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Human Amygdala Responses to Fearful Eyes

J. S. Morris,*,†,‡ M. deBonis,§ and R. J. Dolan*,‖,[1]

*Wellcome Department of Imaging Neuroscience, 12 Queen Square, London WC1N 3BG, United Kingdom; †Institute of Cognitive Neuroscience, 17 Queen Square, London WC1N 3AR, United Kingdom; ‡Institute of Child Health, 30 Guildford Street, London WC1N 1EH, United Kingdom; §CNRS-U2R2M, Unité de Résonance Magnédicale, Paris-Sud, 63, rue Gabriel-Peri, 94276 Le Kremlin-Bicetre, France; and ‖Royal Free and University College Hospitals School of Medicine, Rowland Hill Street, London NW3 2DF, United Kingdom

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Fearful facial expressions evoke increased neural responses in human amygdala. We used event-related fMRI to investigate whether eye or mouth components of a fearful face are critical in evoking this increased amygdala activity. In addition to prototypical fearful (FF) and neutral (NN) faces, subjects viewed two types of chimerical face: fearful eyes combined with a neutral mouth (FN), and neutral eyes combined with a fearful mouth (NF). FF faces evoked specific responses in left anterior amygdala. FN faces evoked responses in bilateral posterior amygdala and superior colliculus. Responses in right amygdala, superior colliculus, and pulvinar exhibited significant time × condition interactions with respect to faces with fearful eyes (FF, FN) vs neutral eyes (NF, NN). These data indicate that fearful eyes alone are sufficient to evoke increased amygdala activity. In addition, however, left amygdala displayed discriminatory responses to fearful eyes in different configural contexts (i.e., in FF and FN faces). These results suggest, therefore, that human amygdala responds to both feature-specific *and* configural aspects of fearful facial expressions.

INTRODUCTION

Neuropsychological studies have shown that restricted human amygdala lesions produce selective recognition deficits for fearful facial expressions (Adolphs *et al.*, 1994; Calder *et al.*, 1996). Consistent with these data, functional neuroimaging experiments with healthy subjects have shown that viewing fearful faces elicits increased neural activity in amygdala (Morris *et al.*, 1996; Breiter *et al.*, 1996; Thomas *et al.*, 2001). However, despite this converging evidence of the amygdala's role in processing fearful expressions, the particular feature of fearful faces to which the amygdala is sensitive remains unknown.

Behavioral studies in monkeys indicate that the eyes are critical in threatening and fear-related facial displays (Nahm *et al.*, 1997). A simple stare is often the most effective stimulus in evoking fear or flight responses in nonhuman primates (Emery, 2000). The importance of eyes in conveying fear raises the question of whether the amygdala responds selectively to the eyes in fearful expressions. Evidence consistent with this conjecture is provided by electrophysiological studies in monkeys showing that amygdala cells have selective responses to direct eye gaze (Brothers *et al.*, 1990; Brothers and Ring, 1993). Human amygdala activity is also modulated by eye gaze: functional neuroimaging studies have shown that faces making direct eye contact evoke increased responses in right amygdala (Kawashima *et al.*, 1999), while covariation of response between amygdala and face-related neocortical regions is enhanced by faces with a direct gaze orientation (George *et al.*, 2001). However, the question of whether amygdala responses to fearful faces are specifically related to the eyes has not previously been addressed.

Detailed neural representation of faces appears to involve specialized regions of occipital, temporal, and prefrontal neocortex (Haxby *et al.*, 1994; Nakamura *et al.*, 1999). These neocortical regions are necessary for verbal labeling (e.g., naming, semantic categorization) and other *explicit* cognitive processing of faces (Haxby *et al.*, 1994). However, *implicit* processing of fearful expressions and other fear-related stimuli has been shown to engage subcortical visual structures, i.e., pulvinar and superior colliculus (Whalen *et al.*, 1998; Morris *et al.*, 1998, 2001). It has been proposed that pulvinar and superior colliculus may represent a parallel subcortical visual pathway by which simple, fear-relevant visual signals are able to reach the amygdala (Morris *et al.*, 1999). An analogous subcortical fear pathway involving auditory stimuli (comprising inferior colliculus, medial geniculate nucleus, and amygdala) has been described in rats (LeDoux, 1996). This low-resolution subcortical pathway may, therefore, provide a potential route by which neural responses to fearful eyes can reach the amygdala independently of the geniculostriate neocortical system.

[1] To whom correspondence should be addressed.

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In the present study, we used event-related functional magnetic resonance imaging (fMRI) to investigate neural responses elicited by chimerical emotional faces in healthy volunteers. The chimerical faces included fearful eyes combined with a neutral mouth (FN) and neutral eyes combined with a fearful mouth (NF). In view of our conjecture concerning the critical importance of eyes in fear processing, we predicted that FN (but not NF) faces would elicit enhanced amygdala responses. Additionally, in view of evidence implicating superior colliculus and pulvinar in processing fear-related stimuli (Morris *et al.*, 1999, 2001), we predicted that activity in these structures would also be greater for FN than for NF faces.

METHODS

Subjects. Twelve right-handed subjects (6 male, 6 female, mean age 24.6 years) were recruited by advertisement. Subjects had no history of neurological or psychiatric problems, and were not taking any medication at the time of study. All subjects gave informed consent and the study was approved by the local hospital ethics committee. Due to technical problems, the scanning session for one (male) subject was aborted prematurely. Data from this subject were excluded from the final analysis.

