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Parallel amygdala and inferotemporal activation reflect emotional intensity and fear relevance

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Much research demonstrates that emotional stimuli prompt increased amygdala and visual cortical activation. Here we measure functional activity in the visual cortex and amygdala with fMRI while selected fearful and control participants view a range of neutral, emotionally arousing, and fear-relevant pictures. BOLD signal in the amygdala and inferotemporal visual cortex closely covaried during emotional picture viewing, increasing systematically with rated picture arousal. Furthermore, fearful individuals reacting to specific fear cues show parallel, heightened activation in these two structures compared with non-fearful controls. The findings suggest an individually-sensitive, positive linear relationship between the arousing quality of visual stimuli and activation in amygdala and ventral visual cortex, supporting the hypothesized functional connectivity described in the animal model.

Keywords: Emotion; Attention; Functional imaging; Visual cortex; Amygdala; Human

It has been repeatedly demonstrated that the human amygdala is recruited in the processing of emotional stimuli (see Zald, 2001). In the animal model, amygdala activation triggers a cascade of physiological mobilization and vigilance toward, or escape from, the triggering event (Davis, 1992; Everitt et al., 2003; LeDoux, 1990). The psychophysiology of human emotional stimulus processing is highly consistent with patterns of reactivity seen in the animal model, including peripheral mobilization, startle reflex modulation, and directed or "motivated" attention (Bradley, 2000; Lang et al., 2000).

In the primate, a cortical site of dense amygdala connectivity is the inferior temporal visual cortex (Amaral et al., 1992; Shi and Davis, 2001; Spiegler and Mishkin, 1981). Indeed, the ventral visual cortex shows heightened activity during the processing of emotional relative to neutral visual stimuli in humans (Bradley et al., 2003; Breiter et al., 1996; LaBar et al., 2001a,b; Lang et al., 1998; Sabatinelli et al., 2004; Sprengelmeyer et al., 1998) and has been clearly implicated in the processing of color, faces, and semantic categories (Bartels and Zeki, 2000; Chao et al., 1999; Gauthier et al., 2003; Grill-Spector et al., 2004). Furthermore, recent diffusion tensor imaging work has identified a direct white matter tract between secondary visual and anterior temporal cortex (Catani et al., 2003). It is therefore reasonable to posit that inferior temporal visual effects associated with emotional picture processing may be related to activation in the amygdala.

Here we investigate the relationship between amygdala and ventral visual system activity using fMRI while volunteers view a broad range of affective and neutral pictures. We expect that both amygdala and ventral visual activity will show sensitivity to the rated affective intensity of picture stimuli. A stimulus set covering a range of affective intensities, with the potential to elicit a corresponding range of functional activity, provides more convincing support for interrelated amygdala and inferior temporal activity than a simple emotional-versus-neutral contrast.

Additional evidence of interrelated amygdala and inferior temporal activity is provided by a between-subjects manipulation of stimulus fear relevance. Small animal phobia offers an efficient means of investigating strong defensive reactivity in the laboratory, as these participants show unusually strong and reliable fear potentiated startle, as well as enhanced peripheral reactivity to fear-relevant pictures (Cuthbert et al., 2003; Hamm et al., 1997; Sabatinelli et al., 2001). In the current study, if amygdala and inferior temporal visual cortex are functionally associated, we expect an increase in amygdala activity in fearful subjects during fear-relevant picture processing (Birbaumer et al., 1998; Dilger et al., 2003; Schneider et al., 1999) to be accompanied by a corresponding increase in inferior temporal activity relative to a unselected sample of volunteers.

Method

Participants

Eighteen female volunteers (18.5 years, SD 0.7) participated to fulfill a requirement of a psychology course. All participants were

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screened for claustrophobia, and reported remaining awake and comfortable throughout the procedure. Half of the sample were selected after reporting elevated snake fear on a prescreening inventory and were included in a high snake fear group after completing a 30-item snake fear questionnaire (SNAQ; Klorman et al., 1974, mean 18; SD 3; 90th percentile for women). The remaining participants were unselected and reported common levels of fear (SNAQ mean 5, SD 3).

