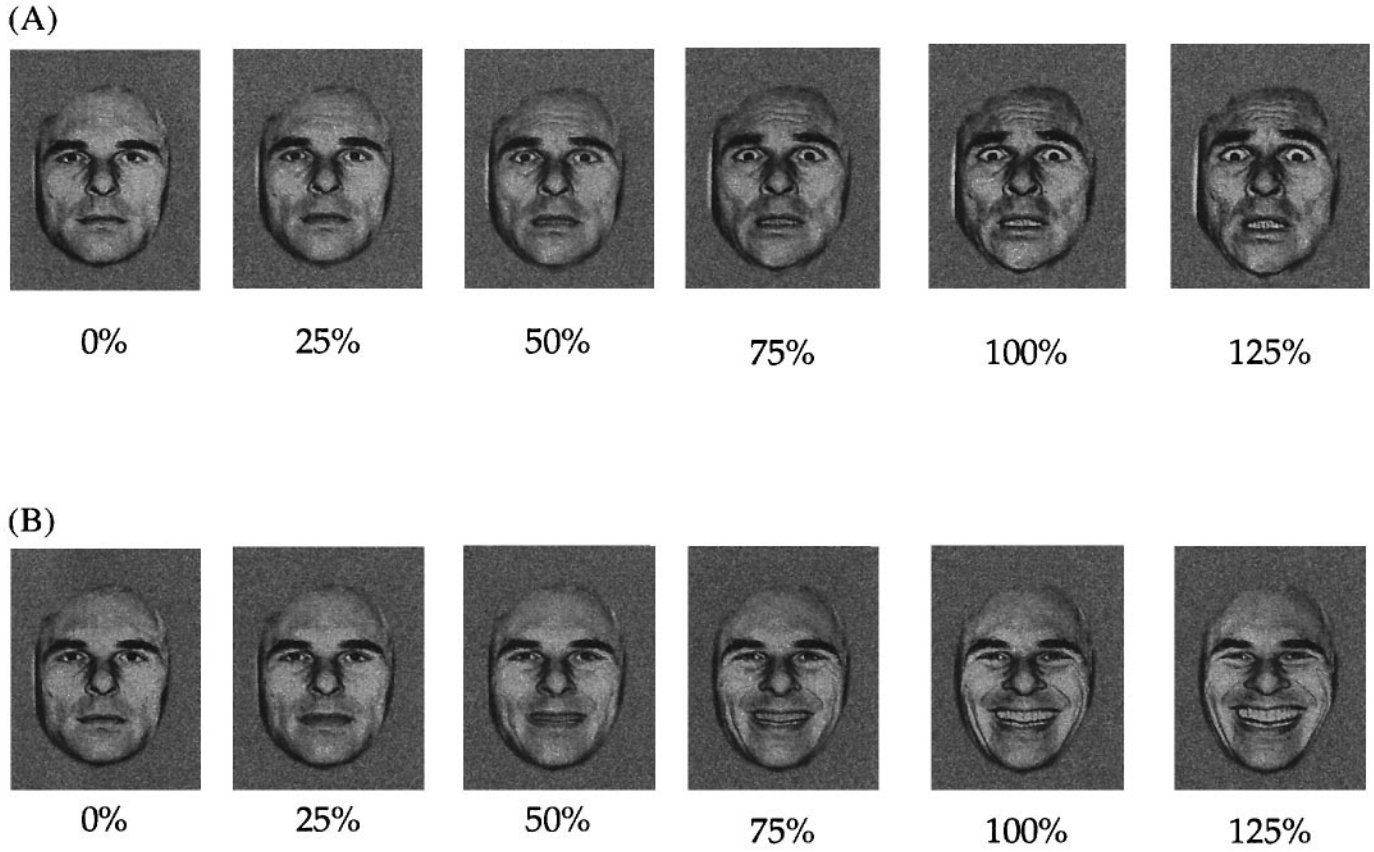

Fig. 1 The range of emotionally expressive facial stimuli. In both **A** and **B**, the 0% face is the neutral prototype. The 100% face is the prototype for happy (**A**) and fearful (**B**) expressions. The other faces were produced by computer graphical manipulation (see Methods section).

towards the fear or happy prototype (100%). The 125% face was an extrapolation, created by shifting the shape of the fear or happy prototype 25% away from neutral (i.e. increasing by 25% any differences from neutral). For each subject, separate scans were acquired for each intensity level, in a 2×6 (category $\times$ intensity) factorial experimental design. In the category contrast of fearful and happy expressions (Table 1A and B), the neutral (0%) faces were excluded. In the contrast of emotional and neutral conditions (Table 1C), the 25% face was included in the neutral condition, since it was not reliably distinguished from the 0% (neutral) face in explicit behavioural tests.