Stimuli. Grayscale images of 6 different individuals (3 male and 3 female) were taken from a standard set of pictures of facial affect (Ekman and Friesen, 1976). In addition to prototypical neutral (NN) and fearful (FF) expressions, two chimerical emotional faces (FN and NF) were produced for each of the 6 individuals by a computer graphical manipulation (morphing) technique. In the FN face, the upper part (i.e., predominantly the eyes) was contributed by the prototypical fearful expression; the lower part of the FN face (i.e., predominantly the mouth) was contributed by the prototypical neutral expression. In the NF face, the upper part (i.e., eyes) was neutral, while the lower part (i.e., mouth) was fearful. The chimerical faces were tested in a separate behavioral study prior to scanning. Twenty right-handed volunteers (11 males and 9 females) viewed the faces in a random order, each projected singly for 1-min onto a screen. None of subjects in this behavioral study participated in the later scanning experiment. Subjects were required to indicate which emotions they perceived in each face from an extensive list of 19 emotion words. Details of the morphing technique and the behavioral testing method have been described previously (de Bonis *et al.*, 1999).

EXPERIMENTAL DESIGN

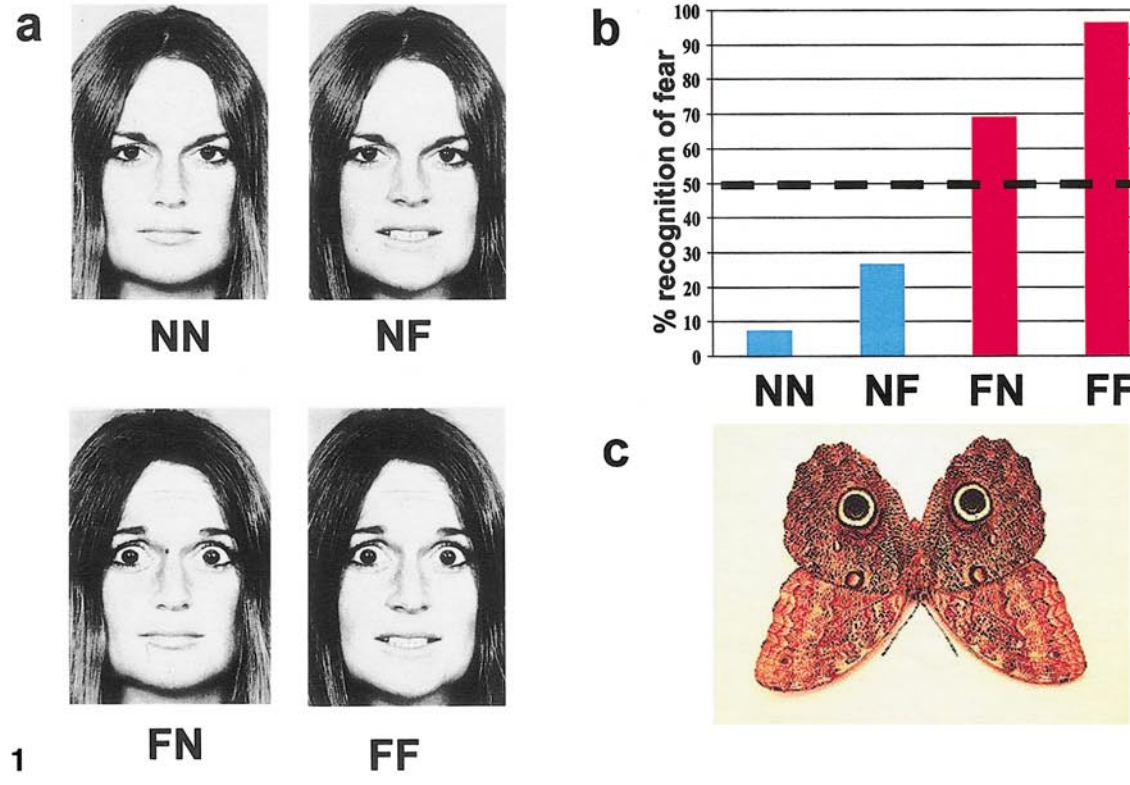
During scanning, subjects viewed the different face stimuli (all 6.6 × 4.4° in size) projected singly for 500 ms onto a screen placed above the head volume coil of the fMRI scanner. The interstimulus interval was randomly varied between 2.5 and 3.5 TRs (i.e., 10.25–14.35 s) to ensure that event onsets were evenly distributed in time across image slices. Each of the 6 faces under the 4 conditions (FF, NN, FN, and NF) was shown 4 times making a total of $6 \times 4 \times 4 = 96$ trials. Condition order was randomized. Subjects' explicit task was to decide the sex of each face, making responses by right-hand button presses.

Data acquisition. Neuroimaging data were acquired with a 2 T Magnetom VISION whole body MRI system equipped with a head volume coil. Contiguous multislice T2* weighted echoplanar images were obtained using a sequence that enhanced blood oxygenation level-dependent (BOLD) contrast (FOV = 192 mm, TE = 40 ms, flip angle = 90°). Volumes covering the whole brain (48 slices, slice thickness 2 mm) were obtained every 4.1 s (TR). A T1 weighted anatomical MRI was also acquired for each subject.

