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Amygdala Activation to Sad Pictures During High-Field (4 Tesla) Functional Magnetic Resonance Imaging

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Fear-related processing in the amygdala has been well documented, but its role in signaling other emotions remains controversial. The authors recovered signal loss in the amygdala at high-field strength using an inward spiral pulse sequence and probed its response to pictures varying in their degree of portrayed sadness. These pictures were presented as intermittent task-irrelevant distractors during a concurrent visual oddball task. Relative to neutral distractors, sad distractors elicited greater activation along ventral brain regions, including the amygdala, fusiform gyrus, and inferior frontal gyrus. In contrast, oddball targets engaged dorsal sectors of frontal, parietal, and cingulate cortices. The amygdala's role in emotional evaluation thus extends to images of grief and despair as well as to those depicting violence and threat.

The amygdala is a critical brain region for the evaluation of sensory stimuli that have social and emotional significance to the organism. Recent neuropsychological and functional neuroimaging studies in humans have emphasized its role in processing aversive stimuli that have high arousal content. Scenes depicting images of threat, violence, mutilation, and disease activate the amygdala in healthy adults (Hamann, Ely, Hoffman, & Kilts, 2002; Irwin et al., 1996; Lane et al., 1997; Taylor et al., 1998; Yamasaki, LaBar, & McCarthy, 2002; reviewed in Zald, 2003), and amygdala-lesioned patients do not show a retention advantage for these kinds of stimuli relative to neutral ones (Cahill, Babinsky, Markowitsch, & McGaugh, 1995; Hamann, Monarch, & Goldstein, 2000; Kensinger, Brierly, Medford, Growdon, & Corkin, 2002). Similar findings have been reported for arousing lexical stimuli (Isenberg et al., 1999; LaBar & Phelps, 1998; Phelps et al., 1998). Within the general domain of negative affect, fear is the emotional category that has been most consistently associated with amygdala function. The amygdala is responsive to facial expressions of fear (Breiter et al., 1996; LaBar, Crupain, Voyvodic, & McCarthy, 2003; Morris et al., 1996; Pessoa, McKenna, Gutierrez, & Ungerleider, 2002; Phillips et al., 1998, 1997; Vuilleumier et al., 2001; Whalen et al., 1998, 2001; but see Kesler-West et al., 2001; Pine et al., 2001; Sprengylmeyer, Rausch, Eysel, & Przuntek, 1997), and amygdala-lesioned patients have difficulty evaluating the intensity of fearful expressions in posed facial displays (Adolphs, Tranel, Damasio, & Damasio, 1994; Adolphs et al., 1999; Anderson & Phelps, 2000; Anderson, Spencer, Fulbright, & Phelps, 2000; Broks et al., 1998; Calder et al., 1996; Sato et al., 2002; Young et al., 1995; but see Hamann et al., 1996). The human amygdala has also been implicated in fear conditioning (Bechara et al., 1995; Büchel, Dolan, & Armony, 1999; Büchel, Morris, Dolan, & Friston, 1998; Cheng, Knight, Smith, Stein, & Helmstetter, 2003; Furmark, Fischer, Wik, Larsson, & Fredrikson, 1997; LaBar, Gatenby, Gore, LeDoux, & Phelps, 1998; LaBar, LeDoux, Spencer, & Phelps, 1995; Phelps et al., 1998) and anticipatory anxiety (Phelps et al., 2000; but see Chua, Krams, Toni, Passingham, & Dolan, 1999).

The extent to which the amygdala processes other emotional categories, however, continues to be debated (Adolphs et al., 1999; Damasio et al., 2000; Hamann et al., 2002; Kesler-West et al., 2001; Lane et al., 1997). Of particular interest here is its role in evaluating sad stimuli. Sadness is typically considered an emotional category that is negative in valence but low in arousal (Russell, 1980). In this latter regard, it differs from other basic aversive emotions, including fear. Neurobiological studies of depression suggest the involvement of this brain structure (reviewed in Drevets, 2003), yet evidence for amygdala processing of sadness in healthy participants is mixed.

Two general experimental approaches have been adopted to investigate this topic: evaluation of sad facial expression and experiential dysphoria through sad mood induction. The former approach emphasizes perceptual decoding of sadness in posed facial displays. Neuroimaging studies in healthy participants have yielded contradictory evidence regarding the relationship between amygdala activity and sad facial expression. In a parametric study, Blair and colleagues (Blair, Morris, Frith, Perrett, & Dolan, 1999) reported a positive relationship between amygdala activation and intensity of portrayed sadness in morphed facial stimuli. However, when sad faces are contrasted directly with neutral ones, most

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studies fail to find amygdala activation (Blair et al., 1999; Kesler-West et al., 2001; Phillips et al., 1997; but see Yang et al., 2002). One further complication to these imaging studies is the use of blocked design protocols, which potentially induce sad mood states across the face presentation blocks. Studies in neurologic patients have been similarly mixed. Although deficits in judging the intensity of sad expression have been reported in some cases (Anderson & Phelps, 2000; Anderson et al., 2000), other patients with amygdala lesions tend to have normal evaluation of sad facial expressions (Adolphs et al., 1999).

