Mood Alters Amygdala Activation to Sad Distractors During an Attentional Task

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Background: *A behavioral hallmark of mood disorders is biased perception and memory for sad events. The amygdala is poised to mediate internal mood and external event processing because of its connections with both the internal milieu and the sensory world. There is little evidence showing that the amygdala's response to sad sensory stimuli is functionally modulated by mood state, however.*
Methods: *We investigated the impact of mood on amygdala activation evoked by sad and neutral pictures presented as distractors during an attentional oddball task. Healthy adults underwent functional magnetic resonance imaging during task runs that were preceded by sad or happy movie clips. Happy and sad mood induction was conducted within-subjects on consecutive days in counterbalanced order.*
Results: *Amygdala activation to sad distractors was enhanced after viewing sad movies relative to happy ones and was correlated with reaction time costs to detect attentional targets. The activation was higher in female subjects in the right hemisphere. The anterior cingulate, ventromedial and orbital prefrontal cortex, insula, and other posterior regions also showed enhanced responses to sad distractors during sad mood.*
Conclusions: *These findings reveal brain mechanisms that integrate emotional input and current mood state, with implications for understanding cognitive distractibility in depression.*

H ealthy mood is predicated on a balance between cognitive and emotional information processing in the brain. In depressive states, perception is colored such that greater sadness is inferred from social cues, recurrent and prolonged sad thoughts disrupt attentional focus, and memory is biased toward negative life events (Mineka and Nugent 1995; Niedenthal et al 2000; Seibert and Ellis 1991; Siegle et al 2001). The neural substrates that relate internal mood states, sensory representations of sad stimuli, and cognitive processes remain unclear, despite the central importance of these associations in the phenomenology of mood disorders (Baker et al 1997; Elliott et al 2002; Lewis et al 2005).

The amygdala is a limbic brain region in which responses to emotional stimuli may be altered by internal states because of its extensive visceral and sensory anatomic connections (Amaral et al 1992). Previously it was shown that amygdala responses to appetitive stimuli are modulated by current motivational state. When images of food stimuli were presented to subjects in a hungry state, activation in the amygdala and related temporal lobe regions was increased relative to the same images presented during a satiated state (Holsen et al 2005; LaBar et al 2001). Additional comparisons showed that the effect of hunger did not extend to nonfood images. These results provide evidence that the response of the amygdala to salient sensory stimuli is not fixed but instead varies according to the current motivational state of the individual. It is unknown whether these findings extend to paradigms that experimentally manipulate mood state or if the signal changes impact concurrent cognitive processing.

Neuroimaging studies of mood disorders have revealed changes in an emotional circuit that includes regions of the prefrontal cortex, basal ganglia, anterior cingulate, and amygdala (Beyer and Krishnan 2002; Drevets 2000; Mayberg 1997; Phillips et al 2003). Depressed patients exhibit amygdala responses to emotionally negative words that are prolonged in time compared with control subjects (Siegle et al 2002). In addition, they show exaggerated amygdala activation to sad and fearful facial expressions that attenuates following antidepressant treatment (Fu et al 2004; Sheline et al 2001). Complementary treatment changes occur in the anterior cingulate and insula in response to emotional scenes (Davidson et al 2003), and functional connectivity among the amygdala, anterior cingulate, and prefrontal cortex is altered in depression in response to these scenes (Anand et al 2005; Irwin et al 2004). Neuroimaging findings during emotional challenges differ somewhat from scans taken during resting conditions, where hypofrontality is often observed in depression, and changes in the amygdala are minimal relative to those in the anterior cingulate and prefrontal cortex (Mayberg et al 1999).

Fewer neuroimaging studies have examined mood induction in healthy adults. Schneider and colleagues have consistently reported amygdala activation during transient sadness induced via cueing by sad facial expression (Posse et al 2003; Schneider et al 1997). Other techniques of mood induction, however, have shown variable results (Aalto et al 2002; George et al 1996; Lévesque et al 2003; Liotti et al 2000). One issue that may account for this variability is the role of internal versus external cues in mood elicitation. Reiman et al (1997) found greater activity in the amygdala and other temporal lobe regions during transient sadness induced by film clips relative to autobiographical cueing methods, which suggests more involvement in externally triggered sad mood. In contrast, the insula signaled internally generated mood to a greater extent (Reiman et al 1997), consistent with the role of this region, along with the cingulate gyrus, in monitoring visceral responses (Critchley et al 2004). These findings may help reconcile the relative engagement of different frontolimbic structures in resting versus activation studies of depression.

