

Effects of Attention and Emotion on Face Processing in the Human Brain: An Event-Related fMRI Study

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Summary

We used event-related fMRI to assess whether brain responses to fearful versus neutral faces are modulated by spatial attention. Subjects performed a demanding matching task for pairs of stimuli at prespecified locations, in the presence of task-irrelevant stimuli at other locations. Faces or houses unpredictably appeared at the relevant or irrelevant locations, while the faces had either fearful or neutral expressions. Activation of fusiform gyri by faces was strongly affected by attentional condition, but the left amygdala response to fearful faces was not. Right fusiform activity was greater for fearful than neutral faces, independently of the attention effect on this region. These results reveal differential influences on face processing from attention and emotion, with the amygdala response to threat-related expressions unaffected by a manipulation of attention that strongly modulates the fusiform response to faces.

Introduction

Adaptive behavior requires the brain to deal with opposing demands: the selection of goal-relevant stimuli for privileged processing by mechanisms of attention, but also the detection of potentially significant events that may occur unpredictably outside the focus of attention. At the neurophysiological level, functional imaging in humans (Corbetta et al., 1990; Kastner et al., 1998; Rees et al., 1999) and single-cell recording in monkeys (Chelazzi et al., 1998; Moran and Desimone, 1985) indicate that neural responses to unattended stimuli can be greatly reduced or even suppressed as compared to attended stimuli. Similarly, at the psychological level, stimuli that are unattended are often perceived less accurately and may even escape awareness (Mack and Rock, 1998; Neisser and Becklen, 1975; Rock and Guttmann, 1981).

On the other hand, there is evidence to suggest that information about stimuli with emotional significance may be processed outside the focus of attention or even in the absence of awareness for stimulus occurrence. Psychophysical studies have shown that normal observ-

ers exhibit fast involuntary responses to emotional stimuli, in particular, when these are related to potential threats, such as faces with fearful expressions or aversive pictures (Globisch et al., 1999; Lang et al., 1998; Öhman et al., 1995; Wells and Matthews, 1994). Thus, skin conductance changes can be elicited by masked fear-conditioned faces, even when subjects fail to report these stimuli (e.g., Öhman et al., 1995). Such automatic, apparently “preattentive” processing of emotional stimuli might serve to prioritize responses toward particularly significant stimuli. In keeping with this, behavioral studies in normal subjects (Bradley et al., 1997; Pratto and John, 1991; Roskos-Ewoldsen and Fazio, 1992) and in brain-damaged patients with deficits in attention, such as spatial neglect (Vuilleumier and Schwartz, 2001), have found that emotional stimuli may capture attention more readily than neutral stimuli.

In the present study, we used event-related functional magnetic resonance imaging (fMRI) to examine whether neural responses to emotional face stimuli will be affected by a manipulation of spatial attention that has previously been shown (Wojciulik et al., 1998) to influence the fusiform response to faces with neutral expressions. Our specific goals were to determine whether processing of fearful expression in faces can occur even when attention is directed elsewhere for a demanding task and to assess whether the degree of such processing is modulated by attentional condition. The design of our study manipulated attention (i.e., whether stimuli appeared at task-relevant or task-irrelevant locations) and facial expression as independent factors, allowing us to examine the effects on neural processing produced by each factor separately and to test for their interaction.

Previous neuroimaging studies have established that faces can activate relatively specific areas in the fusiform gyri (Clark et al., 1996; George et al., 1999; Kanwisher et al., 1997; Puce et al., 1995). The degree of activation in these regions appears to depend on the degree of attention toward faces or their task relevance (Clark et al., 1997; Haxby et al., 1994; O’Craven et al., 1999; Wojciulik et al., 1998). Early studies on this issue used blocked designs that may have confounded modulation of purely stimulus-locked responses with task-related “baseline shifts” in activity (see Kastner et al., 1999). However, modulation of fusiform responses to faces by attention has since been confirmed with event-related designs (O’Craven et al., 1999).

Emotional expressions in faces are known to activate several distinct regions, including amygdala, cingulate gyrus, orbitofrontal cortex, and other prefrontal areas (Blair et al., 1999; Breiter et al., 1996a; Dolan et al., 1996; Morris et al., 1996; Nakamura et al., 1999). The amygdala in particular has consistently been activated by fearful faces (Breiter et al., 1996a; Morris et al., 1996, 1998a; Whalen et al., 1998c). Such activity may be relatively “automatic,” as it can arise without any requirement for explicit judgement of facial expression (e.g., as when subjects make gender judgements; Morris et al., 1998b) and even without actual awareness of the faces (i.e.,

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when faces are masked; Morris et al., 1998b; Whalen et al., 1998c). In the latter studies, however, subjects were still required to direct spatial attention to the location of the effective stimuli, without any concurrent competing distractors in the scene. Subliminal responses to fear-related stimuli therefore do not necessarily imply that emotional processing will be immune to modulation by spatial attention (Lavie, 1995; Maruff et al., 1999). Our design enabled a direct test of this.

We manipulated emotional expression of faces within a paradigm that has previously been found to show significant attentional modulation of fusiform responses to faces. Wojciulik et al. (1998) presented subjects concurrently with a pair of faces and a pair of houses while requiring a same/different judgement on just one of the stimulus pairs (i.e., either the two faces or the two houses) during separate trial blocks. Fusiform activation was greater when attending to faces than when ignoring these and judging the houses instead. Here, we modified this paradigm in two critical respects. First, all our comparisons were event related rather than blocked, so that we measured stimulus-locked responses when the particular stimulus type (house or face) appearing at the task-relevant locations could not be anticipated (i.e., the relevant locations were blocked but the stimulus type appearing there was not). Second, we manipulated the emotional expression of the faces (fearful or neutral), independently of whether faces or houses were presented at the task-relevant locations. This enabled us to assess neural responses specific to fearful faces, as a function of whether these faces appeared at task-relevant or irrelevant locations. Given the results of Wojciulik et al. (1998), we predicted greater fusiform responses to faces when presented at relevant locations. The critical new question concerned responses to fearful (versus neutral) faces at relevant versus irrelevant locations, in the amygdala and related structures. If the amygdala response is driven by face processing in the fusiform, it follows that it should show similar modulation by spatial attention. However, if amygdala activity reflects an obligatory threat-related response independent of the focus of attention, possibly driven by other pathways (LeDoux, 2000; Morris et al., 1999), then unlike the fusiform it should not be affected by the attentional manipulation.