The second approach has investigated the effect of sad mood induction on amygdala activation in healthy participants. The majority of these studies used cued recall of personal life episodes to induce sad mood states, although presentation of film clips (Lane et al., 1997) and the multimodal Velten method (Baker, Frith, & Dolan, 1997) have also been tried. In a series of experiments, Schneider and colleagues (Posse et al., 2003; Schneider et al., 1997, 1995, Schneider, Habel, Kessler, Salloum, & Posse, 2000) reported amygdala activation during recall of sad memories that were cued by presentation of mood-congruent facial expressions. However, others have not replicated this effect using similar (George, Ketter, Parekh, Herscovitch, & Post, 1996; George et al., 1995) or other recall cueing procedures (Damasio et al., 2000; Lane et al., 1997; Liotti et al., 2000; Mayberg et al., 1999; Pardo, Pardo, & Raichle, 1993). Autobiographical studies are difficult to accommodate to neuroimaging methods (see Maguire, 2001), in part because the time course of retrieval is varied, retrieval success is often not verified, and other phenomenological properties of the memories can influence brain activity (e.g., remoteness, rehearsal). There is additional but mixed evidence for involvement of the amygdala in autobiographical retrieval (Fink et al., 1996; Maguire & Frith, 2003; Markowitsch et al., 2000), but these studies were not focused on sad episodes per se. To our knowledge, there are no neuropsychological studies in amygdala-lesioned patients that examined recollection of sad autobiographical experiences.

The available evidence is thus inconclusive with regard to amygdala processing of sad affect. The majority of imaging studies implicating the amygdala have used protocols that involve congruence between sensory stimuli (posed displays of sad facial affect) and internal dysphoric states induced either through trial blocking or concurrent recall of sad life events. The present study was conducted to evaluate the amygdala's role in signaling transient responses to discrete sad stimuli. A new set of pictorial stimuli were developed that depicted sad expression within socioemotional contexts of grief, isolation, poverty, and despair. These stimuli were intermixed with neutral pictures and presented as novel, task-irrelevant distractors during a visual oddball task. To improve sensitivity to detect signal changes from the amygdala (LaBar, Gitelman, Mesulam, & Parrish, 2001), imaging was conducted at 4T using an inward spiral pulse sequence that reduces susceptibility artifact in the medial temporal and ventral frontal lobes relative to conventional echoplanar imaging protocols (Guo & Song, 2003).

Using a similar oddball task design, we previously reported activation of the amygdala (AMG), inferior frontal gyrus (IFG), fusiform gyrus (FFG), and anterior cingulate (ACg) to task-irrelevant, emotionally arousing scenes depicting themes of violence, threat, mutilation, and disease (Fichtenholtz et al., 2004; Yamasaki et al., 2002). Activity in these ventral regions was greater than that to emotionally neutral task-irrelevant distractors and was contrasted with that of dorsal frontoparietal cortices, which signaled the task-relevant oddball targets. On the basis of these and related findings, we hypothesized that sad distractor stimuli would engage the amygdala and associated ventral regions, including the FFG, IFG, and ACg, particularly in its subgenual portion (reviewed in Phan, Wager, Taylor, & Liberzon, 2002). In contrast, oddball targets would activate dorsal sectors of frontal, parietal, and cingulate cortices, including the middle frontal gyrus (MFG), supramarginal gyrus (SMG), intraparietal sulcus (IPS), posterior cingulate gyrus (PCg), and ACg. The results from the present study will thus contribute to an understanding of how distracting, sad stimuli transiently activate the amygdala and related ventral brain regions, and the extent to which these regions show dissociable patterns from dorsal brain areas recruited during a concurrent, attentionally demanding task.

Method

Participants

Fourteen right-handed healthy participants volunteered for the experiment. Two participants were dropped because they did not use the full range of the sadness rating scale (described below). The final group of 12 participants (7 women) had a mean age of 25.9 $\pm$ 4.4 years. Participants were screened by phone and by questionnaires for history of neurologic and psychiatric disorders, drug abuse, and current medication use. Participants were compensated at a rate of $20 per hour. All participants completed written informed consent, and the protocol was approved by the Institutional Review Board at Duke University Medical Center.

Stimulus Development

An initial pool of 100 sad pictures were culled from an online photo collection (http://www.photos.com). All of the pictures contained scenes of humans crying or portraying sad facial expressions. Most of the scenes included additional socioemotional contextual cues centered on themes of despair, grief, interment, incarceration, and poverty. The number of distinguishable faces was restricted to fewer than 6 per picture. All images were converted to grayscale. A pilot behavioral study was conducted with 10 healthy volunteers to evaluate the consistency of sadness ratings for each image. Participants were shown all 100 images sequentially on a computer screen in a pseudorandom order (stimulus duration = 2,000 ms, interstimulus interval = 3,000 ms) and were asked to rate each image on a 3-point sadness intensity scale (1 = *not sad/unsure*, 2 = *mildly sad*, 3 = *sad*). Only images with an average sadness rating of 2 or higher were included in the final pool of sad images. Fifty images out of this reduced pool of 56 images were chosen for inclusion in the functional magnetic resonance imaging (fMRI) study.

A similar procedure was used to obtain matched neutral pictures. An initial pool of 99 neutral pictures was obtained from the same Web site and matched as closely as possible to the final pool of sad pictures for presence and number of human figures in the image, postural features, gaze direction, and gender. Each sad picture had between one and three candidate-matching neutral pictures. A pilot behavioral study was conducted with the same

volunteers using a similar rating task as described above. This study generated a reduced pool of 54 neutral images, 50 of which were chosen for inclusion in the functional magnetic resonance imaging study.

Experimental Design

The experimental design was based on Yamasaki et al. (2002). A visual oddball paradigm was used that contained infrequent circles as target stimuli (3.33%), sad (3.33%) and neutral (3.33%) pictures as novel distractors, and frequent phase-scrambled pictures as standards (90.0%) (see Figure 1). The standards were phase-scrambled versions of the target and novel pictures. Mean luminance was equivalent among standards, targets, and the two kinds of distractors. The whole imaging session consisted of 10 runs, and each run contained 150 stimuli. Stimulus duration was 1,500 ms, and the interstimulus interval was 2,000 ms. The interval between successive rare stimuli (targets and/or distractors) was randomized between 18 s and 22 s to allow hemodynamic responses to return to baseline.