Although studies of healthy adults have examined amygdala activation during sadness, they have not addressed whether its response to external sad stimuli is altered by current mood state. The activation studies of depression indicate that amygdala

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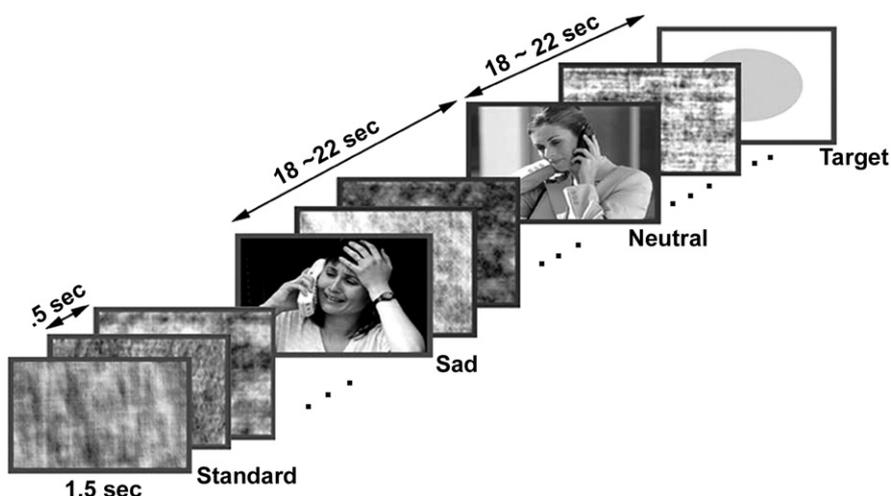
Figure 1. The oddball task consisted of four stimulus types: standards (90% of trials), targets (3.3%), neutral distractors (3.3%), and emotional distractors (3.3%). Participants were required to detect target circles and respond with a speeded button-press response. All other stimuli were task-irrelevant. Each session consisted of 10 oddball runs. Before each run, a happy or sad movie clip was shown. Happy and sad mood induction occurred in separate testing sessions conducted on consecutive days. The photos were adapted from photostogo.com and indexstock.com with permission.

responses to sad or aversive stimuli normalize following treatment and may serve as a useful outcome measure. These findings imply that differences in activation patterns across depressed patients and control subjects at baseline may relate in part to current mood state differences across the samples rather than to trait markers of depression. Therefore, investigating how experimental manipulation of mood states affects neural responses to sad stimuli is critical for understanding mechanisms of transient sadness in healthy individuals as well as for interpreting clinical studies of mood disorders using brain activation paradigms.

The amygdala and associated frontolimbic structures are important not only for processing emotional stimuli but also for mediating emotional influences on other brain systems, including those that relate to attention, memory, and decision making (Adolphs 2005; Dolan 2002; Phelps 2004). These brain regions may thus play a role in the impact of mood-enhanced emotional stimulus processing on cognitive symptoms in depression (Baker et al 1997; Elliott et al 2002; Lewis et al 2005). In this study, we were particularly interested in investigating the influence of current mood on emotional distraction during an attention demanding task. It is well known that recurrent sad thoughts in depression contribute to slowed information processing and attentional distraction. To model these effects in healthy adults, we developed an oddball paradigm in which participants detected rare visual targets (circles) embedded in a stream of frequent standards (rectangles) while distracting sad and neutral scenes were intermittently presented (Wang et al 2005; also see Figure 1). Consistent with our previous neuroimaging work (Yamasaki et al 2002), the emotional oddball task showed a clear dorsoventral segregation of activation such that hemodynamic responses to the attentional targets were focused in dorsal frontoparietal and cingulate cortices whereas responses to the sad distractors were focused in the amygdala and ventral sectors of the occipitotemporal and frontal lobes (Wang et al 2005). Because the sad stimuli are task-irrelevant, sporadic, and temporally distinct from the attentional targets, this paradigm emulates cognitive distraction that accompanies depression in naturalistic settings.

For this study, we investigated whether the amygdala's response to the sad distractors would be altered by experimental manipulations of mood state via presentation of happy and sad movie clips. In addition, we wanted to determine whether the degree of amygdala activation to sad distractors was related to performance on the target detection task. Happy and sad mood induction occurred on consecutive days in a counterbalanced order to provide a within-subject comparison. In addition, the movies were interleaved with oddball task trials to ensure the stability of the mood induction during the task itself. Film clips were chosen on the basis of pilot work showing that they selectively elicited the target emotions and not others (e.g., fear) and that happy and sad mood induction yielded equivalent arousal levels (see Methods and Materials). To validate the mood manipulation, a behavioral study was conducted in a mock magnetic resonance imaging (MRI) scanner in a separate group of participants for whom runs of the oddball task were periodically interrupted to obtain self-report measures of current mood (see Methods and Materials and Figure 2A).