Materials

Stimuli consisted of 60 color pictures (Lang et al., 1999) divided into 6 content categories, including complex neutral scenes, neutral people, non-threatening animals, snakes, erotica, and mutilations. Each picture category was then divided into two blocks of 5 pictures each, statistically matched for normative ratings of valence and arousal (Lang et al., 1999).[1] Thus, 2 distinct but equivalent sets of 30 pictures depicting the 6 content categories were presented in two separate runs of data collection. IAPS normative ratings (Lang et al., 1999) for arousal (9 = most arousing, 1 = least arousing) averaged 2.95, 3.57, 4.43, 6.17, 6.20, and 6.65, and for valence (9 = most pleasant; 1 = most unpleasant) averaged 3.70, 4.90, 7.84, 5.06, 6.77, and 1.85. Picture stimuli were also balanced by category to be statistically equivalent in brightness, contrast, mean spatial frequency, and 90% quality JPEG file size (Junghoefer et al., 2001).

Procedure

Pictures were rear-projected (Kodak Ektapro 9000), subtending a 20° visual angle, on a translucent slide screen situated at the subject's feet, visible via a coil-mounted mirror. Foam pads within the head coil limited head motion. Picture presentation was time-locked to functional image acquisition by a PC-compatible computer interfaced to the MR scanner, running VPM stimulus control software (Cook et al., 1987). Participants were asked to remain still and fixate on a laser point at the center of the slide screen throughout the alternating picture (6 s) and dark-screen (12 s) intervals. The picture viewing session was divided into two 9-min blocks of 30 pictures each, separated by a rest period of approximately 1 min.

Data acquisition

The scanning sequence began with the acquisition of a 90 slice sagittal scout set using a standard T1-weighted sequence on a 3 T GE Signa scanner. This volume was used to prescribe the location of two 10-slice coronal functional prescriptions acquired using a T2*-weighted gradient echo, echo planar sequence (64 × 64, 20 cm FOV, 90° flip angle, TE 40 ms, TR 1500 ms). To provide sufficient signal quality in anterior subcortical areas prone to susceptibility artifact, two separate functional prescriptions were sampled. In the posterior visual cortex, where susceptibility artifact is minimal, a 10-slice coronal prescription originated 1 cm anterior to the occipital pole and extended anteriorly (5 mm slices, 1 mm gap), replicating coverage used previously (Bradley et al., 2003). In anterior subcortical areas, a 10-slice coronal prescription was centered on the anterior commissure and thinner slices were specified (3.5 mm, 0.5 mm gap) to improve signal quality (Chen et al., 2003; Merboldt et al., 2001), while maintaining a reasonably fast sampling rate (1500 ms). If both visual and subcortical areas were collected in a single thin-slice coronal prescription, a prohibitively long TR (~12 s) would be necessary. The 2 prescriptions were used alternately in block 1 or block 2 across participants such that order of picture block presentation and prescription acquisition were counterbalanced.

Data preprocessing and analysis

Trials with head motion greater than 1 mm (<2%) were removed from the time series. The raw data were then slice-time corrected, linearly detrended, highpass filtered at 3 Hz, spatially filtered with a 2 voxel (6.25 mm) full-width at half maximum kernel, and coregistered with each participant's structural volume using Brain Voyager 4.6 (BrainInnovation, Maastrict, The Netherlands). These volumes and coregistered functional data were then transformed into standardized coordinate space (Talairach and Tournoux, 1988).

Analyses focus on the relationship of inferior temporal visual cortex and amygdala BOLD signal. For each participant and each block, an ANOVA identified voxels following the timecourse of picture presentation after convolution with a hemodynamic response function. These individual functional maps were thresholded at an uncorrected alpha level of $P < 0.000001$ and 100-ml regions of interest were sampled in each participant's significant voxels within the left and right amygdala, and left and right inferotemporal cortex. ROI signal change scores were calculated from 6 to 13.5 s after picture onset (the peak of signal change) using the scan preceding picture onset as baseline. These scores were entered into a multivariate ANOVA to establish the sensitivity of BOLD signal change in the inferotemporal cortex and amygdala to picture category, snake fearfulness, and hemisphere.