Participants pressed a response button using their right index finger upon detection of a target stimulus. All stimuli were projected centrally on a 10-in. [25-cm] wide screen located within the open magnet bore directly behind the participant's head. Stimuli were viewed through customized goggles.

Image Acquisition

Functional images were acquired on a 4.0 Tesla GE scanner. Head movement was minimized using a vacuum cushion. The anterior commissure (AC) and posterior commissure (PC) were identified in a sagittal localizer series. Oblique spoiled gradient-recalled acquisition (SPGR) images (three-dimensional, whole-brain) were acquired parallel to the AC-PC plane for high-resolution T1-weighted structural images with the following parameters: repetition time (TR) = 12.2 ms; echo time (TE) = 5.3 ms; field of view (FOV) = 24 cm; flip angle = 20°; matrix = 256 × 256; 68 contiguous images, slice thickness = 1.9 mm. Inward spiral gradient images (Glover & Law, 2001; Guo & Song, 2003) were acquired with the following parameters: TR = 2,000 ms; TE = 31 ms; FOV = 24 cm; flip angle = 90°; matrix = 64 × 64; 34 contiguous images, slice thickness = 3.75 mm, isotropic voxels. Customized software was used for regridding and image reconstruction.

Subjective Ratings of Sadness

Immediately following the MRI scan, all of the picture distractors were presented to the participant in a random order. Participants were asked to rate each picture on a sadness scale by pressing a button corresponding to one of five rating categories: mildly happy, neutral, mildly sad, sad, and very sad. Only those images rated as "sad" or "very sad" by the participant were included in the data analysis for that participant. These images were combined to constitute a "sad" category and compared with those rated "neutral" by the participant. On average, 65% of the total pool of 50 sad images and 81% of the total pool of 50 neutral images were included in the data analysis for each participant.

Voxelwise fMRI Data Analysis

Functional images were temporally adjusted for interleaved slice acquisition and realigned for motion to the image taken proximate to the anatomic study using affine transformation routines implemented in SPM99 (Wellcome Department of Cognitive Neurology, London, England). The realigned scans were coregistered to the anatomic scan obtained for each participant and normalized to SPM's template image, which conforms to the Montreal, Quebec, Canada, Neurologic Institute's standardized brain space. The functional data were spatially smoothed with a 8-mm isotropic Gaussian kernel prior to statistical analysis.

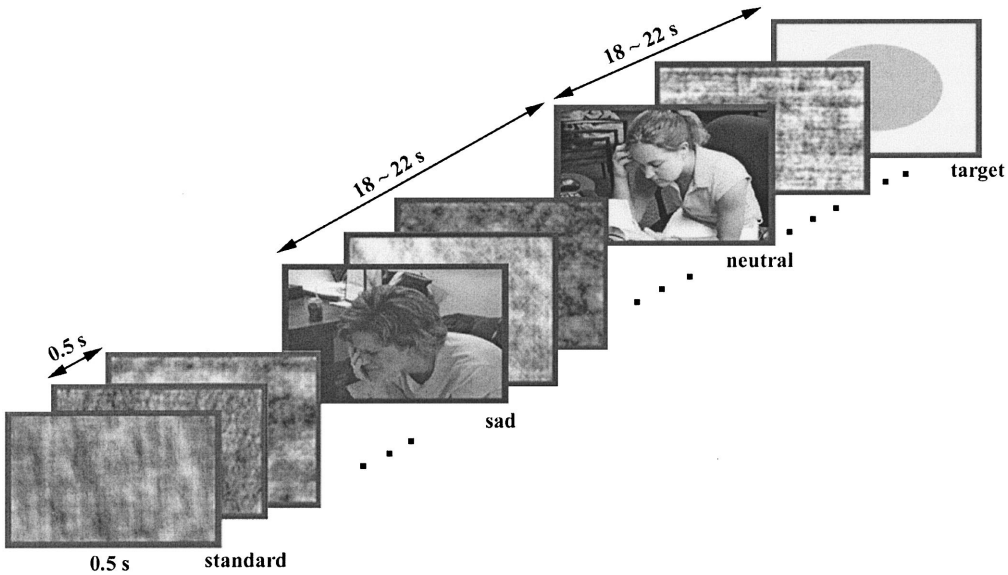

Figure 1. Design of the experimental paradigm. Participants were presented with rare circle targets (oddballs) and frequent phase-scrambled pictures (standards) interspersed with rare sad and neutral distractors.

Responses to the infrequent stimulus categories were isolated by convolving a vector of onset times of the targets, sad distractors, and neutral distractors with a synthetic hemodynamic response function that emphasized transient activity in response to these events. The general linear model was used to model the effects of interest and other confounding effects, including session effects and motion-related artifacts, for each participant. Statistical contrasts were set up using a random-effects model to calculate signal differences between the conditions of interest across participants. Statistical parametric maps were derived by applying linear contrasts to the parameter estimates for the events of interest, resulting in a *t* statistic for every voxel. Then, group averages were calculated by using pairwise *t* tests on the resulting contrast images. This sequential approach accounts for intersubject variability and permits generalization to the population at large. The resultant statistical parametric maps were thresholded at a voxelwise uncorrected $p < .001$ and a spatial extent of five contiguous voxels.