Results

Event-related fMRI was performed in 12 healthy volunteers while they viewed brief visual displays that, across all experimental conditions, always contained four stimuli—two faces and two houses—arranged in vertical and horizontal pairs (Figure 1). The two faces either both had a neutral expression or both had a fearful expression (unlike Wojciulik et al., 1998). Stimulus position (vertical pairs of faces and horizontal pairs of houses or vice versa) and emotional expression (fearful or neutral faces) varied in a counterbalanced and randomized order. During four successive series of trials, subjects had to attend selectively either to the vertical pair of stimuli or to the horizontal pair of stimuli and perform a demanding same/different matching judgement for just these two stimuli. Task-relevant locations (vertical or horizontal

positions) were blocked during each series of trials, whereas the two experimental factors of interest (i.e., effects of *attention*, with either faces or houses appearing at the relevant locations, and effects of *emotion*, with fearful versus neutral expressions in faces) were varied independently and thus were entirely unpredictable on a trial-by-trial basis. This led to four critical event-related conditions: attending to faces with a neutral (Attended-Neutral [AN]) or fearful expression (AF) at task-relevant locations, in the presence of houses at irrelevant locations; or judging houses in the presence of faces at irrelevant locations that again could have neutral (Unattended-Neutral [UN]) or fearful (UF) expressions. This 2×2 factorial design allowed for a direct comparison of the effects of emotional expression for faces presented at task-relevant versus irrelevant locations.

Central fixation was required throughout and monitored online. Note that the cross format of the displays discourages any shift of gaze prior to the displays, as fixating toward one of the two relevant stimuli would impair acuity for the other relevant stimulus (Duncan, 1980; Wojciulik et al., 1998). Note also that the display duration (250 ms) was too brief for saccades to occur and alter visual inputs during each display.

Behavioral Performance

Median response times and error rates in same/different matching judgements, performed during fMRI scanning, were computed for each subject in each of the four critical conditions and then submitted to repeated-measure ANOVA, with the factors of attention (judging faces or houses at the relevant locations) and of emotion expression (neutral or fearful faces). Analysis of reaction times (RTs) showed that subjects were significantly slower to make same/different judgements in displays with fearful compared to neutral faces [mean 1020 versus 975 ms; $F(1,10) = 19.4$, $p = 0.001$]. The interaction between attended stimulus type and emotion did not reach significance [$F(1,10) = 1.6$, $p = 0.22$]. However, planned comparisons revealed that matching of houses was slower in the presence of irrelevant faces when fearful versus neutral [1002 versus 935 ms; paired t test $t(11) = 3.29$, $p = 0.007$]. By contrast, RTs did not differ significantly for matching fearful versus neutral faces at relevant locations [1038 versus 1016 ms; paired t test $t(11) = 1.13$, $p = 0.28$]. These results indicate that fearful expression in task-irrelevant faces can interfere with performance, consistent with some emotional information being extracted even from task-irrelevant stimuli.

Mean error rate was 16%. Subjects made more errors overall when judging faces than houses [20% versus 14%, $F(1,10) = 13.6$, $p < 0.004$]. Emotional expression had no effect on error rate, and there was no interaction. The overall error rate indicates that the task was attention demanding, as confirmed subjectively by subjects.

Eye Movement Monitoring

Eye position was recorded online during fMRI scanning and analyzed to assess any differences in fixation or saccade patterns across conditions. The number of saccades and maximal deviation from central fixation (in horizontal and vertical directions) were calculated dur-

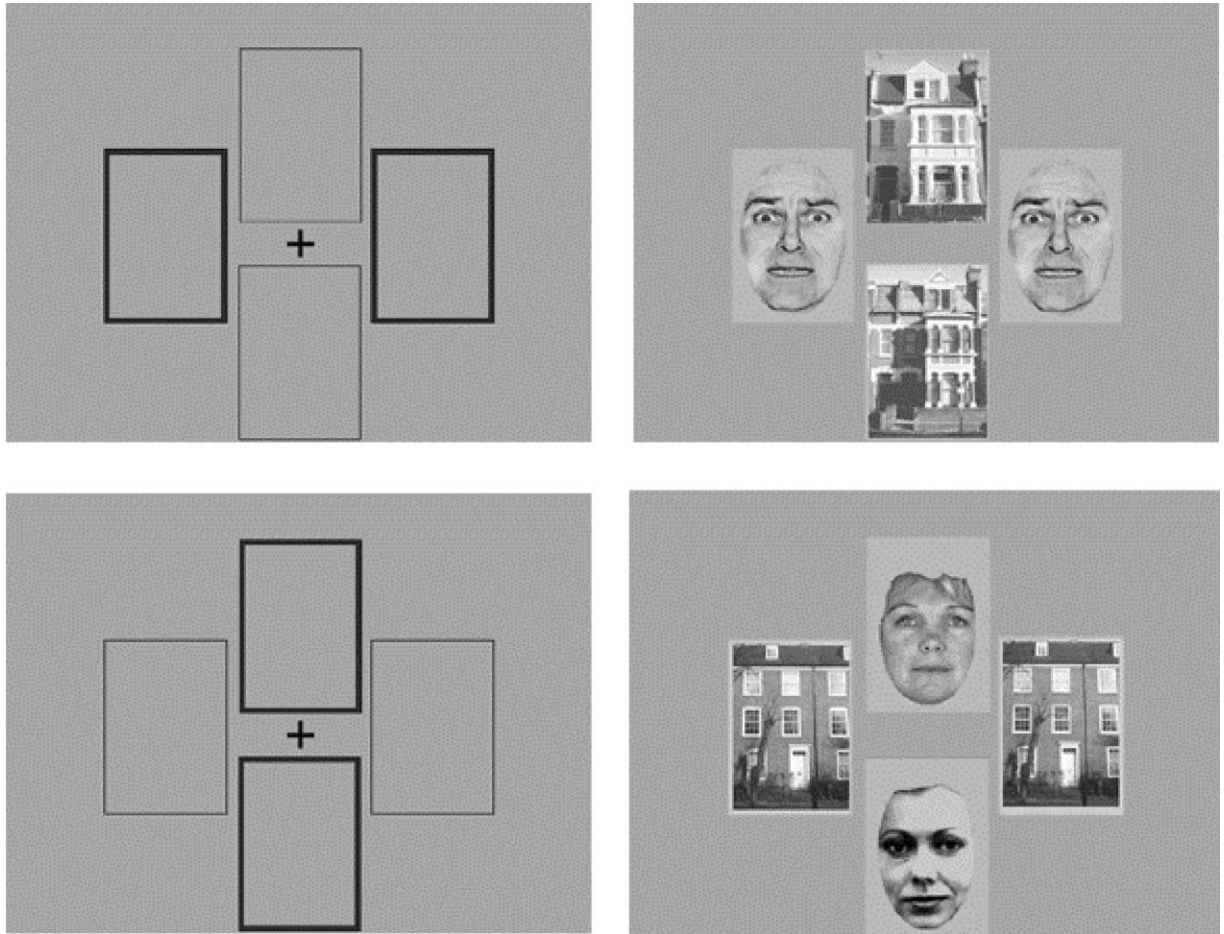


Figure 1. Example of Stimuli

Each display included two faces and two houses, arranged in vertical and horizontal pairs. Faces could be arranged vertically and houses horizontally or vice versa in an unpredictable sequence. Each pair of faces or houses could show the same items or different items from the same category. Both faces had a neutral expression, or both were fearful. At the beginning of each of four different random sequences of trials, a display with four boxes instructed subjects to attend and match only the vertical pair of stimuli or only the horizontal pair, in order to judge whether this pair showed the same or different pictures.