A separate analysis compared the activity of the 2 ROIs across picture categories to investigate the correspondence of signal change in these structures. This comparison depends on a consistent activation of these structures to specific classes of visual scenes for any given participant, as the pattern of activity across the 6 picture contents in the amygdala is driven by one block of 30 pictures, while the pattern of activity in inferotemporal cortex is driven by a different block of 30 pictures. For comparison of amygdala and inferotemporal cortex ROIs, these scores were z transformed according to each participant's signal mean and standard deviation across all trials. Because these areas were sampled in different acquisitions, connectivity analyses such as those described by Buchel and Friston (2001) were not feasible.

To demonstrate emotional intensity differences in both amygdala and inferotemporal cortex across the sample (Fig. 2), a contrast of functional maps during arousing picture perception (erotica,

[1] International Affective Picture System (IAPS) stimuli used in this experiment include erotica, 4611, 4641, 4658, 4659, 4666, 4676, 4677, 4680, 4681, and 4690; non-threatening animals, 1440, 1460, 1463, 1530, 1540, 1590, 1610, 1710, 1750, and 1920, neutral people; 2191, 2214, 2215, 2372, 2383, 2393, 2394, 2480, 2595, and 7550; neutral scenes, 5740, 7036, 7041, 7050, 7100, 7130, 7161, 7224, 7234, and 7500; snakes, 1010, 1019, 1050, 1052, 1090, 1110, 1111, 1113, 1114, and 1120, and mutilations; 3000, 3051, 3060, 3068, 3069, 3071, 3100, 3101, 3266, and 3400. The IAPS and technical manual are available on CD-ROM and as photographic slides, available on request from the authors at the NIMH Center for the Study of Emotion and Attention, Box 100165 HSC, University of Florida, Gainesville, FL 32610-0165, USA.

mutilation) and neutral picture perception (complex neutral scenes, neutral people) was conducted for the anterior ($t > 2.60$, $P < 0.01$) and visual cortex prescriptions ($t > 8.00$, $P < 0.000001$). Setting the same threshold for anterior and visual cortical prescriptions for this picture processing task led to overwhelming significant activity in the visual system relative to amygdala activity, and thus comparable thresholds were chosen for display purposes.

Results

Region of interest (ROI) locations

Mean (SD) Talairach coordinates of amygdala and inferior temporal ROIs are $x = \pm 22$ (5), $y = -6$ (4), and $z = -14$ (5) for the amygdalae, and $x = \pm 31$(6), $y = -54$(3), $z = -16$(5) for inferior temporal cortex, in the region of the fusiform gyrus. All participants showed significant activity in the left and right inferotemporal cortex during picture perception. All participants also showed significant picture-prompted activity in the left amygdala, while 83% (15/18) showed significant activity in the right amygdala. Analyses including hemisphere as a factor yielded no significant interactions in either ROI, thus data were collapsed across hemisphere and analyses were recalculated.

Amygdala ROI

Signal change in the amygdala ROI differed across picture content according to fear group (Content X Fear $F(5,12) = 4.77$, $P < 0.05$; Control X Fear linear $F(1,16) = 8.00$, $P < 0.05$). Both groups showed reliable effects of picture content (Control $F(5,4) = 58.37$, $P < 0.01$; Fearful $F(5,4) = 31.85$, $P < 0.01$), as well as significant linear trends (Control $F(1,8) = 235.19$, $P < 0.01$; Fearful $F(1,8) = 13.69$, $P < 0.01$). Control participants showed the greatest amygdala activity when viewing erotic and mutilation pictures, relative to other picture contents, while snake fearful participants showed an equivalently elevated signal when viewing erotic, mutilation, and snake pictures. A between-group comparison of signal change in the amygdala during snake picture perception showed greater activity in snake fearful, relative to control, participants ($F(1,16) = 5.86$, $P < 0.05$). Fig. 1 illustrates the pattern of amygdala BOLD signal change across all picture contents for control and snake fearful groups.

Inferior temporal ROI

Greater signal change was elicited in inferotemporal ROIs during perception of affectively arousing, relative to neutral pictures (Content $F(5,12) = 15.47$, $P < 0.001$; linear trend $F(1,16) = 63.60$, $P < 0.001$). In the snake fearful group, greater inferotemporal ROI signal change was elicited while viewing snake pictures, relative to pictures of neutral people ($F(1,8) = 12.04$, $P < 0.01$), while the control group did not show a difference ($F(1,8) = 1.89$, $P > 0.20$).