For each presented face, subjects made a gender classification (male or female) by pressing left or right response buttons. No explicit recognition or categorization of the emotional expression was required during the scans, and post-scan debriefing confirmed that subjects were not aware that the implicit emotional variable was crucial in the experimental design. After scanning, all subjects performed explicit tests of categorization and intensity discrimination using the same facial stimuli. Subjects were asked to categorize singly presented faces as happy, fearful, neutral or 'other' (which they could specify) and to rate the intensity of the expression on a seven-point scale. In a separate discrimination test, different faces were presented in pairs, and subjects were required to select the more intense expression.

During each scan, 10 photographs of faces were presented, one at a time, on a computer monitor screen. Each presentation lasted 3 s, and was followed by a 2-s interval in which the screen was blank. The 10 faces were of different individuals (five males and five females), but all had the same category and intensity of emotional expression. The faces of the same 10 individuals were used in all 12 scans, in a randomized order. The emotional category and intensity of the faces were varied systematically across scans. The order of presentation of happy and fearful conditions was counterbalanced across subjects. The six different intensity levels were given in a counterbalanced order within and across subjects.

Results

Behavioural tests

In the gender classification task performed during scanning, all five subjects identified gender correctly 90–100% of the time. There was no association between gender classification errors and facial expression. In the post-scanning explicit

Table 1 *Regions selectively activated in the contrasts of (A) fearful versus happy, (B) happy versus fearful and (C) emotional versus neutral conditions*

Area	Coordinates (*x*, *y*, *z*)	*Z*-score
(A) Fearful versus happy contrast		
Left amygdala (including periamygdaloid cortex)	–14, –8, –20	4.26
Left cerebellum	–42, –68, –20	3.57
Right superior frontal gyrus (BA6)	22, 4, 64	3.22
Left cingulate gyrus	–10, 28, 16	3.18
(B) Happy versus fearful contrast		
Right middle temporal gyrus (BA 21)	54, 4, –20	3.55
Right putamen	22, –4, 12	3.48
Left superior parietal lobule (BA 5)	–28, –40, 60	3.41
Left superior parietal lobule (BA 7)	–24, –72, 44	3.12
Left calcarine sulcus	–10, –92, 4	3.06
(C) Emotional versus neutral contrast		
Left occipitotemporal sulcus	–40, –32, –12	3.53
Right orbitofrontal cortex	12, 12, –20	3.35
Left pulvinar	–4, –32, 8	3.10

Coordinates of the maximal points of activation and the associated *Z*-values are shown. The activations in all regions are significant at $P < 0.001$ (uncorrected). In (C) the neutral condition includes the 0% and 25% faces. In the amygdala, the only area predicted to show a response, this is equivalent to a significance level of $P < 0.05$, corrected for multiple spatial comparisons in a $2 \times 2 \times 2$ cm search region. The activations in the other brain regions would have had the same corrected level of significance if they had also been predicted *a priori*. All *P*-values are one-tailed.

tasks, fearful and happy emotional categories were classified correctly 96.5% of the time. The emotional intensity ratings correlated highly with the proportion of the fearful or happy prototype in the morphed face (correlation coefficients: $r = 0.772$ for fearful, $r = 0.826$ for happy), although the 25% faces were not reliably distinguished from 0% (neutral). In the intensity discrimination task there was also a close agreement between perceived and 'morphed' intensities: 69.4% of ratings agreed for pairs differing by 25% in their percentage of prototype, 83.3% agreed for pairs differing by 50%, and there was 100% agreement for pairs differing by >50%.