ing a 250 ms period preceding and a 250 ms period following stimulus onset, for each trial and each subject. Saccades were very rare. A few saccades occurred after stimulus onset (mean $2.9 \pm$ SD 2.8 per event type; 4%), with even less before stimulus onset (mean $1.1 \pm$ SD 1.6; 1.5%). Analysis of variance revealed no significant difference between conditions in the number of saccades as a function of stimulus type at the relevant locations (faces versus houses) or emotional expression of faces (fear versus neutral), neither before nor after stimulus onset [Friedman $\chi^2(3) = 1.56$ and 4.10, respectively, $p \leq 0.25$]. Similarly, the amplitudes of any deviations from central fixation were small and not significantly influenced by experimental condition. While the means of the maximal distance from fixation were slightly greater after stimulus onset as compared to before stimulus onset (0.58° versus 0.47°), a four-way ANOVA with the factors of time (before versus after stimulus onset), task-relevant locations (judging stimuli at horizontal or vertical positions), stimulus type at relevant locations (faces or houses), and emotional expression

(fearful versus neutral) showed no significant effects or interaction (all $F_s \leq 2.8$, $p \geq 0.09$). Importantly, these data indicate that saccades were rare, with no major differences in eye position associated with the experimental factors critical in the fMRI analysis (i.e., attending to faces versus houses at relevant locations and emotional expression of faces).

fMRI Data

Main Effects of Attention and Fear

We first determined which brain regions showed a main effect of the attentional condition. This was assessed by comparing all events where the different stimulus types (faces versus houses) appeared at the task-relevant locations, regardless of any emotional effect due to fearful expression in the faces (see Table 1). Attending to faces at relevant locations ($AF + AN > UF + UN$) produced a marked increase of activity in the fusiform gyrus of the right hemisphere, as well as in the fusiform and inferior temporo-occipital gyri of the left hemisphere (Figure 2). These fusiform areas were remarkably sym-

Table 1. Main Effects of Attention and Emotion Expression

Side	Area	Coordinates			Z Value	P
		X	Y	Z		
Effects of Spatial Attention						
Faces > houses						
Right	fusiform gyrus	44	-54	-20	4.78	0.042
Left	fusiform gyrus	-44	-54	-20	3.46	<0.0001**
Left	inferior temporal gyrus	-40	-78	-18	3.27	<0.0001**
Houses > faces						
Right	parahippocampal gyrus	32	-44	-10	>10	<0.05
Right	parahippocampal gyrus	28	-40	-16	>10	<0.05
Left	parahippocampal gyrus	-26	-42	-14	>10	<0.05
Right	retrosplenial cortex	16	-56	16	6.99	<0.05
Left	retrosplenial cortex	-12	-56	18	5.47	<0.05
Right	lateral occipital gyrus	36	-82	24	5.89	<0.05
Left	lateral occipital gyrus	-32	-86	34	5.88	<0.05
Effects of Facial Emotion						
Fear > neutral						
Left	temporal pole (uncus)	-30	6	-26	4.75	0.047
Left	amygdala	-26	0	-20	4.51	0.001*
Left	anterior cingulate gyrus	-14	52	14	3.76	<0.0001**
Right	fusiform gyrus	44	-52	-20	3.73	<0.0001**
Right	lateral orbitofrontal cortex	30	40	-16	3.73	<0.0001**
Right	superior colliculus	8	-36	-18	3.73	<0.0001**
Left	superior colliculus	-10	-38	-16	3.61	<0.0001**
Neutral > fear						
Right	superior prefrontal cortex	34	34	28	4.2	<0.0001**
Right	medial prefrontal cortex	10	40	48	4.05	<0.0001**

p values are corrected for entire brain volume, except *, p value corrected for volume of interest, and **, p value uncorrected.

metrical and correspond to regions previously found to respond more to faces than other classes of stimuli (e.g., Kanwisher et al., 1997; Puce et al., 1995). Note that here such activation was purely driven by attentional modulation of stimulus processing, as the visual displays themselves were equivalent across the conditions, and the attended stimulus category could not be anticipated (see also O'Craven et al., 1999).

Attending to houses rather than faces at the relevant locations (UF + UN > AF + AN) activated a distinct network of regions in both hemispheres, with the very same stimuli, including parahippocampal gyrus, retrosplenial cortex, and lateral occipital regions (Table 1 and Figure 3). These areas have been implicated in the processing of places and navigation landmarks (e.g., Aguirre et al., 1998; Epstein et al., 1999).

We next determined the main effect of fearful expression, by identifying brain regions activated by fearful face stimuli irrespective of the condition of spatial attention (see Table 1). This was assessed by comparing all events with fearful faces in the display to events with neutral faces, regardless of whether subjects made judgements on faces or houses (AF + UF > AN + UN). Peaks of activation were found in the left amygdala (Figure 4A), as well as in a distinct cluster in the most anterior and medial part of the inferior temporal pole, corresponding to the region of the uncus (semilunar gyrus/anterior collateral sulcus). In addition, fearful versus neutral expressions produced significant activation in anterior cingulate gyrus (rostral pregenual), lateral orbitofrontal cortex, right fusiform gyrus, and bilateral superior colliculi (Table 1). Similar areas have been acti-

vated by a variety of emotional stimuli in previous studies (e.g., Dolan et al., 1996; George et al., 1993). The left fusiform gyrus showed no main effect of fear ($Z = 2.1$, $p > 0.01$, uncorrected), unlike the right fusiform. Displays with neutral faces evoked greater activity in the right superior and medial prefrontal cortex, by comparison to fearful faces (see Table 1).

Effects of Fear Independent of Attentional Condition

The relationship between effects of fear and the attentional manipulation was examined by analysis of simple main effects (i.e., for each attentional condition separately). This confirmed that the left amygdala response to fearful expression was significant (Figure 4B), even when considering only the subset of events where subjects judged the house stimuli, with the fearful or neutral faces appearing at the task-irrelevant locations (UF > UN). This comparison showed amygdala activation both in the left ($x, y, z = -20, -2, -18$; $Z = 3.26$, $p < 0.001$, corrected for volume of interest) and right hemisphere ($16, -10, -18$; $Z = 3.51$, $p < 0.001$, corrected for volume of interest). The anterior cingulate cortex in the left hemisphere ($-14, 50, 12$; $Z = 3.57$) and the right hemisphere ($8, 52, 18$; $Z = 3.29$) as well as the right fusiform gyrus ($42, -54, -20$; $Z = 3.13$) also showed enhanced activation ($p < 0.001$, uncorrected in all cases).

On the other hand, attending to fearful as compared to neutral faces (AF > AN) increased activity not only in the left amygdala ($-26, -2, -20$; $Z = 4.05$, $p < 0.001$, corrected for volume of interest) but also in the left temporal pole ($-30, 4, -30$; $Z = 5.17$) and both fusiform gyri ($Z \geq 3.21$, $p \leq 0.001$, uncorrected).