Because of our a priori hypotheses, the focus of this report is on amygdala activation using an anatomic region-of-interest (ROI) approach in which this structure was outlined by hand on individual structural MRI scans. In addition, we conducted exploratory voxelwise analyses on the rest of the brain to characterize enhanced responses to sad stimuli during sad mood more broadly.

Methods and Materials

Subjects

Ten male (mean age = 23.0 years) and 10 female (mean age = 23.4 years) right-handed subjects participated in the imaging study. Subjects had no self-reported history of neurologic or psychiatric illness or drug addiction. All participants were screened for depression using the Beck Depression Inventory and had scores < 9, indicating that they were not depressed. The study was approved for ethical treatment of human subjects by the Institutional Review Board at Duke University, and all subjects provided written informed consent.

Development of Mood Induction Materials

The sad and happy movie clips (each 3–7 min in length) were selected from popular American films and television programs (e.g., *Titanic, Bambi, Terms of Endearment,* and *I Love Lucy*) and were initially screened to depict death of a beloved character in sad movie clips and humorous episodes in happy movie clips. Most participants were familiar with the movies. The emotions the movies elicited were determined by a pilot behavioral study conducted in 16 young adults (8 male, 8 female). Subjects viewed 20 sad and 20 happy movie clips on 2 separate days in a
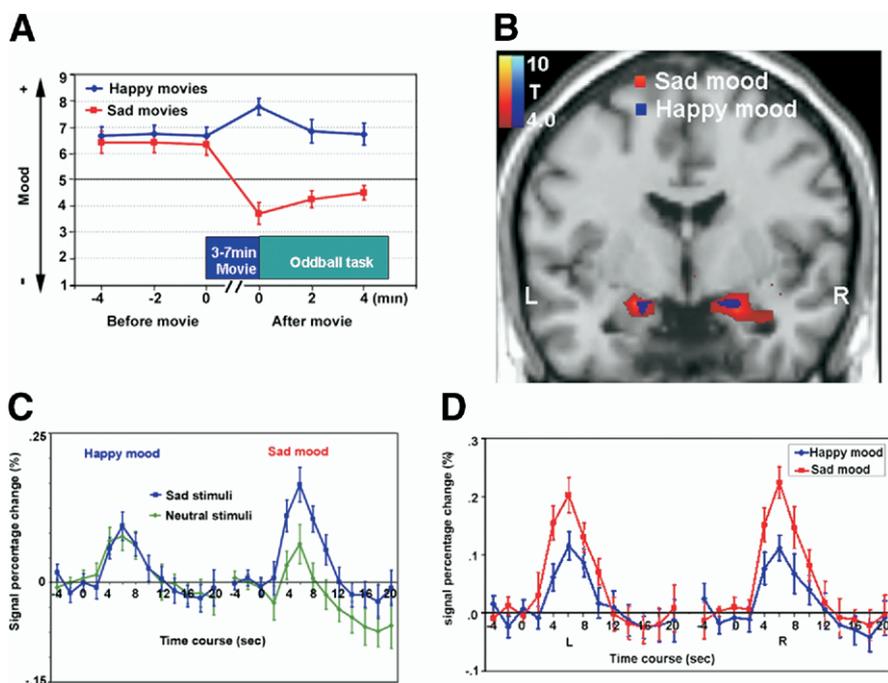
Figure 2. **(A)** A separate behavioral study in a mock magnetic resonance scanner validated the mood manipulation by taking mood ratings before and after viewing the sad (red line) and happy (blue line) movies. Small values indicate increasingly sad mood. Participants rated their mood at various time points while performing the oddball task in the period after the movie. **(B)** Voxel-based random-effects analysis of amygdala activation to the sad distractors relative to baseline as a function of mood state (peak Talairach coordinates: sad mood, left −22, −8, −12 and right 26, −8, −15; happy mood, left −19, −8, −12 and right 22, −8, −12). L, left hemisphere; R, right hemisphere. **(C)** Anatomic region-of-interest analysis of amygdala activation elicited by the sad and neutral distractors as a function of mood state. Sad mood selectively enhanced amygdala activation by sad distractors relative to happy mood, resulting in a significant mood × distractor type interaction, * $p < .05$. **(D)** Amygdala activation evoked by sad distractors as a function of mood state for each hemisphere.