A planned group contrast showed that fearful participants demonstrated greater inferotemporal activation during snake picture perception than did control participants ($F(1,16) = 5.40$, $P < 0.05$). A comparison of BOLD signal across snake and (highly aversive) mutilation picture contents across fear and control groups yielded a significant interaction in inferotemporal ($F(1,16) = 8.72$, $P < 0.01$) and amygdala ROIs ($F(1,16) = 17.65$, $P < 0.01$), demonstrating greater signal change in the control group during mutilation relative to snake picture presentations, while snake fearful subjects showed equivalently enhanced activation across snake and mutilation pictures.

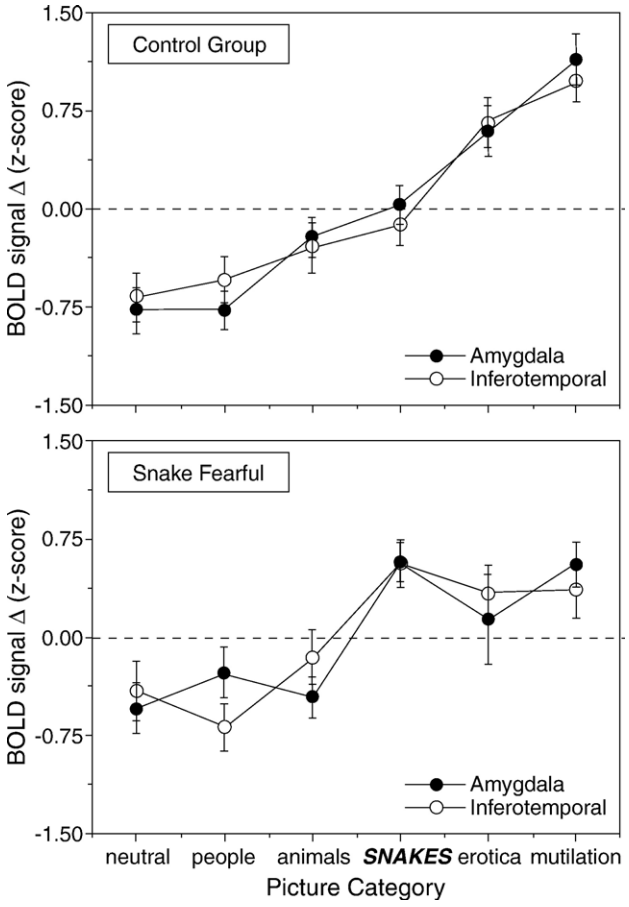

Fig. 1. Effects of emotional intensity and fear relevance on amygdala and inferior temporal ROIs. Standardized BOLD signal change in the Control group (top panel) and snake fearful group (bottom panel) for amygdala (filled circles) and IT cortex (open circles) ROIs, according to picture category along the abscissa, ordered (left to right) according to increasing rated arousal (Lang et al., 1999). Error bars represent standard errors of the mean (SEM).

Amygdala-inferotemporal ROI comparison

BOLD signal change in the amygdala and inferotemporal cortex yielded a strong linear correlation across picture contents, $R = 0.97$, $P < 0.01$. For the control group specifically, the two ROIs showed a correlation of $r = 0.98$, $P < 0.001$, while ROIs from the fearful group correlated at $R = 0.85$, $P < 0.05$. The difference in correlation strength between fearful and control groups was not significant ($z = 1.80$). Additionally, activity in the amygdala and lateral occipital gyrus showed a nonsignificant ($P = 0.20$) correlation of $R = 0.60$; this relationship was significantly weaker than between amygdala and inferotemporal areas ($t = 5.63$, $P < 0.001$). Furthermore, BOLD signal change observed in the caudate, while significantly active during picture processing, did not correlate with activity in inferotemporal cortex ($R = 0.23$, ns).