For completeness, we also examined the simple ef-

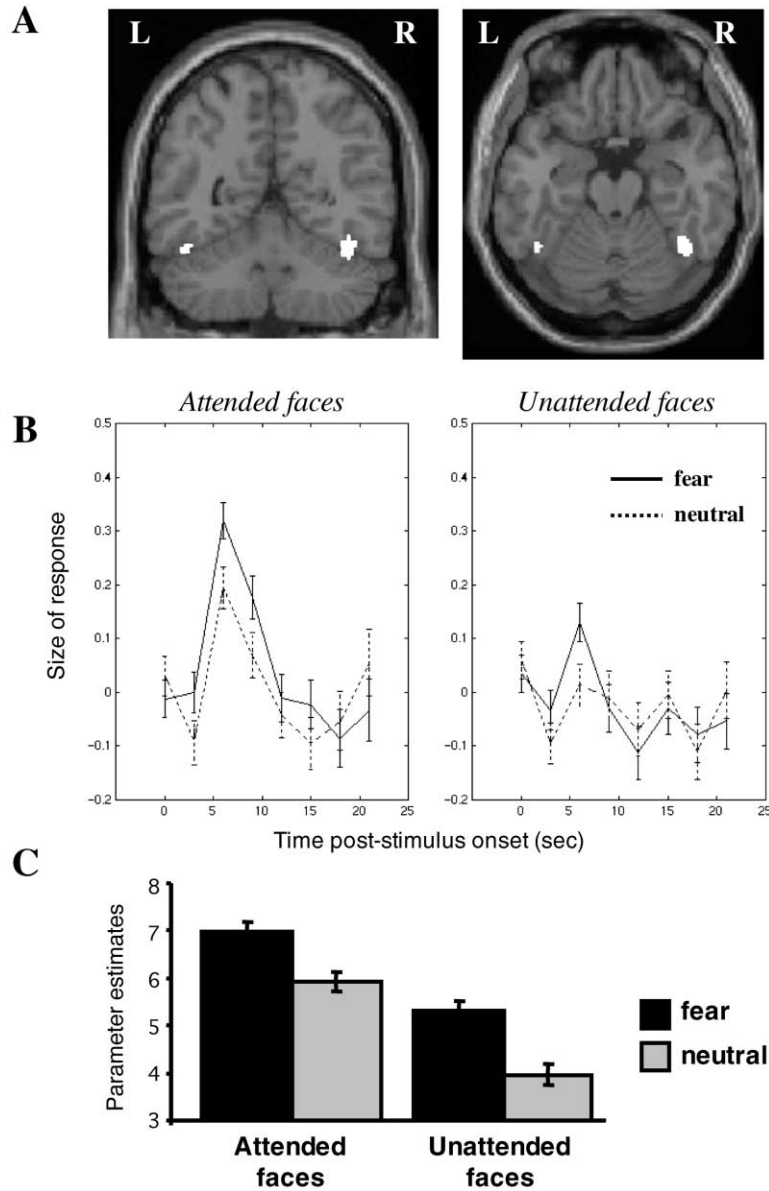


Figure 2. Activation of Fusiform Cortex
(A) Fusiform gyri in both hemispheres showed increased activity when subjects attended to faces versus houses at the relevant locations, regardless of emotion expression. Group results are superimposed on a single-subject T1-weighted MRI (activated voxels at $p < 0.05$, corrected for whole brain).
(B) Peristimulus time histograms showing the time course of activity (arbitrary units) in the right fusiform peak, for the four different conditions, demonstrating greatly attenuated responses when faces appeared at task-irrelevant locations as compared to relevant locations but still a significant response when task-irrelevant faces had a fearful expression.
(C) Parameter estimates of activity (arbitrary units) for the right fusiform gyrus in each condition, confirming that its response not only increased when faces were attended, regardless of expression, but also increased when faces were fearful rather than neutral, regardless of the attentional manipulation, with these two effects being additive (error bars represent 1 SEM).

fects of attention separately for each emotional condition of face expression. When considering just those events with fearful faces, judging faces versus houses (AF > UF) produced no significant effect in the amygdala ($Z = 0.35$, $p = 0.36$), consistent with the lack of attentional modulation in this region for the main effect of fear considered above. However, there was increased activity in the left fusiform (-44 , -52 , -20 ; $Z = 3.58$, $p < 0.001$, uncorrected) and left temporal pole (-32 , 2 , 32 ; $Z = 3.95$, $p < 0.001$, uncorrected) but no significant increase in right fusiform. In contrast, when considering only events with neutral faces, there was a significant increase in the right fusiform (44 , -56 , -20 ; $Z = 3.84$, $p < 0.001$) when judging faces versus houses (AN > UN). This pattern suggests that the right fusiform gyrus was independently modulated both by attention and emotional expression (consistent with the results for the main effects above), whereas activity in the left fusiform

gyrus appeared to be dependent on attention, with any additional modulation by emotional expression occurring only when faces were at task-relevant locations. The additive influences of emotional and attentional factors on activity in the right fusiform cortex are depicted in Figures 2B and 2C.

We note that there was no effect of facial emotion in the parahippocampal gyrus ($Z < 1$, $p > 0.10$, on both sides) or in any other regions that responded more to houses than to faces, confirming that emotional modulation was anatomically specific, involving the fusiform (plus amygdala and related areas) but not other extrastriate visual areas (see Figure 3B).

Interactions between Fear and Attention

The fully factorial design of our study allowed us not only to examine responses to fearful versus neutral faces but also to examine whether such responses were significantly modulated by the attentional manipulation. The

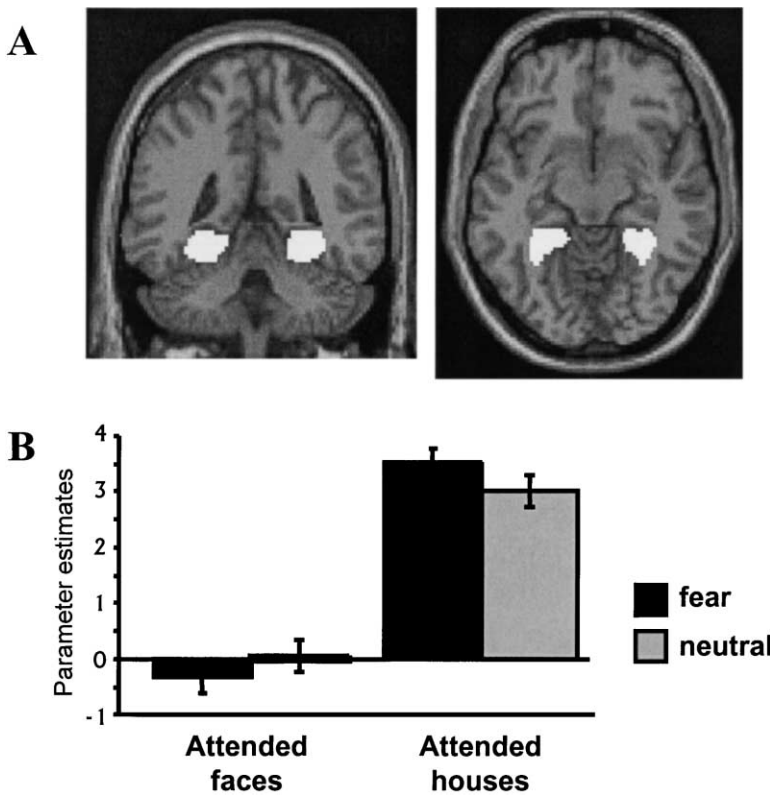


Figure 3. Activation of Parahippocampal Cortex

(A) The parahippocampal gyri showed increased activity in both hemispheres when subjects attended to houses versus faces at the relevant locations, regardless of the expression of the faces. Group results are superimposed on a single-subject T1-weighted MRI (activated voxels at $p < 0.05$, corrected for whole brain).