Data analysis. The fMRI data were analyzed using statistical parametric mapping with SPM99 (Friston *et al.*, 1995) (see also http://www.fil.ion.ucl.ac.uk/spm). Following realignment to the first volume, the functional (T2* weighted) scans were spatially normalized

FIG. 1. (a) Prototypical and chimerical faces. FF and NN are prototypical faces, fearful and neutral, respectively. FN is a chimerical face in which the upper half (eyes) is derived from the fearful prototype and the lower half (mouth) from the neutral prototype. NF is a chimerical face with neutral upper half and fearful lower half. (b) Plot of percentage scores for explicitly labeling each face condition (FF, FN, NF, NN) as "fearful". Twenty healthy volunteers were tested prior to scanning using all the face stimuli under the 4 conditions and a list of 19 emotion words. (c) Distinctive eye spots on the wings of the Owl butterfly (*Caligo memnon*). An example of how eye-like stimuli act as signals of danger or threat.

FIG. 2. (a) A statistical parametric map (SPM) showing an increased response in right posterior amygdala to fearful eyes (FF and FN faces) compared to neutral eyes (NN and NF faces). The SPM is displayed on orthogonal sections of a canonical MRI centered on the maximal voxel in right amygdala($x = 20, y = -8, z = -12$). A P value of 0.01 (uncorrected) was used as the threshold for displaying the contrast. (b) A graphical representation of mean BOLD (blood oxygen level dependent) fMRI signal change (as a percentage of global mean intensity) at the maximal