Analyses of brain activity using emotional categories

In the contrast of all fearful versus all happy conditions, the left amygdala (including left periamygdaloid cortex) was the most significant area of activation (Fig. 2). Other significantly activated regions are detailed in Table 1A. The opposite contrast of all happy versus all fearful conditions revealed activations in left striate cortex, left superior parietal lobule, right middle temporal gyrus and right putamen (Table 1B). The contrast of emotional (fearful and happy) versus neutral conditions produced activations in the left pulvinar and right orbitofrontal cortex (Table 1C). All reported activations are significant at $P < 0.001$ (uncorrected).

Parametric analyses of brain activity

By weighting the different conditions according to the proportion of the fearful, happy and neutral prototypes in the presented faces, contrasts were performed which revealed brain areas sensitive to the emotional intensity of the facial expressions. Brain areas responsive to increasing intensity of fear were identified in the left anterior insula, left pulvinar and right anterior cingulate (Fig. 3; Table 2A). The left amygdala was also identified in this contrast, although at a lower level of significance ($P < 0.05$, uncorrected).

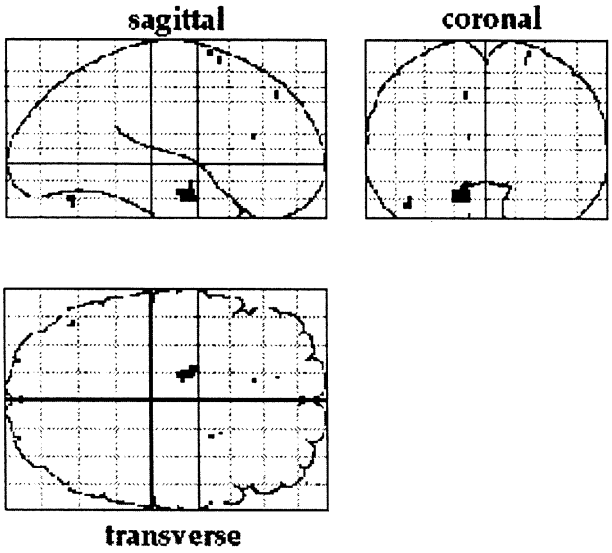

Fig. 2 An SPM showing brain regions significant in the contrast of fearful minus happy conditions. An uncorrected *P*-value of 0.001 was used as the threshold for the contrast. The maximal foci of activation and the associated *Z*-values are given in Table 1A.