Region-of-Interest (ROI) fMRI Data Analysis

Because of our a priori hypotheses and previous work using a similar paradigm, we also conducted anatomically based ROI analyses following methods described in Jha and McCarthy (2000), Yamasaki et al. (2002), and Fichtenholtz et al. (2004). Briefly, ROIs were drawn on the basis of each participant's normalized high-resolution structural images. These ROIs were analogous to those in our previous reports (AMG, FFG, IFG, ACg, PCg, IPS, SMG, and MFG). ROIs were drawn on a slice-by-slice basis using an in-house mouse-driven computer program (Brain Imaging and Analysis Center, Duke University Medical Center, Durham, NC) run within the Matlab environment (Mathworks Inc., Natick, MA) on a PC-DOS platform. Anatomic borders were defined for each participant individually and were guided by descriptions in standard brain atlases (Duvernoy, 1999; Talairach & Tournoux, 1988) and our prior work. Slices were indexed relative to the AC for evaluating the distribution of activation within each ROI across participants. ROIs were drawn separately for each hemisphere in coronal section. The number of slices contributing to each ROI were as follows: AMG = 4, FFG = 12, IFG = 8, ACg = 8, PCg = 8, IPS = 6, SMG = 9, MFG = 8.

For statistical analysis of the ROI data, volumes were corrected for their interleaved acquisition sequence using cubic spline interpolation. Epochs were extracted from the time-series data, and the MR signal was selectively averaged from 4 s before to 20 s after each rare stimulus event (sad, neutral, and target). Mean signal change for all voxels within each ROI was computed for each time point included in the epoch to visualize the hemodynamic response profile for each ROI. The mean signal values were converted to percentage of signal change relative to the 4-s prestimulus baseline. The stimulus type (sad, neutral, target) effect on percentage of signal change at the peak time point was analyzed using repeated measures analyses of variance (ANOVAs) followed by Bonferroni-corrected post hoc dependent *t* tests. An alpha level of $p < .01$ was used for all ROI analyses. Hemisphere was included as a factor in the ANOVAs. However, this factor was only significant in the IFG (greater right-hemisphere activation for sad distractors). Because no other hemispheric effects were found, they are not discussed further.

Results

Ventral Stream Processing of Sad Distractors

Results from the SPM analysis showed greater activation to sad versus neutral distractors in the AMG, IFG, occipitotemporal junction (OT), FFG, and extrastriate cortex (see Table 1, Figure 2A).

Table 1
Brain Regions Showing Significant Signal Differences in the Sad Versus Neutral and Target Versus Neutral SPM Contrasts

Condition	Brain region	BA	Hemisphere	x	y	z	t^a
Sad > neutral	Occipitotemporal junction	37/39	R	49	−63	7	5.01
	Fusiform gyrus	19/37	L	−32	−81	−25	3.95
			R	42	−56	−25	3.88
	Extrastriate cortex	18	L	−7	−109	4	4.79
			R	18	−105	11	4.68
		19	L	−14	−81	−21	3.48
	Amygdala		R	14	−7	−18	3.67
	Inferior frontal gyrus	45	R	49	25	7	3.38
Target > neutral	Anterior cingulate gyrus	32	R	4	35	28	8.09
	Posterior cingulate gyrus	31	L	−4	−32	28	7.22
			R	18	−49	32	3.29
	Thalamus		R	11	−4	14	6.80
	Supramarginal gyrus	40	R	53	−56	32	7.41
	Precuneus	7	R	7	−81	49	5.80
	Superior parietal lobule	7	L	−11	−63	63	5.21
	Middle frontal gyrus	46	L	−42	42	21	5.33
	Inferior frontal gyrus	47	R	53	14	0	5.07
	Retrosplenial cortex	31/19	L	−25	−63	21	4.53
	Ventral striatum		R	21	18	−11	4.02

Note. Spatial coordinates (x, y, z) are in Montreal Neurologic Institute space. BA = Brodmann's area; R = right; L = left.
[a] $df = 11$, $p < .001$.

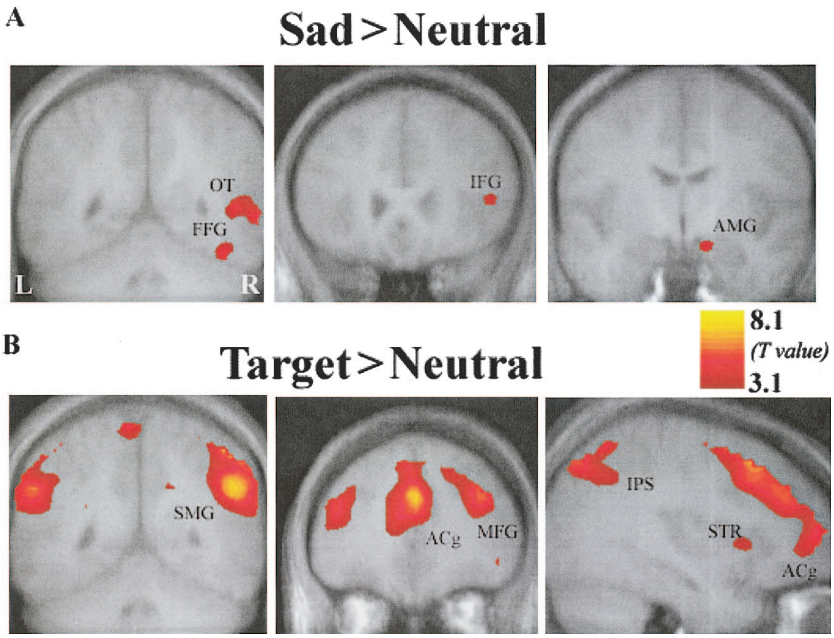

Figure 2. Functional MRI results from the voxel-wise random-effects analysis using SPM99. A: Group-averaged results for the contrast between sad and neutral distractors. B: Group-averaged results for the contrast between attentional targets and neutral distractors. All t values are thresholded at $p < .001$, uncorrected with a spatial extent of five contiguous voxels. OT = occipitotemporal junction; FFG = fusiform gyrus; IFG = inferior frontal gyrus; AMG = amygdala; SMG = supramarginal gyrus; ACg = anterior cingulate gyrus; MFG = middle frontal gyrus; IPS = intraparietal sulcus; STR = striatum.