right amygdala voxel ($x = -20, y = -8, z = -12$) under all 4 conditions. Bars represent 2 standard errors. (c) Peristimulus time histograms of adjusted event-related BOLD signals (as percentage change of global mean) under FF, FN, and NF conditions. Data are averaged over 2-s time bins. Responses to fearful eyes (FF and FN faces) are shown by bold red lines (adjusted data) and by thin red lines (fitted data). Responses to fearful mouth (NF faces) are shown by broken bold blue lines (adjusted data) and broken thin blue lines (fitted data).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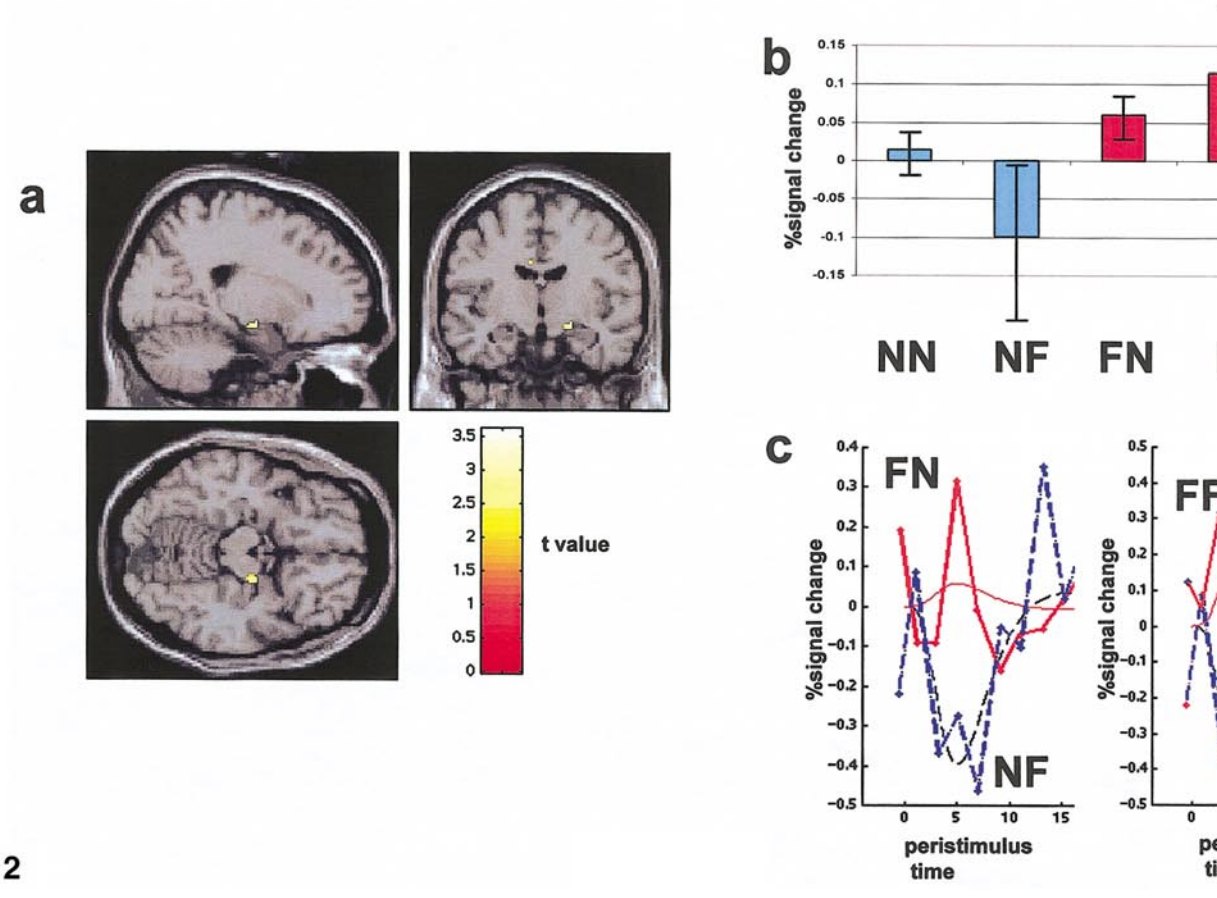
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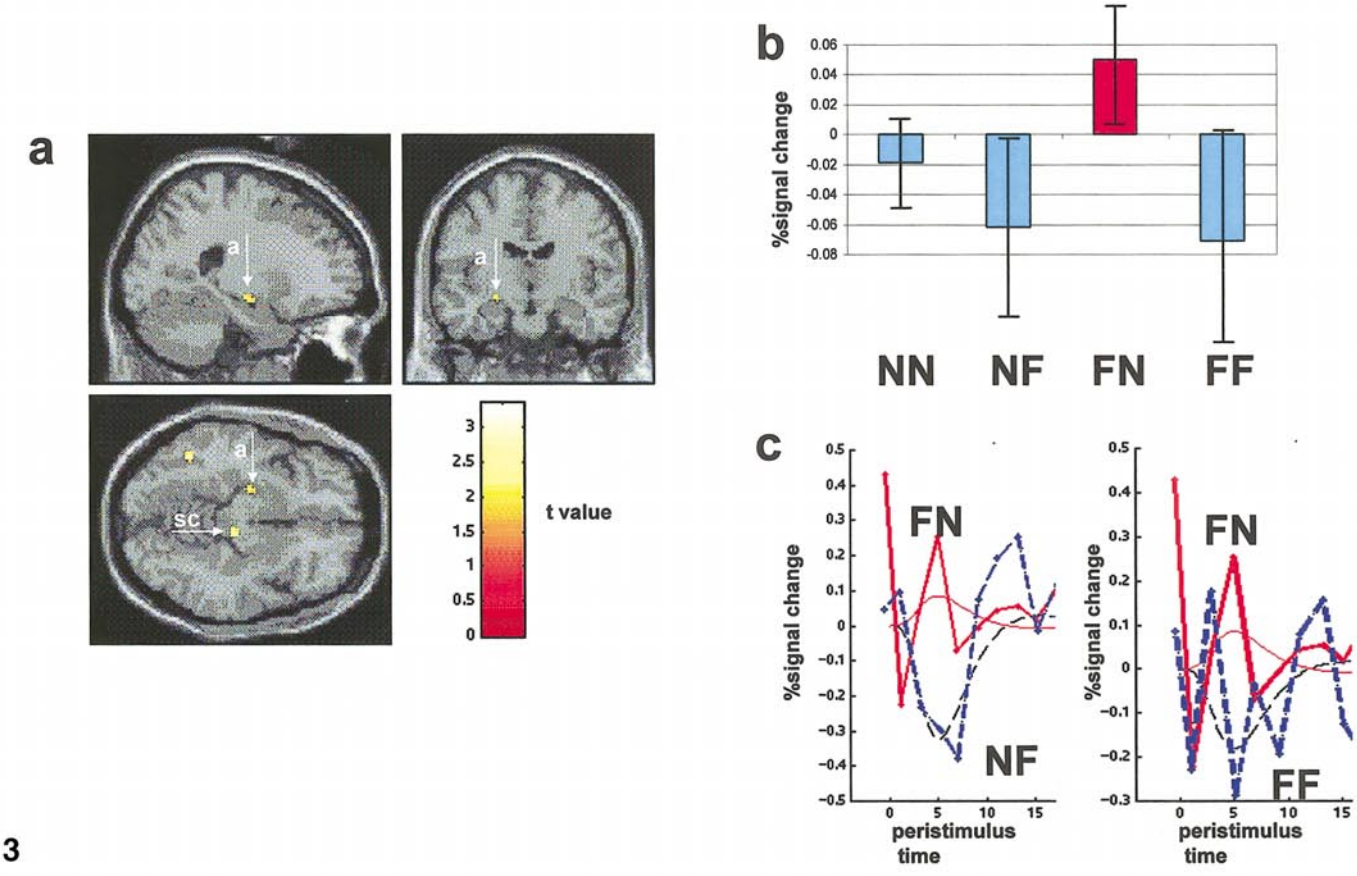
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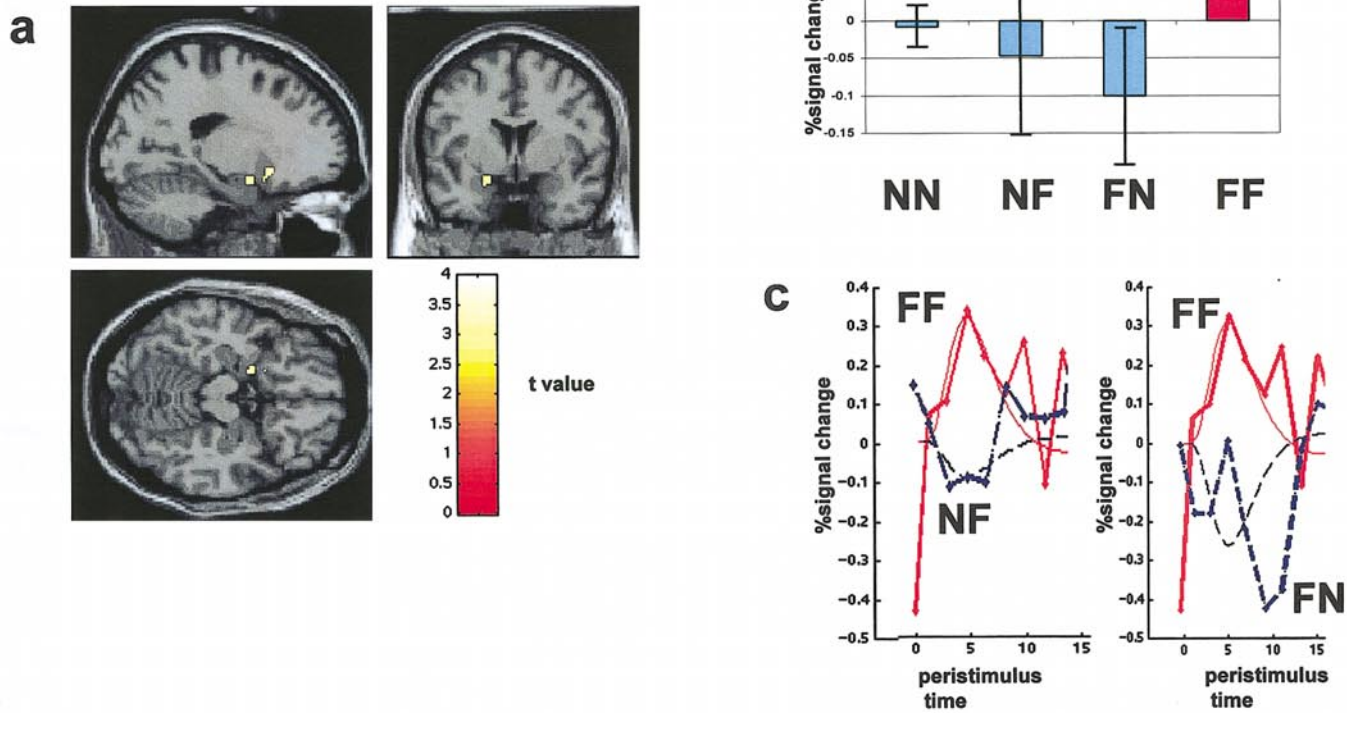
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to a standard template. The structural (T1 weighted) MRIs were coregistered to the functional scans and transformed into a standard stereotaxic space, based on a 152 subject average brain image supplied by the Montreal Neurological Institute. The functional data were smoothed using a 6-mm (full width at half maximum) isotropic Gaussian kernel to allow for corrected statistical inference. The final smoothness FWHM of the images was 8.3 × 8.0 × 7.9 mm. The evoked hemodynamic responses for the four different stimulus events were modeled as delta functions convolved with a synthetic hemodynamic response function and its temporal derivative (Josephs *et al.*, 1997).