counterbalanced order. Each movie clip was rated sequentially on a 9-point Likert-type scale for each of 16 emotion terms to evaluate their affective properties. The 16 items consisted of the following emotions: amusement, anger, arousal, confusion, contempt, contentment, disgust, embarrassment, fear, happiness, interest, pain, relief, sadness, surprise, and tension. Only those movies that were rated high on sadness and pain and low on other emotions were selected for the sad mood induction. Ten of the sad and 10 of the happy movie clips were chosen accordingly for inclusion in the imaging experiment. Each clip was only shown once throughout the imaging study to avoid habituation effects. For the selected sad movies, the mean (± SEM) of the ratings on sadness was 3.7 (± .30), was 1.2 (± .23) on other negative emotions, and was .5 (± .15) on positive emotions. Movie clips with high ratings of happiness, contentment, and amusement and low ratings of negative emotions were used for happy mood induction. For these film clips, the mean (± SEM) score on the positive emotions (happiness, contentment, and amusement) combined was 3.8 (± .29) and .2 (± .11) on all negative emotions. The ratings across the emotion categories significantly differed across the two sets of film clips, $F(1,62) = 195.91$, $p < .001$. We also asked participants to rate their arousal levels on a similar scale immediately following presentation of each film clip. There were no significant differences in self-reported arousal after viewing sad and happy movies, $F(1,15) = .03$, $p = .873$.

Behavioral Study to Validate Mood Ratings in Mock MRI Scanner

An independent group of 12 young adults (six women) participated in a second and subsequent behavioral study to determine the time course of mood changes elicited by the movies (Figure 2). This study was conducted in a mock MRI scanner to create environmental conditions identical to that encountered by the participants in the functional MRI (fMRI) study. We intentionally validated the mood manipulation in a separate group of participants from those in the fMRI study because we wanted to assess the impact of mood state on brain activation as it would occur naturally without requiring subjects to focus explicitly on their mood state during the attentional task, which provides greater ecologic validity and generalizability. Furthermore, we were concerned that intermittent interruption of the oddball task to provide mood ratings during fMRI scanning would introduce an additional, confounding distraction that would limit our interpretation of the relationship between the brain imaging data and performance on the attentional task.

Each participant was tested on 2 consecutive days, with sad movies tested on one day and happy movies tested on the following day, in a counterbalanced order. Using a 9-point scale, participants evaluated their mood three times (−4, −2, 0 min) before each movie, and three times (0, +2, +4 min) after the completion of each movie. To maintain consistency with the main imaging experiment, the participants were engaged in an oddball task immediately following the completion of each movie, which was interrupted to rate their mood. As seen in Figure 2A, the sad movie clips induced a sad mood shift that was maintained for at least 4 min after the movie ended, showing persistence of the mood change during the oddball task. The happy movies induced a positive but more transient mood shift because of the relatively happy baseline mood of the participants. The difference in mood following sad and happy mood induction was significant at all time points following completion of the movie clips (two-tailed paired t tests, ps < .05).

Stimulus Development for the Oddball Task

The stimuli and design of the emotional oddball task were identical to that described previously (Wang et al 2005). Briefly, all distractor pictures were obtained from online photo collections (http://www.photos.com and http://www.superstock.com). All of the sad pictures contained scenes of humans crying or portraying sad facial expression and depicted scenes of despair, grief, internment, incarceration, and poverty. The number of distinguishable faces was restricted to less than six per picture. All images were converted to grayscale. A pilot behavioral study was conducted in which 10 participants rated each picture on a Likert-type scale of sadness–happiness from a

pool of 200 sad images. One hundred sad images were chosen for inclusion in the task based on the consistency of sadness ratings. Each sad picture had from one to three candidate matching neutral pictures according to the presence and number of human figures in the image, postural features, gaze direction, and gender. The same volunteers rated the neutral pictures on similar scales, and 100 of the pictures were chosen for inclusion in the fMRI study according to the consistency in the ratings for emotional neutrality.

Experimental Design

To avoid habituation effects, all of the distractors were trial-unique. The attentional targets were circles of varying sizes and luminance, and the standard stimuli were phase-scrambled and luminance-matched versions of the distractors (see Figure 1). The presentation frequency for targets, sad distractors, and neutral distractors was 3.33% each, with standards comprising the remaining 90%. The imaging session consisted of 10 runs, each containing 150 stimuli (stimulus duration = 1500 msec, interstimulus interval = 2000 msec). The interval between successive rare stimuli (targets, distractors, or both) was randomized between 18 and 22 sec to allow hemodynamic responses to return to baseline.