(B) Parameter estimates of activity (arbitrary units) in the right parahippocampal gyrus for each condition, showing increased responses when houses were attended and no significant influence of emotional expression of the concurrent faces (error bars represent 1 SEM).

most direct test to determine any effect of attention on the response to fearful expressions is to identify brain regions showing a significant interaction between the two factors across all trial conditions. Three areas responded more to fearful faces when these appeared at task-relevant rather than irrelevant locations ($[AF - AN] > [UF - UN]$): the uncus region in inferior left temporal pole, anterior cingulate cortex (caudal), and occipital visual cortex (see Table 2 and Figures 4C and 4D). Critically, the response to fearful faces in the amygdala itself was not significantly modulated by the attentional manipulation ($Z = 1.0$, $p = 0.16$; see Figures 4A and 4B). Some areas showed enhanced activation to fearful faces when appearing at task-irrelevant locations ($[UF - UN] > [AF - AN]$), including nucleus accumbens in the ventral striatum, anterior cingulate gyrus (rostral), medial orbito-frontal cortex, and primary motor cortex (see Table 2).

No Effect of Fearful Faces at Task-Irrelevant Locations on the Activations for Attended Houses

Given the demanding task, the blocking of task-relevant locations, the brief duration for each display of competing stimuli, and the strong effects of the attentional condition on fusiform responses to faces, it seems unlikely that subjects inadvertently attended to fearful faces when these appeared at task-irrelevant locations. But if fearful faces at task-irrelevant locations did capture attention, one could then predict that those areas specifically activated when subjects were required to attend and judge the houses (e.g., parahippocampal gyri) should show reduced activation when fearful rather than neutral faces appeared as distractors. However, this comparison ($UN > UF$) showed no significant effect in any of the areas driven by task-relevant houses (e.g., for right

and left parahippocampal gyri, $Z = -1.47$ and -0.71 , respectively; see also Figure 3B).

Behavioral Study of the Effects of Attentional Conditions on Face Perception

An additional behavioral study ($n = 40$) was conducted to assess how much subjects perceive of faces appearing at task-relevant versus irrelevant locations, as a further check on whether fearful faces attract attention in our paradigm. This study used a method adapted from the behavioral literature on “inattentive blindness” (see Mack and Rock, 1998). A group of 40 participants performed the same task, with the same face and house stimuli, as we employed during fMRI. At the end of a block of 48 trials, three questions were posed on the computer screen, in sequence, concerning the pair of (identical) faces from the very preceding trial. Each question about these faces was in a two-alternative forced-choice format: what was their expression (fearful or neutral), their gender (male or female), and their identity (indicated by selecting one of two face probes, each with the same gender and expression, presented on the screen after completion of the two previous questions). The questions were posed for faces that had appeared at either the task-relevant locations or the task-irrelevant locations on the previous trial; expression in these faces had been either neutral or fearful, and the task-relevant locations were either the vertical or horizontal positions in the cross format—all this was counterbalanced across participants.

The results showed that subjects were able to judge the expression, gender, and identity of faces that had appeared at task-relevant locations (85%, 90%, and 100% correct, respectively) but were at chance in judg-

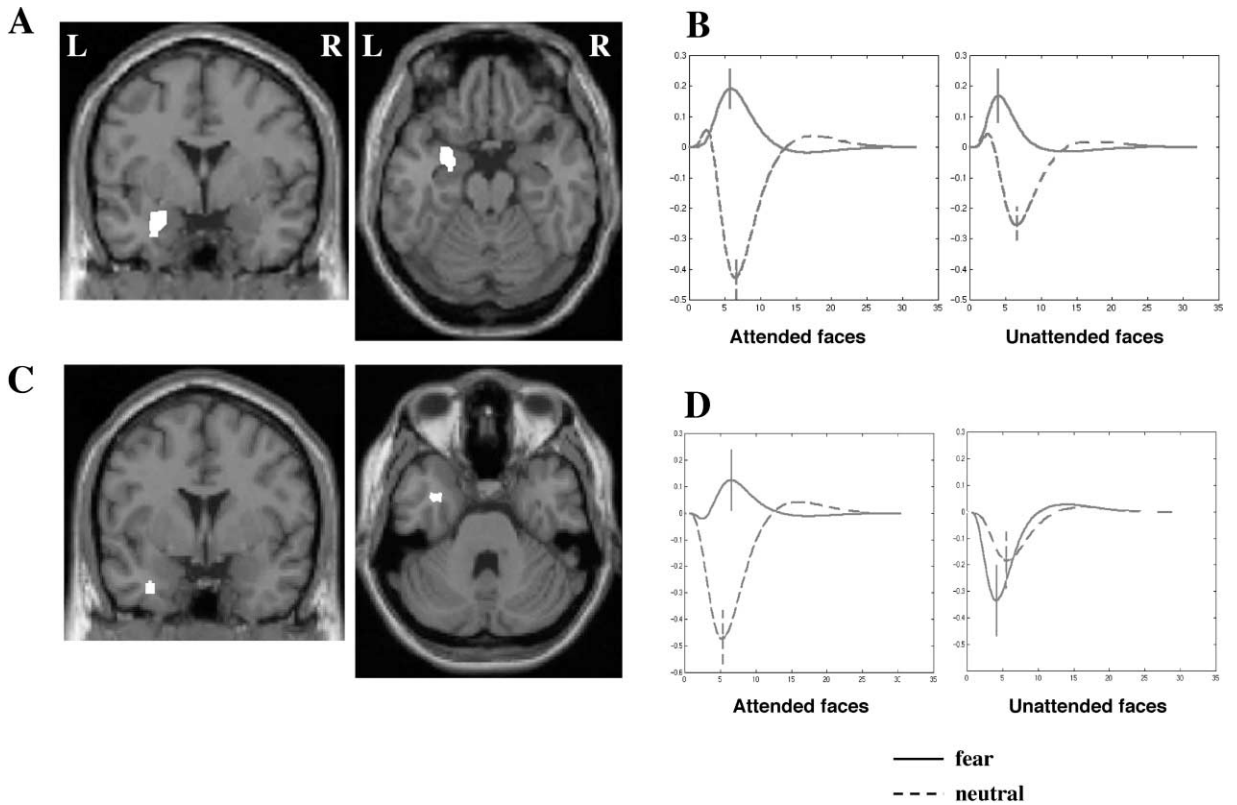


Figure 4. Activation of Amygdala and Medial Temporal Cortex

(A) Activation of the left amygdala produced by fearful expression of faces, regardless of the spatial attention manipulation. Group results are superimposed on a single-subject T1-weighted MRI (activated voxels at $p < 0.05$, corrected for whole brain).
 (B) Fitted hemodynamic response (arbitrary units) in the left amygdala for each experimental condition, showing that the magnitude of activation elicited by fearful face expression did not significantly differ when faces appeared at the relevant versus irrelevant locations.
 (C) Activation in the inferomedial part of the temporal pole (anterior end of the collateral sulcus underneath the uncus), produced by fearful faces only when these appeared at task-relevant locations (activated voxels at $p < 0.001$, uncorrected). This interaction of emotional and attentional effects did not involve the voxels in the amygdala (see [A]) that showed a main effect of fear.
 (D) Fitted hemodynamic response (arbitrary units) in the inferior temporal pole, showing a different pattern of event-related activity as compared to the amygdala (error bars represent 1 SEM).