Specific effects (e.g., (FF + FN) − (NF + NN)) were tested by applying linear contrasts to the parameter estimates for each event. The resulting t statistic at every voxel constitutes an SPM. Reported P values are corrected for the number of comparisons made within each a priori region of interest, i.e., amygdala, superior colliculus, and posterior thalamus (pulvinar) (Worsley *et al.*, 1996). The regions of interest were defined by spheres centered on the anatomical center of each structure, with radii of 8 mm for amygdala, 6 mm for superior colliculus, and 10 mm for pulvinar. Reported P values are for the voxel level significance. A fixed-effects group analysis was performed. In order to reflect intersubject variability and protect against individual subject bias, conjunctions of subject-specific contrasts were applied across all 11 subjects (Friston *et al.*, 1999). A time by event interaction analysis was also performed by multiplying the regressors for the stimulus events with a mean corrected exponential function having a time constant one-quarter of the session length. Here, contrasts tested for the difference of the interaction terms between the different conditions (i.e., (FF + FN) vs (NF + NN)).

RESULTS

Behavioral. Behavioral testing of the chimerical faces prior to scanning indicated a crucial role for the eyes in conveying fear. The FN (fearful eye) chimerical face was labeled fearful on 69% of trials, while only 26% of NF (fearful mouth) face presentations were described as fearful (Fig. 1). During scanning, all subjects performed at ceiling (>95% correct) on the behavioral sex decision task.

Neuroimaging. We first identified brain regions that responded to fearful eyes by contrasting responses to FF and FN faces with those to NF and NN faces. Right posterior amygdala (maximal voxel $x = 20$, $y = -8$, $z = -12$; $Z = 3.34$; $P < 0.001$, small volume corrected) showed increased mean responses to both FF and FN faces (Fig. 2, Table 1a). We next determined brain regions with specific responses to fearful eye chimerical faces by contrasting the activity evoked by the FN face with that elicited under the other three conditions (FF, NF, and NN). A posterior region of left amygdala (maximal voxel $x = -18$, $y = -10$, $z = -10$; $Z = 2.86$; $P < 0.05$, small volume corrected) and a ventral region of superior colliculus in the midbrain tectum (maximal voxel $x = 10$, $y = -22$, $z = -10$; $Z = 2.61$; $P < 0.05$, small volume corrected) showed a selective response to the FN face (Fig. 3, Table 1b). Finally, we identified brain regions responsive specifically to the prototypical fearful face, i.e., contrasted the BOLD signal evoked by FF with FN, NF, and NN faces. A region of left anterior amygdala (maximal voxel $x = -22$, $y = 4$, $z = -20$; $Z = 2.95$; $P < 0.05$, small volume corrected) exhibited selectively increased responses to the FF face (Fig. 4, Table 1c).