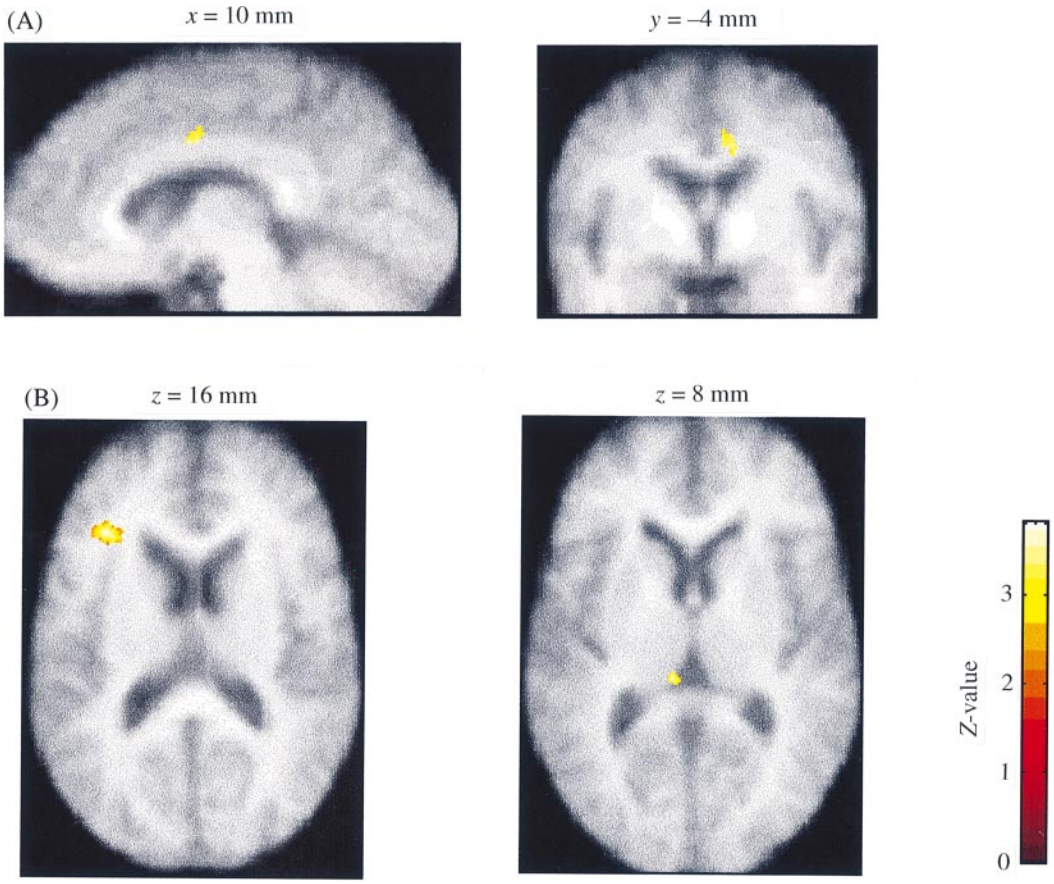

Fig. 3 Statistical parametric maps showing brain regions responsive to increases in the intensity of fearful expression. (**A**) Sagittal and coronal sections showing an area of activation in the right cingulate with a maximal focus $x = 10$, $y = -4$, $z = 32$. (**B**) Transverse sections showing areas of activation in the left anterior insula (in the $z = 16$ mm slice) and left pulvinar (in the $z = 8$ mm slice). In both **A** and **B** an uncorrected *P*-value of 0.01 was used as the threshold for the contrasts. The areas of activation are all displayed on the mean MRI images produced from the co-registered structural MRIs from all five subjects. The maximal foci of activation and the associated *Z*-values are given in Table 2A.

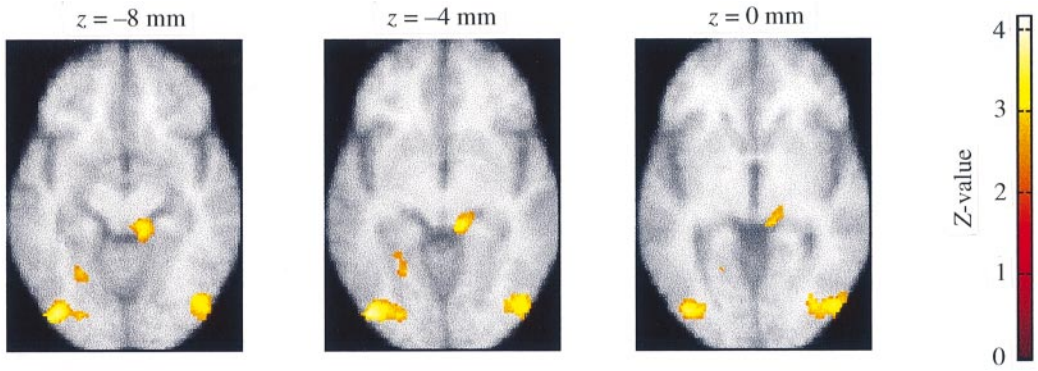

Fig. 4 A statistical parametric map displaying brain regions with an increased contribution from the left amygdala during the presentation of fearful faces (see Table 3A and Fig. 5). Transverse slices at $z = 0$, –4 and –8 mm are displayed using the mean structural MRI image from all five subjects. Bilateral areas of inferior occipital gyri are clearly shown in all slices. Other significant regions in the –4 and –8 mm slices include fusiform and hippocampal gyri and the right dorsal midbrain. In the $z = 0$ mm slice the right pulvinar is shown as a significant region. An uncorrected *P*-value of 0.01 was used as the threshold for the contrast.