Results from the anatomic ROI analysis confirmed the SPM99 findings in the AMG, IFG, and FFG (see Figure 3). In the AMG, ANOVAs revealed a main effect of stimulus type (sad, neutral, target), $F(2, 69) = 24.67$, $p < .001$. Post hoc tests revealed stronger activation to sad distractors compared with both neutral distractors and targets. In the IFG, a main effect of stimulus type was found, $F(2, 69) = 31.99$, $p < .001$. Post hoc tests revealed that sad distractors evoked larger responses than targets, which, in turn, evoked larger responses than neutral distractors. In the FFG, a main effect of stimulus type was found, $F(2, 69) = 17.67$, $p < .001$. Post hoc tests revealed that sad distractors elicited stronger responses than neutral distractors, which, in turn, elicited stronger responses than targets. The distribution of sad-related activity along the length of the FFG had a posterior gradient, with maximal differences elicited 74–78 mm posterior to the AC (see Figure 3D). This region overlaps with the spatial distribution of the putative fusiform face area. Inspection of this graph shows that the signal changes are graduated across the rostrocaudal extent of the FFG and not an artifact of averaging across several coronal sections.

Dorsal Stream Processing of Attentional Targets

Results from the SPM analysis showed greater activation to target stimuli versus neutral distractors in the IFG, MFG, ACg, PCg, SMG, superior parietal lobule, precuneus, retrosplenial cortex, thalamus, and striatum (STR) (see Table 1 and Figure 2B).

ANOVAs conducted on the anatomical ROIs confirmed target-related processing in the IFG, MFG, ACg, PCg, SMG, and IPS (see Figure 3B and Figure 4). Results from the IFG are discussed above. In the MFG, a main effect of stimulus type was found, $F(2, 69) = 14.84$, $p < .001$. Post hoc tests revealed stronger activation to targets than to either distractor category. Moreover, both classes of distractors showed significant deactivations relative to baseline. In the cingulate, both ACg and PCg showed greater responses to targets than to distractors: ACg, $F(2, 69) = 25.37$, $p < .001$; PCg: $F(2, 69) = 16.06$, $p < .001$. The PCg showed an additional deactivation to distractors. In the parietal lobe ROIs, activity to targets was greater than that to distractors: SMG, $F(2, 69) = 45.43$, $p < .001$; IPS: $F(2, 69) = 43.81$, $p < .001$. Both ROIs also showed significant deactivations to distractors.

Recovery of Signal Loss

Contrary to our hypotheses, the results did not yield significant activation to sad stimuli in the subgenual ACg. This brain region is difficult to image at high-field strength. To confirm that we had adequate signal recovery in the subgenual ACg, we thresholded randomly selected raw spiral images from individual participants at 50% of maximal signal intensity and overlaid them onto coregistered anatomic images. This procedure serves as a rough index of the adequacy of signal-to-noise ratios in a given brain region (see LaBar et al., 2001). As shown in Figure 5, we obtained good signal recovery in the subgenual ACg as well as the medial temporal lobe and frontopolar cortex. However, ventral aspects of the orbitofrontal cortex still suffered significant signal loss.