The analyses described above identify overall mean differences in evoked activity within the scanning session. However, previous neuroimaging studies have shown, especially with respect to amygdala activity, that neural responses to a particular stimulus are not necessarily fixed or constant, but may show dynamic, time-dependent changes (LaBar *et al.*, 1998; Buchel *et al.*, 1998). These dynamic changes in condition-related activity may not be revealed in a simple contrast of overall mean responses. We therefore conducted a fur-

FIG. 3. (a) A statistical parametric map (SPM) showing an increased response in left posterior amygdala and superior colliculus to FN faces compared to all other conditions. The SPM is displayed on orthogonal sections of a canonical MRI centered on the maximal voxel in left amygdala ($x = -18$, $y = -10$, $z = -10$). A P value of 0.01 (uncorrected) was used as the threshold for displaying the contrast. (b) A graphical representation of mean BOLD (blood oxygen level dependent) fMRI signal change (as a percentage of global mean intensity) at the maximal left amygdala voxel ($x = -18$, $y = -10$, $z = -10$) under all 4 conditions. Bars represent 2 standard errors. (c) Peristimulus time histograms of adjusted event-related BOLD signals (as percentage change of global mean) under FF, FN, and NF conditions. Data are averaged over 2-s time bins. Responses to FN and FF faces are shown by bold red lines (adjusted data) and by thin red lines (fitted data). Responses to NF faces are shown by broken bold blue lines (adjusted data) and broken thin blue lines (fitted data).

FIG. 4. (a) A statistical parametric map (SPM) showing an increased response in left anterior amygdala to prototypical faces (FF) compared to all other conditions (NN, FN, and NF faces). The SPM is displayed on orthogonal sections of a canonical MRI centered on the maximal voxel in left amygdala ($x = -22$, $y = 4$, $z = -20$). A P value of 0.01 (uncorrected) was used as the threshold for displaying the contrast. (b) A graphical representation of mean BOLD (blood oxygen level dependent) fMRI signal change (as a percentage of global mean intensity) at the maximal left amygdala voxel ($x = -22$, $y = 4$, $z = -20$) under all 4 conditions. Bars represent 2 standard errors. (c) Peristimulus time histograms of adjusted event-related BOLD signals (as percentage change of global mean) under FF, FN, and NF conditions. Data are averaged over 2-s time bins. Responses to prototypical fearful faces (FF) are shown by bold red lines (adjusted data) and by thin red lines (fitted data). Responses to NF and FN faces are shown by broken bold blue lines (adjusted data) and broken thin blue lines (fitted data).

ther analysis in which we modeled changes in condition-specific activity across time using an exponential function. Responses in superior colliculus (maximal voxel $x = 12$, $y = -28$, $z = -14$; $Z = 2.47$; $P < 0.05$, small volume corrected), posterior thalamus (maximal voxel $x = 22$, $y = -24$, $z = 6$; $Z = 2.59$; $P < 0.05$, small volume corrected), and right amygdala (maximal voxel $x = 22$, $y = -4$, $z = -20$; $Z = 1.9$; $P < 0.05$, small volume corrected) exhibited differential time-dependent changes under fearful (FF, FN) and neutral (NF, NN) eye conditions (Fig. 5, Table 1d). Responses to fearful eyes in these regions were initially enhanced relative to neutral eyes but then habituated across the scanning session (Fig. 5).

DISCUSSION

The present findings provide evidence that fearful eyes alone are sufficient to evoke increased neural responses in human amygdala. These neuroimaging data accord, therefore, with behavioral findings in both monkeys (Nahm *et al.,* 1997; Emery, 2000) and humans (de Bonis *et al.,* 1999) that eyes have a critical role in conveying fear in facial expressions. In addition to amygdala, other subcortical visual structures, notably the superior colliculus and posterior thalamus, were also implicated in processing fearful eyes (Figs. 3 and 5). The involvement of these subcortical structures supports the proposal that neural signals relating to fearful eyes may access the amygdala via a pathway that bypasses specialized visual areas in occipital and temporal cortices (Morris *et al.,* 1999).

The superior colliculus receives its visual input primarily from magnocellular retinal ganglion cells with large, rapidly conducting axons (Schiller and Malpeli, 1977). The principal projection of the magnocellular pathway is to the pulvinar nucleus in the posterior thalamus (Benvenuto and Fallon, 1975). Direct projections from pulvinar to the amygdala have been reported in monkey (Jones and Burton, 1976) and rat (Linke *et al.,* 1999). The magnocellular pathway has fewer cells (ca 10^5 in primates) than the neocortical parvocellular pathway (ca 10^6 in primates) and thus has a lower spatial resolution in representing the visual field (Weiskrantz *et al.,* 1974; Miller *et al.,* 1980; Barbur *et al.,* 1980). The colliculo-pulvinar-amygdala system, therefore, may be capable of detecting simple, stereotypical threat stimuli but not possess the spatial resolution necessary for detailed object categorization and discrimination. High-resolution representation of visual objects appears to involve specialized regions of occipito-temporal neocortex that receive visual signals primarily via the geniculostriate parvocellular pathway (Haxby *et al.,* 1994; George *et al.,* 2001).