ing faces that had appeared at task-irrelevant locations on the preceding trial [45%, 40%, and 35% correct, respectively; $\chi^2(1) \geq 7.03$, $p \leq 0.01$ for the difference between conditions in all cases]. Critically, even judgements of the emotional valence of a fearful face were at chance (40%) in this situation. This provides a direct

behavioral confirmation of the effectiveness of the attentional manipulation used in our paradigm. When engaged in the demanding matching task for a pair of house stimuli at the task-relevant locations, subjects cannot report the properties of faces that appear at task-irrelevant locations, not even their emotional valence.

Table 2. Interactions of Attention and Emotion Expression

Side	Area	Coordinates			Z Value	p
		X	Y	Z		
Increased Response to Fear with Attention						
Left	anterior cingulate gyrus	-10	-2	48	4.22	<0.0001**
Left	striate visual cortex	-8	-78	18	4.11	<0.0001**
Left	temporal pole (uncus)	-32	0	-30	3.94	<0.0001**
Increased Response to Fear with Inattention						
Right	ventral striatum	8	20	4	4.5	<0.0001**
Right	anterior cingulate gyrus	8	50	16	4.32	<0.0001**
Left	prerolandic motor cortex	-32	20	36	4.01	<0.0001**
Right	medial orbitofrontal cortex	2	28	-14	3.96	<0.0001**

** p value uncorrected.

Discussion

This study provides novel findings on the combined effects of spatial attention and emotional expression on processing of faces in the human brain. As predicted, fusiform cortex was modulated by selective attention to faces (e.g., see Wojciulik et al., 1998), and the amygdala was activated by fearful expression (e.g., see Morris et al., 1996). Here, such activations were strictly event related, since subjects could not form an expectation for the presentation of a given stimulus type at the task-relevant locations nor for emotional expression of faces on successive trials. By manipulating attention and emotion independently, we were able to demonstrate that whereas the fusiform response to faces was strongly modulated by the condition of spatial attention (i.e., when faces appeared at task-relevant versus task-irrelevant locations), the left amygdala response to fearful expressions was not affected by this manipulation. Right fusiform activity was also influenced by emotional expression, with a greater response to fearful than neutral faces, additive to the effect of attention at this site. By contrast, some cortical and subcortical regions showed differential engagement by emotional faces as a function of the attentional condition, including the anterior medial temporal cortex, anterior cingulate gyrus, orbitofrontal cortex, and ventral striatum.

Amygdala

A crucial role of the amygdala in emotional processing is indicated by previous evidence from animal studies (Aggleton, 1992; LeDoux, 2000), from patients with focal brain damage (Adolphs et al., 1995; Young et al., 1995), and from functional neuroimaging in normal humans (Breiter et al., 1996b; LaBar et al., 1998; Morris et al., 1996, 1998a, 1998b; Whalen et al., 1998b). In particular, the amygdala is involved in the recognition of threat-related stimuli and acquisition of fear-conditioned responses (Armony and LeDoux, 2000; Buchel et al., 1998, 1999; LeDoux, 1992, 2000). Previous studies using positron emission tomography (PET) (Morris et al., 1996, 1998a, 1998b) or blocked fMRI (Breiter et al., 1996a; Irwin et al., 1996; Whalen et al., 1998b) found preferential activation of left amygdala by fearful as opposed to neutral faces. This accords with the present event-related results, showing left amygdala activity as a main effect of fearful faces in the visual field, regardless of the attentional condition, and thus of the initial allocation of spatial attention. It has been proposed that the amygdala might be specialized for fast detection of emotionally relevant stimuli, operating in a largely automatic manner, independent of higher cognitive control and awareness (LeDoux, 2000; Morris et al., 1998b; Öhman et al., 1995). Our study provides the first evidence that response to fear stimuli in the human amygdala is not modulated by a manipulation of spatial attention that is sufficient to elicit a significant modulation of the fusiform response to faces. Thus, amygdala activation by fearful expression was similar when subjects selectively processed faces at relevant locations or, instead, judged concurrent (house) stimuli while the faces appeared at task-irrelevant locations. The very same attentional manipulation significantly influenced the fusiform response to

faces (Figure 2) while leaving the amygdala response to fearful expression unaffected (Figure 4).

These imaging results for the amygdala may relate to one aspect of our behavioral findings during scanning, which also provided some evidence for processing of emotion at task-irrelevant locations. RTs for matching task-relevant house stimuli were slower when irrelevant faces were fearful rather than neutral, suggesting that emotional features were extracted even from task-irrelevant face stimuli. This accords with the fMRI results showing higher amygdala activity evoked by fearful versus neutral expressions, even for just those faces that were presented at the to-be-ignored locations during trials in which houses were judged (i.e., $UF > UN$).

Given our task conditions (i.e., demanding matching task and brief displays with multiple competing stimuli) and the strong attentional modulation observed for fusiform activity, it seems unlikely that the amygdala responses found for fearful faces at task-irrelevant locations were caused merely by inadvertent shifts of attention to such stimuli. But even if the fearful faces might tend to attract more attention than neutral faces at task-irrelevant locations, some involuntary “preattentive” response to fearful faces would still be required to produce this attention capture, such as the amygdala activity we observed. Moreover, the main thrust of our results would remain: the amygdala response to fearful expressions was unaffected by an attentional manipulation that nonetheless strongly influenced the fusiform response to faces.

Importantly, however, several aspects of our results suggest that fearful faces at task-irrelevant locations actually did remain unattended. In the behavioral control study, we found that subjects could not report the properties of faces presented at the task-irrelevant locations on the immediately preceding trial, not even the emotional valence of fearful faces. Furthermore, in the fMRI data, we found that activity in response to task-relevant houses (e.g., in the parahippocampal gyri) was unaffected by whether fearful or neutral faces appeared as concurrent distractors, suggesting that attention was not significantly diverted from the task-relevant stimuli. This altogether supports the idea that the modulation of left amygdala and right fusiform activity by irrelevant fearful faces occurred independent of the initial allocation of spatial attention.