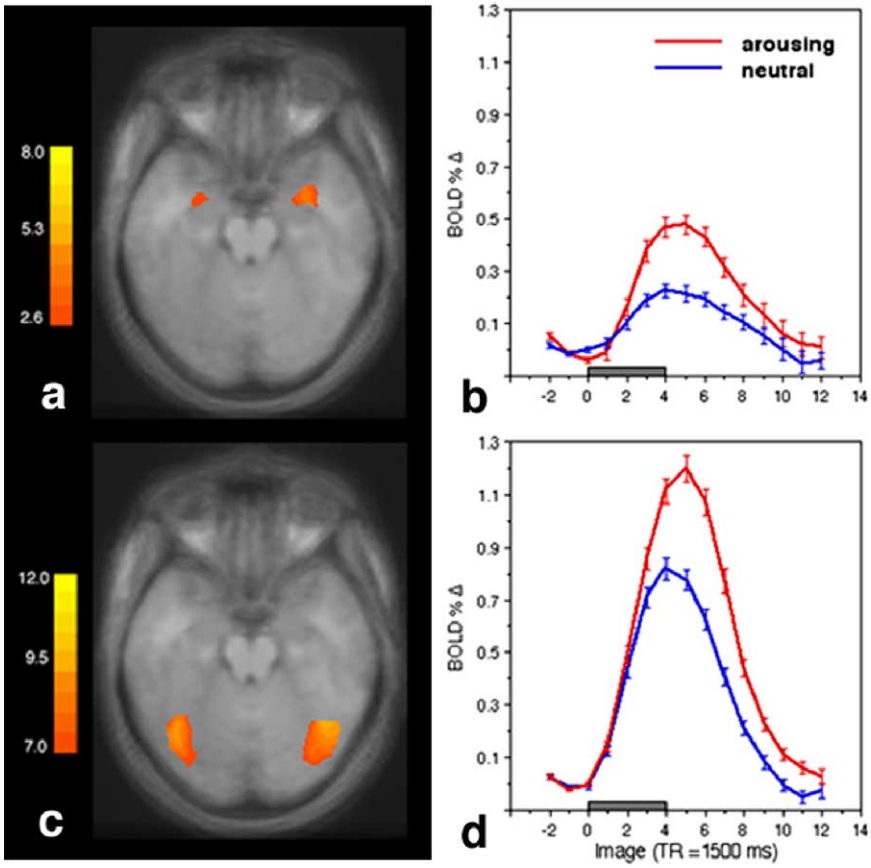

Fig. 2. Effects of emotional intensity on functional activity in amygdala and inferotemporal cortex. Greater signal change was found in bilateral amygdala (a) and inferior temporal visual cortex (c) during emotionally arousing picture perception (erotica, mutilation) relative to neutral picture perception (complex neutral scenes, neutral people), Talairach $z = -17$. Average event-related signal change in amygdala (b) and inferotemporal cortical (d) ROIs shows the timecourse and degree of signal enhancement during emotionally arousing (red lines) versus neutral picture (blue lines) perception, ±SEM.

Fig. 2 depicts the heightened BOLD signal change in the bilateral amygdala and inferotemporal cortex during highly arousing (erotica and mutilation) relative to neutral (neutral people and scenes) picture processing. Peak activity (4500–9000 ms after picture onset) in the amygdalae was reliably greater (0.43%) during arousing, relative to neutral (0.20%) picture presentations ($F(1,16) = 21.59$, $P < 0.001$), and did not significantly differ as a function of fear group (Arousal X Fear Group $F(1,16) = 1.96$, ns). Inferotemporal signal also showed reliable enhancement during arousing (1.00%) relative to neutral (0.67%) pictures ($F(1,16) = 46.62$, $P < 0.001$) and did not significantly differ as a function of fear group (Arousal X Fear Group $F(1,16) = 1.57$, ns).

Discussion

Viewing arousing pictures (both appetitive and aversive) led to greater BOLD signal in the bilateral inferotemporal cortex and bilateral amygdala, increasing linearly with the rated affective arousal of the picture categories (Lang et al., 1999). In the amygdala, peak activity during arousing picture perception doubles relative to neutral pictures (Fig. 2b). The increase in inferotemporal activity during arousing picture perception is also sizable (Fig. 2d), highlighting the role of motivational relevance in directing attention and perceptual processing.