The importance of eyes as potentially threatening stimuli is not restricted to primates. Species as diverse as mice (Topal and Csanyi, 1994), birds (Jones, 1980), iguanas (Burger *et al.,* 1991) lemurs, and jewelfish (Coss, 1978, 1979) have been shown to display more avoidance behavior to horizontally oriented schematic eyes (e.g., two black circles) than to the same stimuli in a vertical orientation or to nonethological stimuli such as squares. Several species of butterfly have evolved eye spots on their wings that act as threatening deterrent signals to potential predators (Fig. 1c). These phylogenetic observations suggest that the neural mechanisms involved in detecting and processing "eye-like" stimuli as signals of threat and danger have been highly conserved across different species. Homologues of amygdala, superior colliculus, and pulvinar are present in birds and reptiles as well as in mammals, and therefore these subcortical visual structures appear more likely candidates to subserve an evolutionarily ancient fear system than more recently evolved visual neocortex.

Although fearful eyes (compared to fearful mouth) appear to be *sufficient* to evoke increased responses in human amygdala, our present results also indicate that the amygdala (especially in the left hemisphere) is responsive to features other than eyes in fearful expressions. Activity in left amygdala clearly showed discriminatory responses to prototypical fearful faces (FF) and chimerical faces (FN) (Figs. 3 and 4). The specifically increased response to FF faces (relative to FN faces) in left anterior amygdala suggests that this region is sensitive to the configural *conjunction* of fearful eye and fearful mouth (Fig. 4). By contrast, a separate region in left amygdala, posterior to the FF-selective area, showed a selective response to FN faces (Fig. 3). These segregated, discriminatory responses indicate a considerable degree of both specificity and complexity in left amygdala processing of fearful facial expressions. It is notable that several neuroimaging studies have reported left lateralization of amygdala responses to fearful faces (Morris *et al.,* 1996; Breiter *et al.,* 1996; Thomas *et al.,* 2001). Separate anterior and posterior foci in left amygdala responsive to fearful faces have also been reported previously (Breiter *et al.,* 1996). The significance of this anterior-posterior segregation, and its relationship to the known functional nuclear architecture of amygdala is unclear.

Whereas configural, conjunctive processing of fearful facial expressions was evident in left amygdala, simple, context-independent responses to fearful eyes were observed in right amygdala, superior colliculus, and pulvinar (Figs. 2 and 5). It is notable that right amygdala, superior colliculus, and pulvinar have also been implicated in mediating responses to backwardly masked fear conditioned faces that are not explicitly perceived by subjects (Morris *et al.,* 1998, 1999). Fear-related activity in right amygdala, superior colliculus, and pulvinar has also been evoked by fearful faces presented in the blind visual field of a patient (GY) with a striate cortex lesion (Morris *et al.,* 1999, 2001).