Interestingly, the left amygdala was also responsive to decreases in the intensity of happy expression ($P < 0.001$, uncorrected). An analysis of these differential category and intensity responses in the amygdala has been previously reported (Morris *et al.*, 1996). Brain regions sensitive to increasing happy intensity were predominantly posterior

Table 2 *Regions selectively activated with (A) increasing fearful intensity and (B) increasing happy intensity*

Area	Coordinates (*x*, *y*, *z*)	*Z*-score
(A) Increasing fearful intensity		
Left anterior insula	–34,26, 6	3.91
Left posterior insula	–36, –26, –4	3.58
Left inferior frontal gyrus	–24, 40, 0	3.49
Left precuneus	–16, –52, 48	3.47
Left pulvinar	–8, –30, 8	3.36
Right anterior cingulate	10, –4, 32	3.18
(B) Increasing happy intensity		
Left fusiform gyrus	–42, –66, –20	3.90
Left lingual gyrus	–40, –32, –12	3.72
Right calcarine sulcus	16, –70, –12	3.57
Left calcarine sulcus	–10, –98, 0	3.41
Right fusiform gyrus	44, –34, –16	3.28
Right superior temporal gyrus	56, –40, 8	3.15

The contrasts were performed by weighting each condition according to the proportion of fearful or happy prototype in the faces (see Methods section). Coordinates of the maximal point of activation and the associated *Z*-values are shown. The activations in all regions are significant at $P < 0.001$ (uncorrected).

Table 3 *Regions showing an enhanced contribution from the left amygdala during the presentation of (A) fearful and (B) happy faces*

Area	Coordinates (*x*, *y*, *z*)	*Z*-score
(A) Fearful versus happy psychophysiological interactions		
Left inferior occipital gyrus	–40, –84, –4	4.27
Right middle temporal gyrus	38, –56, 12	3.82
Right dorsal midbrain	12, –34, –4	3.67
Right cerebellum	16, –62, –20	3.40
Right inferior occipital gyrus	44, –80, 0	3.54
Left hippocampus	–34, –16, –16	3.50
Right fusiform gyrus	40, –38, –24	3.49
Left cerebellum	–12, –58, –24	3.29
(B) Happy versus fearful psychophysiological interactions		
Left inferior frontal gyrus	–36, 38, 12	3.58
Right uncus	8, 4, –28	3.41
Right precentral gyrus	56, 0, 16	3.23
Left inferior temporal gyrus	–58, –16, –16	3.23

A regression analysis employing the rCBF values for the maximal voxel in the left amygdala ($x = –14$, $y = –8$, $z = –20$) was used to identify the regions (see Methods section). All activations are significant at $P < 0.001$ (uncorrected).

and included bilateral striate cortex, bilateral lingual gyrus, bilateral fusiform gyri and right superior temporal gyrus (Table 2B). All activations reported in Table 2 are significant at $P < 0.001$ (uncorrected).

Regression analyses of brain activity

To test the hypothesis that the amygdala can influence neural activity in other brain regions, regression analyses were performed to test for the presence of psychophysiological interactions (see Methods section). Brain regions demonstrating expression-specific changes in the influence of the amygdala are detailed in Table 3. Areas having a greater contribution from the amygdala during the processing of fearful faces (Table 3A) included bilateral regions of extrastriate cortex (Fig. 4). The category-specific nature of the inferred connectivity between the amygdala and exstrastriate cortex is illustrated graphically in Fig. 5, which shows a positive regression slope between extrastriate and amygdala rCBF values in the fearful condition, and a negative slope in the happy condition. We expand on the interpretation of this interaction in the discussion.