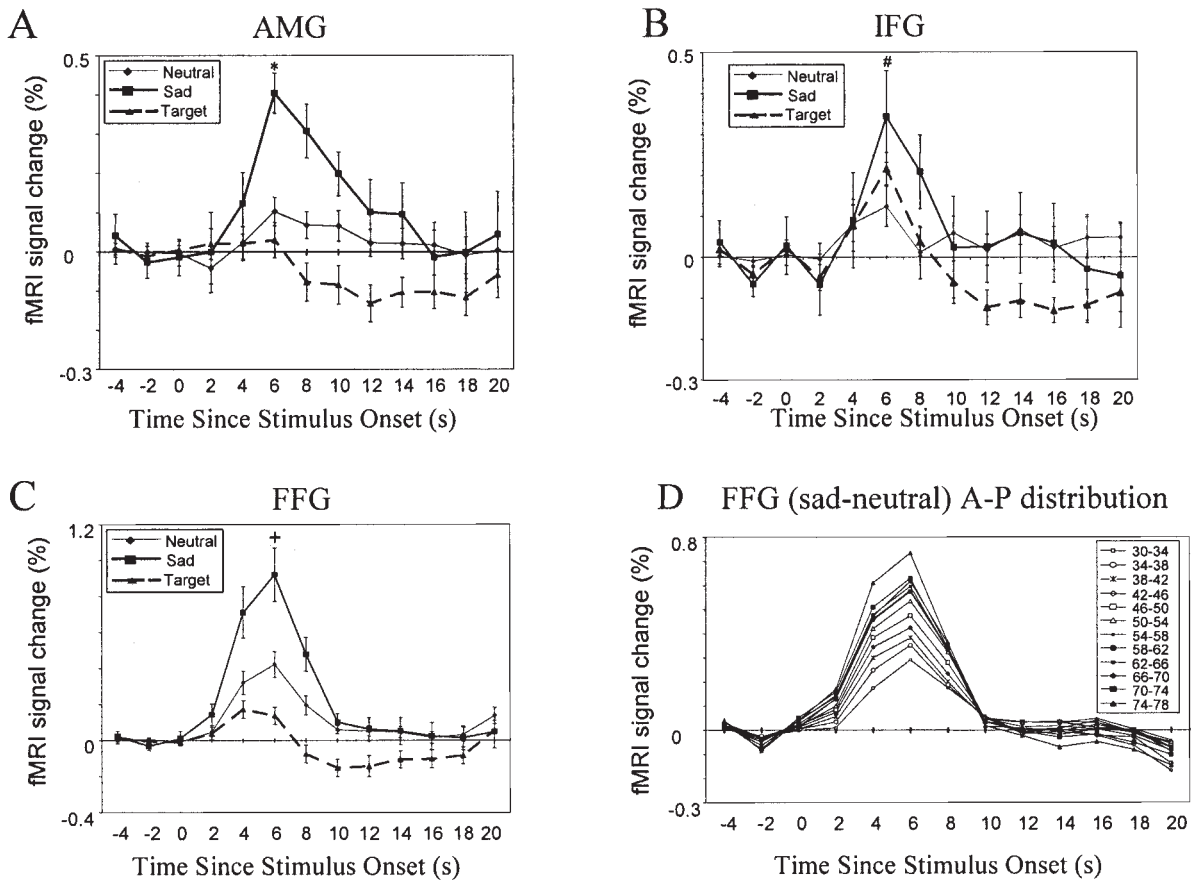

Figure 3. Functional MRI (fMRI) results from the anatomical region-of-interest analysis in ventral brain regions. The mean percentage of signal change (±*SEM*) relative to the prestimulus baseline is selectively extracted for the three stimulus categories and averaged for all voxels within the (A) amygdala (AMG), (B) inferior frontal gyrus (IFG), and (C) fusiform gyrus (FFG). Data are collapsed across hemispheres. The asterisk indicates greater peak activity for sad distractors than both neutral distractors and attentional targets. The plus sign indicates greater peak activity for sad distractors than neutral distractors, which, in turn, elicited more activity than attentional targets. The pound sign indicates greater peak activity for sad distractors than attentional targets, which, in turn, elicited more activity than neutral distractors. D: The anterior-posterior (A-P) distribution of the activation difference between sad and neutral distractors in the FFG. The boxed values indicate relative distance from the anterior commissure in millimeters.

Post Hoc Analysis With Matched Number of Exemplars

Because of differences in the participants' ratings of the pictures, there were different numbers of trials included in the analysis of the sad and neutral categories (8 fewer exemplars in the sad condition, on average). A separate analysis was conducted to determine whether these differences could have skewed the results. The data were reaveraged such that each participant had an equal number of sad and neutral stimuli included in their results ($N = 30$). This was done by choosing a subset of neutral images that were matched for closest trial position to the sad images on a participant-by-participant basis. This procedure resulted in a somewhat noisier dataset because of the reduced number of trials and resulting lower signal-to-noise ratio. Nonetheless, the results confirmed the analyses presented here. The ROI results were identical to the original analysis. The SPM analysis showed slight differences as a consequence of the reduced signal-to-noise—activity in three regions (left amygdala, right FFG, and right IFG) was less significant ($p < .005$ rather than $p < .001$), and activity in three other regions (occipital regions for the sad vs. neutral contrast, and thalamus and precuneus/retrosplenial cortex for the target vs. neutral contrast) was not significant. The results of this post hoc analysis based on matched number of trials largely confirms the original analysis and is presented as supplementary material, which is available on the Web at http://dx.doi.org/10.1037/1528-3542.5.1.12.supp

Discussion

Role of the Amygdala

The results of the present study indicate that the amygdala's role in emotional processing extends to images of sadness. Our experimental design differed in several ways from previous studies, which have yielded contradictory results regarding sad affect and