Participants pressed a response button using their right index finger on detection of a target stimulus (circle). Before each run of the oddball task, participants were shown a 3- to 7-min movie clip. The sad mood and happy mood induction procedures were conducted across 2 consecutive days in a counterbalanced order. To verify the emotional content of the distractors, participants in the fMRI study were asked to rate the distractors on Likert-type scales of sadness–happiness immediately after scanning, as described previously (Wang et al 2005). Following sad mood induction, 90% of the neutral distractors were endorsed as neutral, and 86% of sad distractors were endorsed as sad. Following happy mood induction, 92% of neutral distractors were endorsed as neutral, and 88% of sad distractors were endorsed as sad. The ratings did not interact with type of mood induction.

Image Acquisition and Analysis

Functional images were acquired on a 4.0-Tesla GE scanner and were analyzed as described previously (Wang et al 2005). Oblique spoiled gradient-recalled acquisition (SPGR) images (three-dimensional, whole-brain) were acquired parallel to the anterior–posterior commissure plane for high-resolution T1-weighted structural images with the following parameters: repetition time (TR) = 12.2 msec, echo time (TE) = 5.3 msec, field of view (FOV) = 24 cm, flip angle = 20°, matrix = 256 × 256, 68 contiguous images, slice thickness = 1.9 mm. To reduce susceptibility artifacts in the medial temporal lobe, inward spiral gradient images were acquired with the following parameters: TR = 2000 msec, TE = 31 msec, FOV = 24 cm, flip angle = 90°, matrix = 64 × 64, 34 contiguous images, slice thickness = 3.75 mm, resulting in 3.75 mm^3 isotropic voxels. This protocol yields excellent coverage of ventral frontal and medial temporal lobe regions at high field strength (Wang et al 2005).

The primary outcome measure was the time course of signal intensity within the amygdala in response to the sad and neutral distractors. An anatomic ROI approach was used in which the same expert investigator (L.W.) outlined the amygdala for each participant in each hemisphere based on his or her own coronal anatomic images. Considering the degree of individual anatomic variability in the vicinity of the amygdala (LaBar et al 2001), this

participant-based ROI approach provides a more precise quantification of activity changes relative to voxelwise measures. The rater was blind to the mood condition at the time of ROI drawing.

Watson's method was used in the determination of amygdala borders (Brierley et al 2002). The anterior border was taken where the temporal stalk is connected to the white matter of the insula. It is usually located at the coronal section immediately posterior to the one where the optic chiasm first appears continuous. The posterior border was defined as the point where the white matter first starts to appear superior to the alveus and laterally to the hippocampus head. The inferior horn of the lateral ventricle was used as a border if the alveus was not visible. The amygdala is bounded sagittally by the border of the hippocampus head. Medially, the measurement included the uncus, but the entorhinal cortex covering the medial aspect was excluded. The border was defined laterally by the inferior horn of the lateral ventricle or adjacent white matter. The mean volume of the amygdala across participants was 1183.5 ± 235 mm^3. Because each participant was scanned twice, we computed the intraclass correlation between volume measurements across testing sessions, which yielded a reliability score of 97.3%. The MRI signal from each amygdala was selectively averaged from 4 sec before to 20 sec after each sad and neutral distractor presented during the oddball task. The mean signal change was computed for each time point included in the epoch to visualize the hemodynamic response profile. These values were converted to percent signal change relative to the 4-sec prestimulus baseline for each hemisphere separately. The functional data were corrected for their interleaved slice acquisition using cubic spline interpolation. The amygdala was typically visible across 12 consecutive coronal sections (slice thickness .975 mm), which were averaged before statistical analysis. The statistical analysis focused on the average of the percent signal change elicited from all voxels included in each ROI.

The distractor type (sad, neutral) and mood (sad, happy) effects on percent signal change at the peak time point (6 sec poststimulus) in the amygdala were analyzed by hemisphere using analysis of variance (ANOVA). Linear regression analysis was used to relate peak signal changes in each hemisphere with reaction times to detect attentional targets. An alpha level of $p < .05$ (two-tailed) was used for the amygdala ROI analyses.