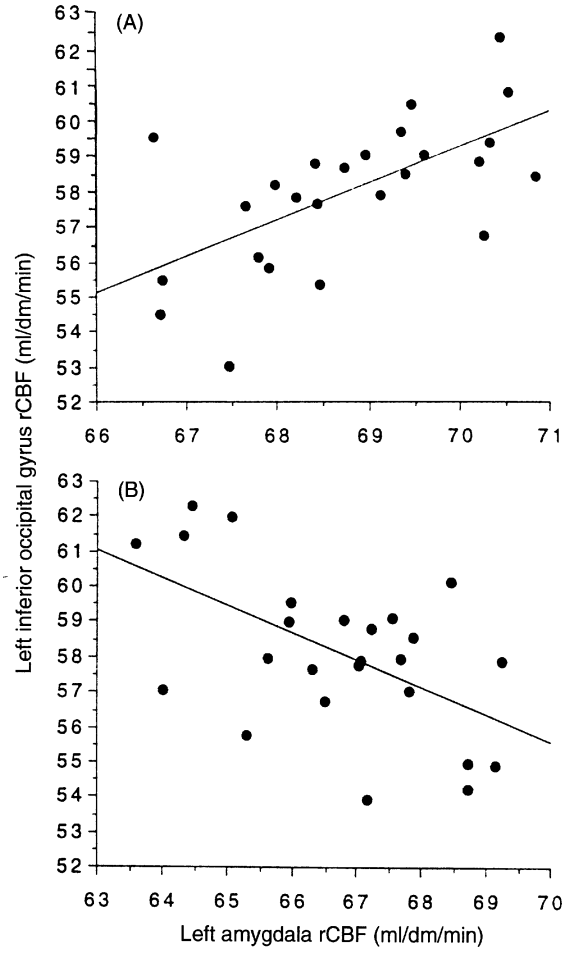

Fig. 5 A graphical display illustrating the psychophysiological interaction between the left amygdala and extrastriate cortex. The rCBF values in ml/dl/min for the voxels (x = –14, y = –8, z = –20) in the left amygdala and (x = –40, y = –84, z = –4) in the left inferior occipital gyrus are plotted against each other in fearful (**A**) and happy (**B**) conditions (see Table 3A and Fig. 4). Regression lines have been fitted to the data, demonstrating a positive gradient (+1.05) in **A** and a negative gradient (–0.78) in **B**; the correlation coefficients (r) are 0.62 and –0.55, respectively. See Methods section for details of the regression analysis.

Discussion

The data from this study provide striking support for the hypothesis, derived from lesion studies (Adolphs *et al*., 1994; Calder *et al*., 1996), that the amygdala has a crucial role in mediating the neural response to fearful facial expressions. Since subjects were engaged in a gender discrimination task during scanning, and the emotional processing was implicit, this response appears to be obligatory and not dependent on voluntary or attentional processes. In addition, the regression analysis of the data, demonstating that amygdalar activity predicts expression-specific responses in extrastriate cortex, supports the hypothesis that the amygdala is engaged in 'top–down' modulation of extrastriate responses. The various neural structures identified in the processing of fearful expressions, and the evidence for the amygdala's modulatory role are discussed in detail below. We had no prior hypotheses about which brain regions might be more responsive to happy expressions, and since there are no neurobiological models to guide interpretation of these data, we have not included any discussion of their significance.

Neural structures with enhanced responses to fearful expressions

Amygdala

In support of our hypothesis, the left amygdala had enhanced responses to fearful faces relative to happy (Fig. 1) and responded to increases in the intensity of fear. The left amygdala also responded to decreases in the intensity of happy expression, which was unexpected, since patients with amygdala lesions do not have problems in recognizing happy expressions (Adolphs *et al*., 1994; Calder *et al*., 1996). An fMRI study has reported, however, an enhanced signal in the left amygdala in response to happy (as well as fearful) faces, relative to neutral stimuli (Breiter *et al*., 1996*b*). Although our PET data (decreased rCBF in the left amygdala to happy faces compared with neutral) are not easily reconciled with the fMRI findings, both studies suggest that the left amygdala's involvement in processing facial emotion is more complex than simply mediating a response to fearful faces.

There was no activation of the right amygdala by fearful expressions, even at low significance thresholds. This lateralization of response to the left amygdala contrasts strongly with other studies which have shown a right hemisphere dominance in the processing of facial emotion (DeKosky *et al*., 1980; Bowers *et al*., 1985; Rapcsak *et al*., 1989; Gur *et al*., 1994; Adolphs *et al*., 1996). However, there are also several reports of left hemisphere involvement in the processing of facial expression. Left hemisphere lesions have been found to produce selective deficits in the recognition of facial expressions (Young *et al*., 1993), and a neuropsychological study of a split-brain patient found evidence of left hemisphere representation of emotional facial expressions (Stone *et al*., 1996). Ratings of the emotional intensity of facial expressions have been shown to be more affected by left amygdalar lesions than right (Adolphs *et al*., 1995). Other functional imaging studies have also reported left lateralized amygdalar activations in the context of processing facial expressions: Breiter *et al*. (1996) found left was greater than right amygdalar activation during viewing of fearful compared with neutral faces; left (but not right) anterior mesial temporal lobe activation, close to the amygdala, has also been reported in a facial emotion matching study (George *et al*., 1993); and procaine-induced emotional states produce left (but not right) amygdala activations that correlate positively with fear and negatively with euphoria (Ketter *et al*., 1996). These findings, together with our data, indicate that the processing of facial emotion in the brain is more complex than might be predicted by a simple model of right-hemisphere dominance. The precise nature of the