The consistent response in the amygdala to fearful faces, regardless of our attentional manipulation, is a noteworthy finding given the abundant evidence that, in other neural systems, the response to task-irrelevant stimuli is greatly attenuated or even suppressed, as compared to selectively attended stimuli (Chelazzi et al., 1998; Corbetta et al., 1990; Moran and Desimone, 1985; Rees et al., 1999), particularly in situations with multiple concurrent competing stimuli (Kastner et al., 1998), as here. Moreover, this result for the amygdala contrasts directly with the robust attentional modulation found for the fusiform response to faces (and likewise for the parahippocampal response to houses). We cannot rule out the possibility that some further manipulation of attention (e.g., an even higher load in the task performed at the task-relevant locations) could in the future reveal some degree of amygdala modulation, unlike the preserved amygdala response we found in the

current study. We consider this unlikely, given that the present task situation is already relatively high in perceptual load (see Lavie, 1995; Lavie and Fox, 2000) and sufficient to produce inattention blindness for faces at task-irrelevant locations, as confirmed by our behavioral control study. In any case, the critical aspect of the present findings is that the amygdala shows a preserved response to fear expression, even under conditions when other neural systems (i.e., ventral extrastriate regions of visual cortex, such as the fusiform) show strong attentional modulation. This argues against the amygdala activity being driven directly by the fusiform response to faces and is consistent with the view (Armony and LeDoux, 2000; LeDoux, 2000) that the amygdala may serve as a dedicated danger detection system, allowing fast responses to emotionally salient but unpredictable events, even when these occur outside the initial focus of attention.

Such proposals of relatively automatic and obligatory amygdala response were previously based on findings that masked presentation of emotional faces or fear-conditioned stimuli can elicit behavioral reactions and amygdala activation (Morris et al., 1998b; Whalen et al., 1998b), despite unawareness of the critical stimuli. Animal studies have suggested that such responses may involve direct projections to the amygdala which bypass primary visual cortex (Amaral et al., 1992; Armony and LeDoux, 2000; Armony et al., 1995; LeDoux et al., 1990). Moreover, a recent human neuroimaging study suggests that activity in superior colliculus and pulvinar may be strongly coupled with amygdala responses to fearful expressions during unconscious processing of masked faces (Morris et al., 1999). This could accord with a subcortical route in processing of fear-related stimuli (Amaral et al., 1992; Morris et al., 1999) and also with the activation of superior colliculi by fear expressions found in the present study, as a main effect independent of attention (Table 1). Alternatively, this collicular activity could reflect an orienting response triggered by fear processing (Armony and LeDoux, 2000; LeDoux, 2000). Note that eye movement recordings during our scanning showed no significant differences in saccade rate or in deviation from fixation in relation to the critical conditions of fearful versus neutral expression while attending to faces or to houses. Saccades were rare (4% of trials) and uninfluenced by emotional expression in faces. This suggests that the present collicular activation produced by fearful faces was not due to differences in overt eye movements.

Fusiform Cortex

Fusiform activity increased bilaterally when attention was directed to faces, irrespective of expression. Such activity has previously been implicated in face processing across a variety of tasks (George et al., 1999; Kanwisher et al., 1997; Puce et al., 1995) and is modulated by attention (O'Craven et al., 1999; Wojciulik et al., 1998) or awareness of the faces (Dolan et al., 1997; Tong et al., 1998). In our study, this modulation was driven solely by spatial attention, since visual displays were the same across conditions, and the stimulus category appearing at the relevant locations could not be anticipated, thus ruling out baseline shifts due to anticipation (Kastner et al., 1999).

Right fusiform activity also increased when faces were fearful, in addition to the effect of attention. Such an additive pattern may suggest independent sources for these two influences (see Figure 2C). This demonstrates that face-responsive regions of human fusiform cortex can be modulated by emotional expression. This is consistent with enhanced responses of face-selective neurons to emotional faces versus faces with neutral expressions in the monkey (Sugase et al., 1999). Fusiform cortex receives prominent feedback projections from the amygdala (Amaral et al., 1992), and such connections could act to enhance processing of emotional stimuli detected by the amygdala (Armony and LeDoux, 2000; Morris et al., 1998a). Indeed, an enhancing influence from the amygdala upon the fusiform response for faces with emotional expressions could underlie the particular saliency of such stimuli, as observed in previous behavioral studies (Bradley et al., 1997; Vuilleumier and Schwartz, 2001) and as indicated in our study by the significant RT cost when faces at task-irrelevant locations had a fearful expression. These independent effects of emotion and attention on right fusiform activity suggest separate modulatory processes that can mediate competitive influences on visual processing in extrastriate areas.

Other Cortical and Subcortical Regions

A number of areas with direct reciprocal connections to the amygdala showed responses to fearful faces that interacted with the condition of attention, with activity increasing in some areas when emotional faces appeared at task-relevant locations, while in other areas activity increased when emotional faces appeared at to-be-ignored locations. The medial temporal cortex underneath the uncus showed enhanced activation to fearful expressions only with attention. Thus, despite its proximity to the amygdala, this cortical region exhibited a pattern of functional activity that was clearly distinct from the amygdala (see Figures 4C and 4D). This region constitutes a transitional zone between the neocortex of anterior parahippocampal gyrus and the allocortex of medial temporal structures and insula, which integrates emotional signals with other sensory information (Markowitsch et al., 1985; Moran et al., 1987). Activity in the uncus may influence bodily reactions and conscious subjective experience of fear, as observed during epileptic seizures involving this region (Bancaud, 1987; Wieser, 1983). Orbitofrontal cortex, also activated by fearful expressions, is implicated in processing emotional stimuli (Blair et al., 1999a; Breiter et al., 1996b; Dolan et al., 1996; Paradiso et al., 1999; Rolls, 1996; Taylor et al., 2000) and controlling behavior in response to different stimulus-reward contingencies (Rolls, 1996; Schultz et al., 2000). Increased activity in medial orbitofrontal areas when emotional faces were task irrelevant would support previous suggestions of a role in suppression of prepotent responses to affective stimuli (Freedman et al., 1998; Rolls, 1996).

Bilateral regions in anterior cingulate cortex (ACC) showed qualitatively different responses to fear, depending on the attentional condition, increasing in rostral ACC when faces were task irrelevant and in caudal ACC when faces were task relevant. Rostral and caudal

cingulate regions have been argued to subserve distinct affective and cognitive processes, respectively (Bush et al., 2000; Whalen et al., 1998a). The former is activated by affect-laden stimuli (Breiter et al., 1996b; Dolan et al., 1996; Elliott et al., 2000; George et al., 1993), aversive conditioning (Buchel et al., 1998, 1999; LaBar et al., 1998), and Stroop-like tasks involving emotional interference (Whalen et al., 1998a), whereas the latter is activated by divided attention and Stroop-like tasks involving abstract response rules (Bush et al., 1998; Carter et al., 1995, 2000; MacDonald et al., 2000). Here, rostral and caudal ACC showed opposite effects of attention within the same task. Note that our subjects had to resist attentional capture by fearful faces when required to judge the houses instead. Rostral ACC activation when salient emotional stimuli must be ignored would be consistent with a role in the control of attention to affective stimuli (Elliott et al., 2000) and evaluation of conflict for processing based on emotional stimulus value (Bush et al., 2000; Carter et al., 2000). The contrasting caudal ACC activation when emotional stimuli are attended suggests a more general role in arousal and engagement of selective attention toward relevant stimuli (Bush et al., 2000; Paus et al., 1998; Posner and Rothbart, 1998).