The primary amygdala ROI analysis was supplemented by a whole-brain voxel-based analysis performed to interrogate activation in other brain regions. Image preprocessing was conducted using temporal realignment for interleaved slice acquisition and spatial realignment to adjust for motion using affine transformation routines implemented in SPM99 (Wellcome Department of Cognitive Neurology, London, United Kingdom). 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 Neurologic Institute's standardized brain space. The functional data were spatially smoothed with an 8-mm isotropic Gaussian kernel before statistical analysis. Responses were isolated from the time series by convolving a vector of stimulus onset times with a synthetic hemodynamic response function that emphasized transient activity in response to each stimulus condition, combining data from all participants. Statistical contrasts were set up using a random-effects model to calculate signal differences between the conditions of interest across participants. Statistical t maps were derived by applying linear contrasts to the parameter estimates for the events of interest, resulting in a t statistic for every voxel. Group averages were calculated by using pairwise t tests on the
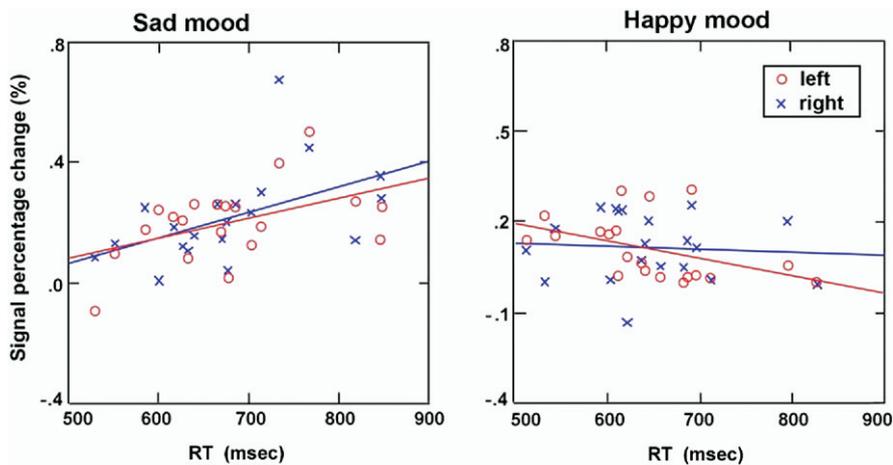
Figure 3. Correlations between amygdala activation to sad distractors and performance on the odd-ball task. **(A)** Individuals who showed the longest reaction times to detect attentional targets also showed the largest bilateral amygdala responses to sad distractors. **(B)** The relationship between amygdala activation to sad distractors and attentional performance did not extend to happy mood.

resulting contrast images. This sequential two-stage approach accounts for intersubject variability and permits generalization to the population at large. The resultant t maps were thesholded at a voxelwise uncorrected $p < .001$ with a spatial extent of three contiguous voxels. A paired t test was conducted to compare peak mean voxel-wise signal changes (4-8 sec poststimulus) in response to sad distractors relative to the immediate prestimulus baseline as a function of mood induction (happy vs. sad).

Results

Amygdala activation was assessed by comparing hemodynamic signal changes evoked by sad and neutral distractors relative to prestimulus baseline as a function of current mood. Overall, the amygdala's response was greater to sad than neutral distractors, $F(1,19) = 13.80$, $p < .001$. This effect was qualified by a distractor type × mood interaction, $F(1,38) = 9.57$, $p < .006$, and a three-way interaction among distractor type, mood, and hemisphere, $F(1,76) = 5.79$, $p < .03$. Post hoc ANOVAs revealed that sad mood increased the amygdala's response to sad pictures compared with happy mood, $F(1,19) = 9.98$, $p < .005$ but had no effect on its response to neutral pictures, $F < 1$ (Figure 2B and 2D). Consequently, there was greater signal differentiation between sad and neutral pictures in the amygdala during sad mood, $F(1,19) = 16.28$, $p < .001$, than during happy mood, $F(1,19) = 1.22$, $p = .28$ (Figure 2C). The enhancement effect of sad mood was mainly in the right amygdala, $F(1,19) = 16.01$, $p < .001$, but not in the left amygdala, $F(1,19) = 2.92$, $p = .10$ (Figure 2B and 2D).

We explored gender differences by including a gender term in the overall ANOVA. Female subjects tended to show higher amygdala activation to sad distractors under sad mood relative to happy mood, but the gender effect did not reach significance (mood × gender × hemisphere interaction, $F(1,76) = 2.56$, $p = .13$; mood × gender interaction, $F(1,38) = 4.08$, $p = .059$). We further computed the gender effect by left and right hemisphere separately (mood × gender). The right amygdala showed a significant gender effect, $F(1,38) = 5.70$, $p < .028$. The Scheffé post hoc analysis revealed significantly higher activation in female relative to male subjects, $t(38) = 2.21$, $p < .033$.

We next examined whether the degree of amygdala activation elicited by sad distractors during sad mood was associated with costs in attentional performance on the oddball task. Overall, reaction time (RT) to detect attentional targets was slower during sad mood relative to happy mood, $t(19) = 2.66$, $p < .02$, confirming slowed information processing during sad mood.