psychological task may be crucial in determining both the extent to which each hemisphere is engaged, and the responses of different neural systems. In our experiment, the implicit nature of the emotional variable or the explicit task (gender discrimination) may have influenced the lateralization of the amygdala response.

Pulvinar

The left pulvinar was found to be responsive to emotional faces (Table 1C) and to increasing fearful intensity (Table 2A; Fig. 2). These activations are consistent with electrophysiological studies in primates which show that the pulvinar is responsive to the salience of visual stimuli (Petersen *et al*., 1985, 1987; Robinson and Petersen, 1992), and they also provide empirical support for a recent neurobiological model which proposes that the pulvinar may play a crucial role in selective visual processing (Olshausen *et al*., 1993). The connections between the primate pulvinar and the amygdala have not been as extensively studied as auditory thalamo-amygdalar pathways in rodents, which have been shown to be crucial in the mediation of fear conditioning (LeDoux *et al*., 1990; LeDoux, 1995). However, a direct pulvinar–amygdalar pathway, bypassing occipitotemporal cortex, has been demonstrated anatomically (Jones and Burton, 1976), and a human neuroimaging study has identified functional interactions between the pulvinar and amygdala during aversive conditioning of facial stimuli (Morris *et al*., 1997). There is, therefore, suggestive evidence that pulvinar–amygdala pathways may be important in mediating responses to salient visual stimuli, and form part of an evolutionarily selected neural system which responds rapidly to threat or danger (Edelman, 1987; Friston *et al*., 1994; LeDoux, 1995). The pulvinar also has reciprocal connections with anterior cingulate cortex (Robinson and Petersen, 1992), another structure implicated in the processing of fearful expressions.

Anterior cingulate

The area of right anterior cingulate cortex (Fig. 3A) found to be sensitive to increasing fearful intensity is close to a similar region identified in a PET facial emotion matching study (George *et al*., 1993). The anterior cingulate gyrus is thought to mediate responses to painful stimuli (Casey *et al*., 1994) and regulate emotional and social behaviour (Devinsky *et al*., 1995). It has reciprocal connections with the amygdala (Amaral and Price, 1984), pulvinar (Robinson and Petersen, 1992) and anterior insula (Augustine, 1985, 1996), as well as strong projections to motor output systems (Frith *et al*., 1991). The activation of anterior cingulate by fearful expressions could therefore be interpreted as the engagement of a neural system co-ordinating behavioural responses to threatening stimuli.

Anterior insula

The brain region most responsive to increasing fearful intensity was in left anterior insula (Fig. 3B). The focus we identified lies only 13 mm from the most significantly activated voxel previously reported in a functional imaging study involving facial emotion matching (George *et al*., 1993). The insula has been implicated in the acquistion of inhibitory avoidance behaviour (Bermudez-Rattoni *et al*., 1991), the perception of noxious stimuli (Casey *et al*., 1994; Derbyshire *et al*., 1994), the experience of phobic symptoms (Rauch *et al*., 1995), cross-modal perception (Paulesu *et al*., 1995) and the control of saccadic eye movements (Petit *et al*., 1993, 1996). One of the postulated general roles for the insula is as a limbic integration cortex that co-ordinates sensorimotor responses to noxious or unexpected stimuli (Augustine, 1996). Its activation by fearful expressions in the present study, together with its extensive reciprocal anatomical connections with the amygdala and anterior cingulate cortex (Augustine, 1985, 1996) is consistent with this putative role.