Amygdala BOLD signal was similarly sensitive to fear relevance. Participants reporting elevated snake fear were more reactive while viewing pictures of snakes than unselected volunteers (Fig. 1). Specific-fear relevant amygdala activity has been inconsistently identified in previous neuroimaging studies. Several PET studies investigating small animal phobia have not found differential amygdala activity during exposure to fear-relevant cues (Fredrikson et al., 1993; 1995; Rauch et al., 1995), perhaps due to limited temporal and spatial resolution. Although fMRI offers greater temporal and spatial resolution than PET, some investigations of small animal phobia have also not reported amygdala activity during fear cue exposure (Paquette et al., 2003; Wright et al., 2003). Significantly, when functional activity is sampled with comparatively small voxels volumes (<30 ml), amygdala activity is selectively elicited by fear relevant stimuli (Birbaumer et al., 1998; Dilger et al., 2003; Schneider et al., 1999). It may be that the acquisition of thin functional slices, coupled with coronal (as done here) or sagittal acquisition planes, is required to minimize subcortical BOLD signal loss due to susceptibility artifact (Chen et al., 2003; LaBar et al., 2001a,b; Merboldt et al., 2001) and may enhance the probability of observing significant amygdala activity.

Clear similarities in the pattern of amygdala and inferotemporal cortex BOLD signal change across picture categories were obtained in both control and snake fearful participants. Pictures

depicting emotionally arousing content prompted the greatest signal change in both ROIs and showed specific sensitivity to individual differences in fear relevance. These data confirm prior indications of amygdala–extrastriate correspondence (Morris et al., 1998; Pessoa et al., 2002) and provide new evidence for the functional integration of these structures in emotional stimulus processing. It is significant that the correspondence identified between amygdala and inferotemporal cortical activity does not depend on specific pictures, but represents a more meaningful structural covariation of semantic stimulus classes. That is, the experimental design was such that the amygdala and inferotemporal data, for individual participants, were not collected at the same time, or from the same pictures. Rather, two matched picture sets were used, with each subject viewing a different set during measurement of anterior and posterior sites. Thus, the activation pattern–the high covariation–is not picture specific, but was determined more broadly by the affective meaning of the emotional contents (erotic, fear-inducing, etc.).

In summary, several novel findings of the current investigation merit reemphasis. The present results show a dimensional relationship between calibrated increases in the emotional intensity of stimuli (judged arousal) and the amplitude of functional activation in both inferotemporal cortex and amygdala. That is, a strong linear function is established between standardized, evaluative judgments of appetitive and aversive picture stimuli, and functional activation evoked in the two ROIs during picture viewing. These data support prior investigations identifying increasing amygdala and visual system activity with increasingly aversive picture perception (Canli et al., 2000; Taylor et al., 2000), and extend this effect to include highly arousing appetitive stimuli.

The present data also show clear differences in the relevant activation between fearful subjects and unselected subjects while viewing visual representations of the feared object. Despite a modest sample size, this difference was evident in both inferotemporal cortex and amygdala. Thus, in addition to showing a brain response relationship between a sample of unselected subjects and standard ratings of emotional arousal, the results also show that this methodology is highly sensitive to individual differences in reported specific fear.

Finally, these results show a high degree of covariation between BOLD signal change in inferotemporal cortex and amygdala, consistent with predictions based on non-human primate data (Amaral and Price, 1984; Amaral et al., 1992, Spiegler and Mishkin, 1981). The current data show clearly that this finding is based on the emotional reactions of individuals and groups, not an artifact of a specific stimulus set. That is, the covariation of activation at amygdala and inferotemporal sites was highly significant despite the fact that these areas were sampled at different times during the imaging session, and despite the fact that the exact picture category exemplars were in fact different. It was significant that cross-content correlations were not evident in other subcortical and visual associative structures—amygdala and lateral occipital did not significantly covary, neither did inferotemporal activity covary with signal change in the caudate.

In conclusion, the present results demonstrate consistent patterns of neural activity in ventral visual cortical and subcortical amygdala during perception of picture stimuli varying in emotional arousal. Future investigations will examine this relationship more closely in space and time, and seek to further specify the mechanism of motivated attention.

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