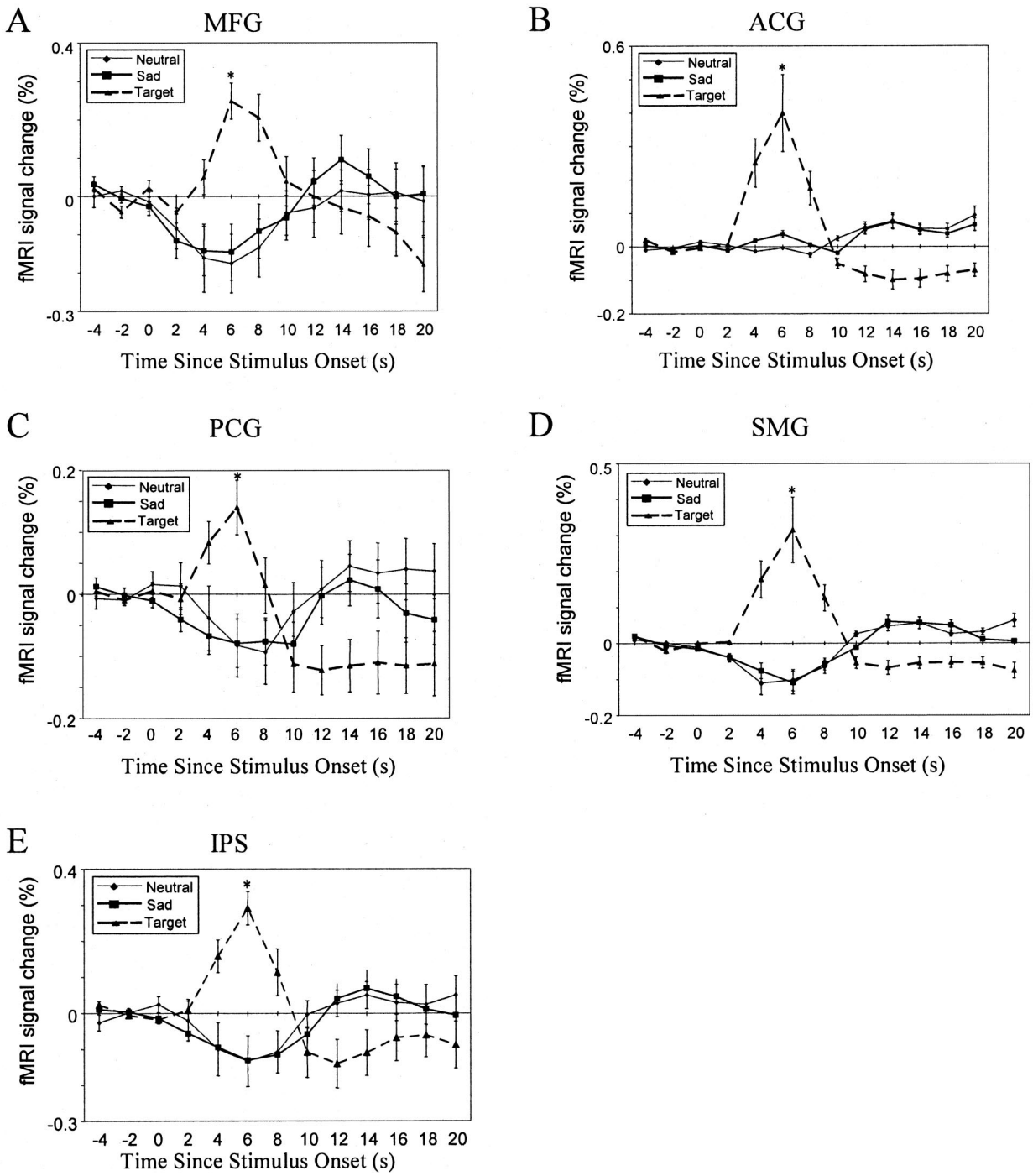

Figure 4. Functional MRI (fMRI) results from the anatomical region-of-interest analysis in dorsal brain regions. The mean percentage of signal change (±*SEM*) relative to the prestimulus baseline is selectively extracted for the three stimulus categories and averaged for all voxels within the (A) middle frontal gyrus (MFG), (B) anterior cingulate gyrus (ACG), (C) posterior cingulate gyrus (PCG), (D) supramarginal gyrus (SMG), and (E) intraparietal sulcus (IPS). Data are collapsed across hemispheres. Asterisks indicate greater peak activity elicited to attentional targets relative to both sad and neutral distractors.

amygdala function. First, the task emphasized transient responses to intermittent, task-irrelevant sad stimuli rather than sustained responses over blocks of sad stimulus trials or during sad mood induction. Second, the majority of the images included additional socioemotional cues beyond sad facial affect in isolation, which potentially enhanced their emotional salience. Emotional salience was also ensured by including in the analysis only those images that were rated as sad or very sad by individual participants.

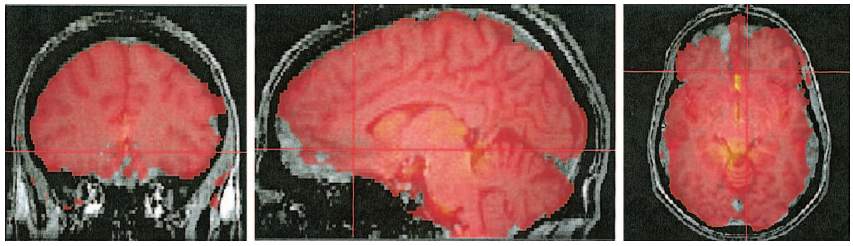

Figure 5. Functional signal recovery using the inward spiral technique. The red map is the reconstructed functional image from 1 participant thresholded at 50% of the peak signal intensity. This map is overlaid on the participant's T1-weighted structural scan. Cross-hair indicates level of the subgenual region of the anterior cingulate gyrus.

Finally, neuroimaging was conducted using a spiral pulse sequence with good signal recovery in the medial temporal lobe at high-field strength, which may have increased our sensitivity to detect amygdala responses.

Because the amygdala activation to sad distractors was greater than that to neutral distractors matched for stimulus frequency, presence of human figures, and other visual features, it is unlikely that other aspects of the stimuli were driving the effects. In addition, the task did not require explicit emotional processing or categorization, which suggests that the amygdala was engaged relatively automatically. In our previous oddball study (Fichtenholtz et al., 2004), the amygdala's response to highly arousing, aversive scenes was similar irrespective of their task relevancy (i.e., whether they were targets or distractors). Other research suggests that amygdala processing of facial expressions is enhanced when the emotion is task relevant (Gur et al., 2002; Hariri, Bookheimer, & Mazziotta, 2000), under conditions of high attention (Pessoa et al., 2002; but see Anderson, Christoff, Panitz, De Rosa, & Gabrieli, 2003; Vuilleumier, Armony, Driver, & Dolan, 2001) or under concurrent mood induction (Schneider et al., 1997). In contrast, other studies have shown enhanced amygdala activity under passive or subliminal processing conditions (Morris, Öhman, & Dolan, 1998; Taylor, Phan, Decker, & Liberzon, 2003). Whether the amygdala's response to sad scenes is modulated by task relevancy or mood induction remains an open question.