Neuromodulatory role of the amygdala

The regression analysis of the rCBF data from the present study suggests that the strength of the neural connection between the amygdala and extrastriate cortex varies as a function of the facial expression being processed (Table 3A; Figs 4 and 5). This is an example of a psychophysiological interaction, i.e. a condition-specific change in the contribution of activity between one brain region and another (Friston *et al*., 1997). One interpretation of this interaction is that there is a modulation by the psychological context (i.e. viewing fearful faces) of the amygdala's connection to extrastriate cortex. This implies that another neural system, capable of distinguishing fearful and happy expressions, acts to enhance the neural connection between the amygdala and extrastriate cortex. Alternatively, and more parsimoniously, the interaction can be taken as evidence that the amygdala itself modulates condition-specific activity in extrastriate cortex (i.e. responses related to fearful faces). Although the first interpretation is not excluded by our data, the second is more consistent with the amygdala's known anatomical connections (Amaral *et al*., 1992), its specific role in processing fearful expressions (Adolphs *et al*., 1994; Calder *et al*., 1996), and its known neuromodulatory activity in other brain regions (discussed below).

Lesion experiments in animals suggest that the amygdala is involved in the neuromodulation of brain regions engaged in emotional learning (McGaugh *et al*., 1992). GABAergic and noradrenergic transmitter systems have been implicated in this modulatory activity (Liang *et al*., 1986; Brioni and McGaugh, 1988), and output pathways via the stria terminalis seem to be crucially involved (Liang and McGaugh, 1983). Other animal studies have revealed how projections from the amygdala modulate brainstem activity associated with startle reflex potentiation (Davis, 1992). This amygdalar activity appears to involve NMDA (*N*-methyl-D-aspartate)-dependent processes and projections to the nucleus reticularis pontis caudalis (Hitchcock and Davis, 1991). The extensive

amygdalar efferents to visual association cortex (Amaral and Price, 1984; Iwai and Yukie, 1987) have also been thought to be neuromodulatory in nature (Amaral *et al*., 1992; Rolls, 1992), although, prior to the present study, there has been no direct evidence for this postulated role. In addition to direct cortical projections, the amygdala also has strong connections with aminergic and cholinergic systems (including the nucleus basalis of Meynert) which are implicated in modulating synaptic connections (Mesulam *et al*., 1983; Russchen *et al*., 1985*b*). It has been suggested that the amygdala may act in a functionally integrated way with the nucleus basalis to modulate neural activity throughout the neocortex (Amaral *et al*., 1992; Rolls, 1992).

The extrastriate regions demonstrating functional interactions with the amygdala (Table 3A; Figs 4 and 5) have been shown to be involved in facial emotion processing in previous PET studies (George *et al*., 1993; Sergent *et al*., 1994). However, these regions were not identified by the categorical analyses in the present study (e.g. Table 1), demonstrating that changes in covariance relationships can occur without significant differences in mean regional brain activity. A recent neuropsychological study has also provided evidence that extrastriate areas have a role in facial emotion processing (Adolphs *et al*., 1996). The occipital regions identified by the lesion analysis of Adolphs *et al*. (1996) are, however, generally more medial to those found in neuroimaging studies. We are not aware of any study, other than the present report, which has provided evidence of the importance of extrastriate–amygdala interactions in facial emotion processing.

It is important to note that the regression analysis in this study (Table 3) provides information specifically about the amygdala's contribution to the neural processing of facial emotion and does not model the functional influence of other brain regions. Other types of network analysis, such as structural equation modelling (McIntosh *et al*., 1994), have been applied *post hoc* to neuroimaging data to model interactions between multiple brain regions and thus give a more complete account of functional neuroanatomy. Such an approach was not implemented in this study, which had a simple prior hypothesis regarding the amygdala's involvement in the neural mediation of fearful expressions, and therefore focused on this structure's functional connections.

Conclusions

This study has demonstrated the involvement of the amygdala in the differential neural response to fearful and happy expressions. Other structures activated in relation to fearful expressions, most notably the pulvinar nucleus of the thalamus, the anterior insula and the anterior cingulate, may represent, with the amygdala, a phylogenetically determined neural system which responds to threatening stimuli. The analysis of amygdalar activity with respect to other regional neural responses has enabled a more detailed characterization of the amygdala's functional interactions, and provides compelling evidence that the amygdala can modulate the processing of particular categories of facial expression in extrastriate cortex.

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