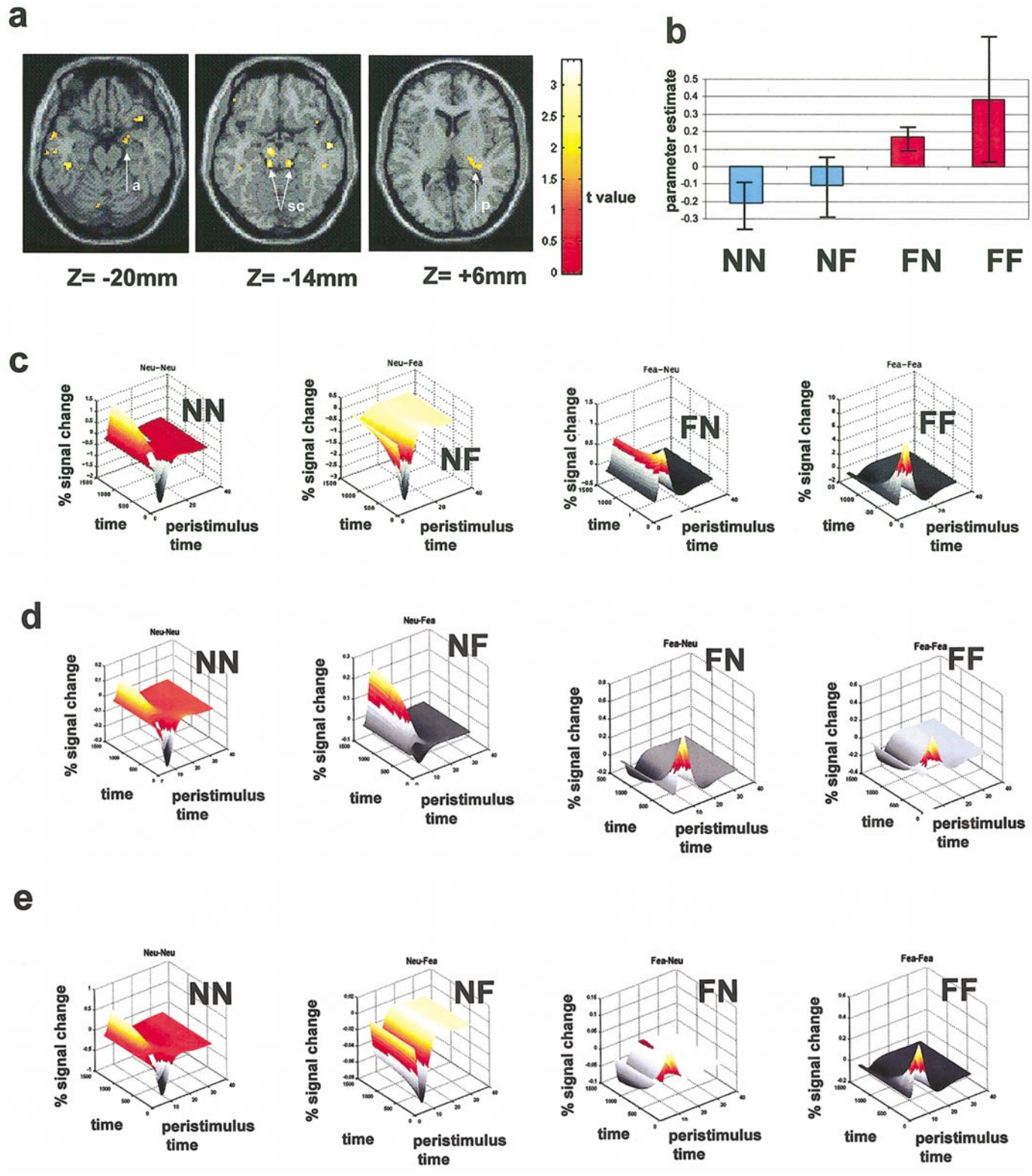

FIG. 5. (a) A statistical parametric map (SPM) showing regions of right amygdala (a) superior colliculus (sc), and pulvinar (p) where responses showed a time-dependent interaction in the comparison of fearful eye (FF and FN) and neutral eye (NF and NN) conditions. The SPM is displayed on transverse sections ($z = -20$, -14, and $+6$ mm) of a canonical MRI. A P value of 0.01 (uncorrected) was used as the threshold for displaying the contrast. (b) A graphical representation of parameter estimates for time-dependent changes in response at the maximal superior colliculus voxel ($x = -12$, $y = -28$, $z = -14$) under all 4 conditions. Bars represent 2 standard errors. (c–e) 3-D plots of time-dependent changes in event-related hemodynamic responses. Time-dependent changes in response were modeled by an exponential function with a time constant one-quarter of the session length in (c) superior colliculus ($x = -12$, $y = -28$, $z = -14$), (d) pulvinar ($x = 22$, $y = -24$, $z = 6$), and (e) right amygdala ($x = 22$, $y = -4$, $z = -20$).

TABLE 1

Regions Selectively Activated in the Contrasts of (a) (FF + FN) − (NF + NN), Fearful Eyes vs Neutral Eyes; (b) FN − (FF + NF + NN), Fearful Eye/Neutral Mouth Chimerical Face vs Rest; (c) FF − (FN + NF + NN), Prototypical Fearful Face vs Rest; (d) (FF + FN) − (NF + NN), Fearful Eyes vs Neutral Eyes Time × Condition Interaction

Area	Coordinates (x,y,z)	Z score
(a) (FF + FN) − (NF + NN)		
Right posterior amygdala	20, −8, −12	3.34
(b) FN − (FF + NF + NN)		
Left posterior amygdala	−18, −10, −10	2.86
Superior colliculus	10, −22, −10	2.61
(c) FF − (FN + NF + NN)		
Left anterior amygdala	−22, 4, −20	2.95
(d) (FF + FN) − (NF − NN) time × condition interaction		
Superior colliculus	12, −28, −14	2.47
Posterior thalamus (pulvinar)	22, −24, 6	2.59
Right amygdala	22, −4, −20	1.9

Note. Coordinates of maximal voxels and associated Z values are shown. All activations are significant at $P < 0.05$ (small volume corrected).

The parallel between these previous studies (Morris *et al.*, 1999, 2001) and our present neuroimaging data is intriguing. One possible interpretation is that visual processing of eye-related fear cues remains intact in the low-resolution colliculo-pulvinar-amygdala pathway following disruption of the high-resolution geniculostriate pathway by lesions or backward masking.

Our present findings of conjunctive, context-dependent left amygdala responses (Fig. 3 and 4) and feature-specific right amygdala responses (Fig. 2) may also have more general theoretical interest. Results from previous behavioral studies using similar emotional chimerical faces have lead to the proposal of a two-process probabilistic theory of emotion perception involving nonlinear combination of facial features (de Bonis *et al.*, 1999). According to the theory, the upper and lower halves of the face represent separate components of emotional expression. Although the upper face is crucial in conveying fear, the emotion expressed in the lower face significantly affects the overall explicit emotional perception. Thus, faces with both fearful upper and lower halves (FF) have a 0.97 probability of being explicitly perceived as fearful; faces with fearful upper and neutral lower halves (FN) have a 0.69 probability of being perceived as fearful; however, faces with fearful upper and happy lower halves (FH) have only a 0.22 probability of being explicitly labeled as fearful (de Bonis *et al.*, 1999). On the basis of these behavioral findings, it has been proposed that the perception of emotional expressions depends on an initial processing of individual facial features followed by a nonlinear association of the different components (de Bonis *et al.*, 1999). The differential amygdala responses to fearful facial features observed in the present study may provide evidence, therefore, of the underlying neural mechanisms in this two-process conjunctive model of facial emotion perception.

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