Individual-difference analysis revealed that participants who exhibited the slowest RT to targets during sad mood were also those who had the largest response in the amygdala to sad distractors (Figure 3A). Linear regression analysis showed that bilateral amygdala activation to sad distractors correlated with RT to targets during sad mood (left hemisphere: $r(19) = .47$, $p < .04$; right hemisphere: $r(19) = .51$, $p < .02$). During happy mood, this relationship showed a reverse trend in the left hemisphere, $r(19) = -.47$, $p = .053$, and no effect in the right hemisphere, $r(19) = .08$, $p = .74$ (Figure 3B). Gender differences in RT were revealed as a main effect, $F(1, 38) = 6.07$, $p < .018$, indicating that women were slower than men irrespective of mood state.

In an exploratory analysis, we identified other brain regions whose responses to sad distractors were elevated during sad mood relative to happy mood (Table 1, Figure 4). These regions included limbic–paralimbic structures (anterior cingulate gyrus, retrosplenial cortex, insula, and orbital and ventromedial prefrontal cortex), visual areas (precuneus, cuneus, and middle occipital gyrus), and the thalamus. All of these regions have either direct or indirect connections to the amygdala (Amaral et al 1992). Inspection of functional ROIs in these areas showed that none of the activations outside the amygdala correlated with RT to attentional targets during sad mood (all $ps > .05$), suggesting some specialization within the limbic forebrain regarding the impact of mood-enhanced sad stimulus processing on attentional distraction (Figure 4, Table 1).

Table 1. Stronger Activation to Sad Distractors Under Sad Relative to Happy Mood

| Brain Region	BA	Side	Tal x	Tal y	Tal z	t Value
Anterior Cingulate Cortex	BA32	L	−4	44	1	7.54
		R	11	48	8	3.7
Retrosplenial Cortex	BA30	L	−4	−50	16	4.34
		R	22	−51	6	5.27
Thalamus		L	−15	−29	12	4.12
		R	22	−14	11	4.14
Ventromedial Prefrontal Cortex	BA10	L	−4	54	−9	4.16
Orbital Frontal Cortex	BA11	L	−7	32	−14	3.75
Insula		L	−37	−3	21	4.89
Precuneus	BA7	L	−11	−78	49	4.07
Cuneus	BA19	L	−19	−97	22	3.76
Middle Occipital Cortex	BA19	R	37	−90	15	5.95
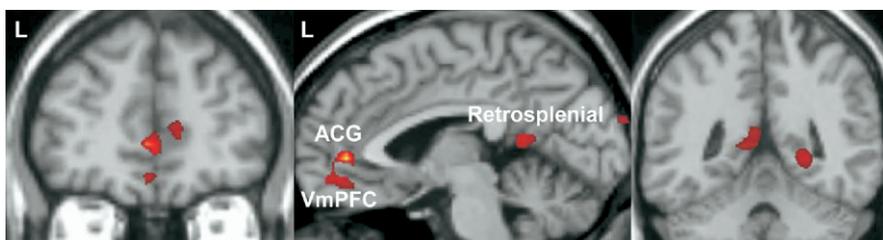
Figure 4. Voxel-based paired *t* test analysis contrasting activation to sad distractors during sad mood relative to happy mood in other regions of the brain. Depicted are responses to sad distractors enhanced by sad mood in the ventromedial prefrontal cortex (VmPFC), anterior cingulate gyrus (ACG), and retrosplenial cortex. L, left hemisphere.

Discussion

The primary results from our study reveal a novel role of the amygdala in relating interoceptive and exteroceptive sadness. Amygdala activation to sad pictures presented as distractors during a concurrent attentional task increased during sad mood induction relative to happy mood induction. Current mood had no effect on the amygdala's response to neutral picture distractors. Consequently, the amygdala showed greater differentiation in its signaling of sad versus neutral pictures during a sad mood state relative to a happy mood state. Note that the mood modulation was observed within subjects. Our findings may help explain why amygdala activation to sad sensory events is not often reported in healthy adults (Blair et al 1999; Liotti et al 2000; Phillips et al 1998) because they are typically scanned in a relatively happy mood (see baseline mood ratings in Figure 2A). A corollary to this effect is that differences in amygdala activation to sad stimuli between healthy and depressed individuals may relate in part to group differences in current mood during the scanning session, which is also supported by treatment studies showing normalization of amygdala responses to emotional stimuli (Fu et al 2004; Sheline et al 2001). Finally, we found a relationship between the degree of amygdala activation to sad distractors and RT costs to detect attentional targets on the oddball task, which occurred only during sad mood. This observation provides additional insight into mechanisms underlying cognitive distractibility in depressive states.