Role of Other Ventral Brain Regions

The amygdala acted in consort with other ventral brain regions, including higher level visual areas and the IFG. Coactivation of the amygdala and visual cortex is often reported during emotion perception tasks and reflects the close anatomical relationship between the amygdala and sensory processing regions (Amaral, Price, Pitkänen, & Carmichael, 1992). The IFG activation was in a lateral aspect of ventral prefrontal cortex where we previously reported activation to aversive scenes (Fichtenholtz et al., 2004; Yamasaki et al., 2002) and aversive facial expressions (LaBar et al., 2003). We were unable to evaluate the role of ventromedial orbitofrontal cortex, which is also anatomically linked with the amygdala because of signal dropoff in this region at high-field strength (see Figure 5).

All of these ventral brain regions showed signal decreases in response to the attentional targets (see Figure 3). Response enhancement to emotional distractors and concomitant response attenuation to attentional targets may indicate reciprocity of cognitive-emotional processing along the ventral stream (Drevets & Raichle, 1998; Yamasaki et al., 2002). The hemodynamic signature of deactivation, however, was generally broad and late, peaking around 12 s poststimulus. In IFG (and to a lesser extent FFG), the signal decrease was preceded by transient activation to the target stimuli and may simply be a result of this activation. Other oddball tasks show considerable variability in IFG activation to target stimuli (Ardekani et al., 2002; Clark, Fannon, Lai, & Benson, 2001; Clark, Fannon, Lai, Benson, & Bauer, 2000; Stevens, Skudlarski, Gatenby, & Gore, 2000), and it is unclear what aspects of the task design might recruit processing in this region. One possibility is that the IFG activity reflects the novelty value of the targets because participants were discriminating circle targets from phase-scrambled standard stimuli (see Figure 1). In our previous oddball studies in which participants discriminated circle targets from square standards, we did not observe IFG activation (Kirino, Belger, Goldman-Rakic, & McCarthy, 2000; Yamasaki et al., 2002). We chose not to use squares in the present study to avoid the presentation of objects in the baseline of event-related epochs extracted around the target and distractor stimulus categories and to equate the baseline of the distractor epochs for lower level visual features (luminance and spatial frequency).

We expected to observe sadness-related activity in the ACg, particularly in its rostroventral portion, given our previous emotional oddball results (Fichtenholtz et al., 2004; Yamasaki et al., 2002) and the role of the subgenual ACg in processing sad affect (reviewed in Phan et al., 2002). Failure to find activation here was not because of technical limitations because we had adequate signal coverage in the ACg (see Figure 5). Previous functional imaging studies of sad affect have shown activity in the subgenual ACg during mood induction procedures (George et al., 1995; Liotti et al., 2000; Mayberg et al., 1999) and during resting state scans in treatment studies of depressed populations (Drevets et al., 1997; Mayberg et al., 1999; Wu et al., 1999). Reiman and colleagues (1997) also failed to find subgenual cingulate activation during sad film clip presentation. One possibility is that the subgenual cingulate may primarily relate to internal generation of sad mood states rather than evaluation of sad exteroceptive cues (see also Phan et al., 2002).

Role of Dorsal Brain Regions

Consistent with previous oddball experiments, we found attentional target-related activity along dorsal parietal, cingulate, and prefrontal cortices (including SMG, IPS/superior parietal lobule,

PCg/retrosplenial cortex, ACg, and MFG) and associated subcortical structures (thalamus, striatum). Target-related activity in these dorsal areas is fairly consistent across studies (Ardekani et al., 2002; Clark et al., 2001, 2000; Fichtenholtz et al., 2004; Kirino et al., 2000; McCarthy, Luby, Gore, & Goldman-Rakic, 1997; Stevens et al., 2000; Yamasaki et al., 2002). Furthermore, ROI analysis of the MFG, IPS, SMG, and PCg showed signal attenuations in response to the distracting stimuli relative to baseline. The hemodynamic profile of these distractor-related deactivations mirrored the profile of target-related activations (see Figure 4). Because the deactivations were similar for both sad and neutral distractor categories, they likely reflect a mechanism for supporting task-appropriate differentiation of stimulus categories.

Study Limitations

Because the emotional images were rare—task-irrelevant distractors—another emotional category could not be included in the experimental design without significantly lengthening the imaging session and reducing the overall "oddball" nature of the paradigm. Thus, it was not feasible to determine whether the amygdala shows emotional category specificity or whether its activity reflects emotional intensity across categories. Furthermore, it is possible that another emotion (e.g., empathy) is being signaled in some of the ventral brain regions during presentation of sad images. Although the general pattern of activation (with the exception of the cingulate region) is similar to our previous emotional oddball studies using arousing aversive scenes as distractors (Fichtenholtz et al., 2004; Yamasaki et al., 2002), direct comparisons are limited because of differences in methodologies used (field strength of 1.5 T vs. 4 T, echoplanar vs. spiral imaging, etc.).

Conclusion

The present study provides a clear demonstration of amygdala processing of sad affect. Several aspects of the experimental design may have facilitated response detection in the amygdala, including the incorporation of social contextual information to facial displays, emphasizing rapid and automatic aspects of exteroceptive stimulus processing, and reducing susceptibility artifact at high-field strength. These features may prove useful to evaluate the amygdala's role in processing emotions other than fear. The amygdala was engaged in consort with other ventral brain regions, whose responses to sad, distracting stimuli were distinguished from dorsal brain regions focused on task-relevant attentional targets. The overall pattern of results suggests that emotional distraction from attentionally demanding tasks is mediated by intermittent activity distributed across dorsal and ventral processing streams in the brain. Many affective disorders, including depression and posttraumatic stress disorder, are characterized by intrusive emotional thoughts, images, or memories that drain processing resources from concurrent attentionally demanding tasks. The present study provides a conceptual framework to model such effects in healthy participants and to investigate dysregulation of the relevant brain networks in affective disorders.

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