The ventral striatum was specifically activated when emotional faces at task-irrelevant locations had to be ignored. Receiving convergent inputs from the amygdala, medial orbitofrontal, and anterior cingulate cortex, with rich dopamine innervation, this subcortical structure is involved in motivation and flexible adaptation of behavior related to affective situations (Everitt et al., 1999; Robbins and Everitt, 1996; Schultz et al., 2000). This includes approach and avoidance learning (Everitt et al., 1999) and suppression of responses to reinforced stimuli that have become irrelevant (Ferry et al., 2000). Previous neuroimaging studies found ventral striatal activation when subjects were exposed to unpleasant visual stimuli (Paradiso et al., 1999) and when preexisting response tendencies had to be changed (Berns et al., 1997). The concomitant activation of ventral striatum and rostral cingulate cortex in our study may thus reflect motivational processes within striatal-cortical limbic circuits, engaged when task-irrelevant yet emotionally salient stimuli must be ignored.

Taken together, our findings delineate a network of interconnected brain areas allowing regulation of attention and responses to emotional stimuli. Whereas activity in the fusiform cortex (and additional areas) was significantly modulated by whether faces appeared at task-relevant versus irrelevant locations, the amygdala showed a consistent response to fearful faces, regardless of attentional conditions. This supports a role for the amygdala in preattentive responses to threatening stimuli. The further modulation of the right fusiform by fearful expression, over and above its modulation by attention, may be consistent with fast and obligatory responses in the amygdala triggering enhanced processing in fusiform cortex when faces have salient emotional expressions.

Experimental Procedures

Subjects

Twelve right-handed subjects (six females, six males; aged 23–35, mean 27.7-years-old) without past neurological or psychiatric his-

tory participated in the imaging study. All gave informed consent according to procedures approved by the Joint Ethics Committee of National Hospitals and Institute of Neurology. A structural MRI scan was taken during the same session as functional MRI scanning (see below) to exclude subjects with any structural abnormality.

Stimuli and Behavioral Task

All stimuli comprised displays of four pictures, with two faces and two houses arranged in vertical and horizontal pairs around fixation (see Figure 1). All pictures were black and white photographs (visual angle $3^\circ \times 5^\circ$) presented on a dark gray background and projected through a mirror mounted onto the headcoil. Faces or houses appeared equally often in the vertically or horizontally paired positions. In different sequences of trials, subjects were instructed to attend either to just the horizontal or just the vertical pair of stimuli and to indicate whether these stimuli were the same or different by pressing one of two keys with the right hand while ignoring the other stimulus pair. For both faces and houses, half of the pairs consisted of the same pictures, and the other half consisted of different pictures. Whether faces and houses in each pair included same versus different stimuli was varied independently. In addition, either both the faces had a neutral emotional expression or both had a fearful expression (half the trials each), with the two faces in a pair always having the same expression, regardless of whether they were the same or different individuals. Overall, there were ten different fearful faces taken from Ekman's series (adapted by D. Perrett and colleagues; see Calder et al., 1997) and ten different neutral faces, together with 20 different houses, all unfamiliar to the subjects. All possible combinations of stimulus position, same/different identity for faces or houses, and facial expression were equally counterbalanced across conditions and presented in random order.

The study was carried out in a single continuous scanning session that included two sequences of attention directed to horizontal positions and two sequences of attention to vertical positions (using different ABAB, BABA, ABBA, or BAAB series across different subjects). All four sequences included 52 trials (total 208 events). To instruct subjects to attend to horizontal or vertical stimulus pairs, each sequence began with a 2 s visual display consisting of four empty frames placed at the location of the stimuli, with either the two horizontal or the two vertical frames being highlighted (see Figure 1). Trials began with a central fixation cross for 1 s, followed by the four-picture display for 250 ms. Subjects were asked to maintain fixation centrally throughout the trials and attend covertly to the stimulus pair in just the relevant locations. The spatial arrangement of the display and the brief exposure time were specifically designed to ensure reliable central fixation, since eccentric eye movements toward one task-relevant stimulus would make the other less visible and so would be counterproductive for the subject's matching performance (see Duncan, 1980; Wojciulik et al., 1998). Moreover, eye movements were monitored online during scanning by an infrared eye tracker (ASL Model 504, Applied Science Group Co., Bedford, MA), custom adapted for use in the scanner. The eye position data were recorded for subsequent analysis offline (except in three subjects, due to technical failure in recording event-specific tags). Response RTs and accuracy in the matching task were also recorded. The intertrial interval varied randomly between 3.5 and 14.5 s, with a mean of 6.6 s (median 5).

MRI Scanning

MRI data were acquired on a 2T Siemens VISION system equipped with a head volume coil. Structural images were acquired with a T1-weighted sequence and functional images with a gradient echo-planar T2* sequence using BOLD (Blood Oxygenation Level Dependency) contrast. A total of 442 functional images were taken for each subject, each comprising a full brain volume of 32 contiguous axial slices (3 mm thickness). Volumes were acquired continuously with an effective repetition time (TR) of 3.17 s. All functional images were acquired within a single continuous scanning session, with eight dummy volumes at the beginning of the session, which were subsequently discarded, to allow for T1 equilibration effects.

Data Analysis

Data were analyzed using the general linear model for event-related designs in SPM99 (Wellcome Department of Cognitive Neurology,

London, UK; see <http://www.fil.ion.ucl.ac.uk/spm>) implemented in MATLAB (Mathworks Inc., Sherborn, MA) and run on a SPARC workstation (Sun Microsystems Inc., Surrey, UK). Scans were realigned, normalized, time corrected, and spatially smoothed by an 8 mm FWHM gaussian kernel using standard SPM methods (Ashburner and Friston, 1997; Friston et al., 1995). Low-pass and high-pass frequency filters were applied to the time series, and any time-related changes specific to each event type were included using a linear trend model (Buchel et al., 1999). Individual events were modeled by a synthetic hemodynamic response and its temporal derivative. Analysis of these data was performed using the general linear model to obtain parameter estimates of event-related activity at each voxel, for each condition and each subject, and to generate statistical parametric maps of the t statistic ($SPM\{t\}$) resulting from linear contrasts between different event conditions (Friston et al., 1995). These were then transformed to a normal distribution ($SPM\{Z\}$) and thresholded at $p = 0.05$, corrected for multiple comparisons across the whole brain for main effects. Interaction effects and other activations resulting from specific comparison of a subset of the events are reported at an uncorrected threshold of $p < 0.001$ for descriptive purposes. For the amygdala, a small volume correction (SVC; see Worsley et al., 1996) was applied where indicated, in keeping with our a priori hypothesis of amygdala involvement in the processing of fearful expressions. This region was defined by an 8 mm sphere centered on coordinates obtained for the amygdala from an entirely independent data set in a previous fMRI study (Buchel et al., 1999) and included the activation found in the current study (see Worsley et al., 1996). There were eight event types in the SPM model, resulting from the combination of all possible stimulus conditions (two attention conditions \times two face expression \times two stimulus positions). Analyses were performed on data collapsed across vertical and horizontal positions of attended stimuli, since this factor was irrelevant to our critical hypotheses and tests.

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