The amygdala's contribution to sad mood may specifically reflect an integrative sensory-visceral function that is exerted via amygdalopetal connections with hypothalamic and brain stem centers for control of the internal milieu and amygdalofugal connections with sensory processing regions (Amaral et al 1992). Sensory modulation is suggested by the enhanced occipital activation observed during sad mood (Table 1). Other paralimbic regions activated in the present report (Figure 4, Table 1) may also be important for the visceral linkage. The ventromedial prefrontal cortex (VmPFC), in particular, is heavily interconnected with the amygdala, diencephalon, and brain stem and plays an important functional role in the neural circuits of motivation and reward (Ongur and Price 2000). Increased activation in the VmPFC, specifically the subgenual cingulate cortex, has been reported to sad stimuli in normal subjects and to decreased cerebral blood flow and volume in major depression (Drevets et al 1997; Mayberg et al 1999). This area is considered a higher order brain structure that could mediate coping behavior when sad stimuli are confronted in depressed states.

Our amygdala results are reminiscent of its role in motivated behavior, where the amygdala signals the appetitive value of food rewards relative to current hunger state in concert with the VmPFC. For instance, amygdala-lesioned rats and monkeys do not exhibit sensitivity to reinforcer devaluation effects (Malkova et al 1997; Pickens et al 2003), and human amygdala activation to food images increase during states of hunger relative to satiety (Holsen et al 2005; LaBar et al 2001). Dynamic representation of mood-relevant and motivationally relevant stimuli is critical for identifying events of immediate importance to the organism. Such processing is associated with performance costs on concurrent attentional tasks (Figure 3A), however, which may have adverse cognitive consequences if allowed to persist pathologically (see also Siegle et al 2001).

It is thought that the amygdala's specialization for certain emotions likely reflects their survival functions (LeDoux 1996). The amygdala is a key brain region for fear perception and memory, but its role in processing other emotions continues to be debated. Amygdalar coding of some emotions, such as fear, may be relatively automatic and "hardwired," but, as shown here, the amygdala's engagement in other emotions depends on the relevance of the stimulus to the current behavioral state of the organism. Thus, internal states contribute to within-subject variation of the amygdala's response to environmental stimuli. These findings have implications for interpreting neuroimaging results from mood-disordered populations and complement other approaches that emphasize between-subject variation in amygdala activation to emotional stimuli as a function of personality, genetics, social attitudes, and gender (Hamann and Canli 2004).

Several studies have revealed that gender can influence the degree and lateralization of amygdala activation to emotional stimuli, although these effects are more consistent with regard to its role in memory (Cahill et al 2004; Canli et al 2002). Stronger activation in women than men has been noted bilaterally in response to negative cues (Klein et al 2003) or in the left amygdala to fearful faces (Killgore and Yurgelun-Todd 2001). Others have reported no differences as a function of gender (George 1996) or less activation in women to sad stimuli (Schneider 1997). There is considerable evidence showing that men and women have different affective styles when evaluating (Asthana and Mandal 1998), expressing and experiencing emotion (Gove and Tudor 1973; Grossman and Wood 1993). Our findings of greater right amygdala activation in women is consistent with the fact that they have reported greater negative affect intensity, a ruminative response style (Nolen-Hoeksema et al 1993) and higher incidence of major depression (20%–25% in women vs. 7%–12% in men). A right hemispheric dominance for negative emotional expression has long been postulated (Davidson 1990; Heller 1990; Silberman and Weingartner 1986) and supported in part by lesion studies (Adolphs et al 1996, 2001; Angrilli et al 1996) and increased metabolic rate (Abercrombie et al 1998). Left or bilateral amygdala activation to negative stimuli in normal subjects (Hamann et al 2002; Lane et al 1997; Posse et al 2003; Schneider et al 1997) and increased activation in the left amygdala in depressed patients have frequently been reported (Drevets 2003; Fu et al 2004; Sheline et al 2001). Differences in experimental design and stimuli used could partially account for discrepancies in lateralization across studies.

Additional research is warranted to determine whether mood effects on amygdala function vary across individuals according to personality characteristics. In addition, it would be useful to

determine whether the brain activation patterns we report extend to other emotions beyond sadness to signal mood congruency more broadly (e.g., enhanced responses to happy stimuli in a happy mood). Future research should also distinguish the role of the amygdala from other corticolimbic regions sensitive to mood manipulations (Table 1 and Figure 4) with respect to their impact on cognitive functions beyond attentional distraction. Delineating the social and genetic factors that contribute to the flexibility of amygdala responses will advance more complex neurobiological accounts of individual differences in emotion, interactions with cognitive systems, and susceptibility to affective illness.

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