Amygdala Reactivity and Mood-Congruent Memory in Individuals at Risk for Depressive Relapse

Wiveka Ramel, Philippe R. Goldin, Lisa T. Eyler, Gregory G. Brown, Ian H. Gotlib, and John R. McQuaid

Background: *According to cognitive diathesis-stress theories, a latent cognitive vulnerability to depression is activated by negative affect in individuals at risk for depressive relapse. This vulnerability can manifest as mood-congruent memory during sad mood and may involve amygdala response, which is implicated in memory for emotionally arousing stimuli. This study examined whether amygdala modulates memory for negatively valenced words before and after a sad mood induction in healthy individuals with and without a history of recurrent major depression.*

Methods: *Fourteen unmedicated remitted depressed (RD) and 14 matched never depressed (ND) individuals were scanned using functional magnetic resonance imaging (fMRI) while performing a self-referent encoding/evaluation task (SRET) preceding and following a sad mood challenge. After each SRET, participants' free recall was assessed.*

Results: *Following sad mood induction, bilateral amygdala response during encoding of valenced words predicted increased recall of negative self-referent words for a subset of RD participants. This association was not present before the sad mood induction and was not evident in individuals without a history of depression, regardless of mood state.*

Conclusions: *These results are consistent with cognitive diathesis-stress theories and suggest a role for the amygdala in modulating mood-congruent memory during transient sad mood in individuals who are vulnerable to depression relapse.*

Key Words: Depression, risk/vulnerability, mood, memory, amygdala, fMRI

Major depressive disorder (MDD) is not only one of the most frequent (Kessler et al 2005) and disabling (Murray and Lopez 1997) disorders, it is also recurrent. Epidemiological data suggest that at least 50% of patients who recover from an initial episode of depression will relapse at least once, and for patients who have had two or more depressive episodes, the risk of relapse is increased to 70% to 80% (Consensus Development Panel 1985; Shea et al 1992). These high rates of relapse underscore the importance of identifying risk factors related to symptom and episode return.

One framework for examining vulnerability to MDD is the cognitive diathesis-stress model. This model posits that individuals at risk for major depressive episodes (MDEs) are characterized by a cognitive vulnerability that remains latent until activated by a stressor that engenders negative affect (Beck 1967). It is postulated that in mild states of dysphoria, latent maladaptive self-representations, or schemas, become accessible and lead to negative patterns of thinking and feeling that may escalate to full-blown depressive episodes (Teasdale 1988). The depressogenic cognitive-affective network appears to strengthen with repeated activations over time, as reflected by the increased risk of depressive relapse with subsequent MDEs. This suggests a deepened encoding of mood and memory associations that are consolidated with repeated MDEs.

Behavioral studies have largely supported the cognitive diathesis-stress model, especially in areas involving effortful elaboration such as retrieval and interpretation (for reviews, see Ingram et al 1998; Williams et al 1997). Individuals at risk for MDEs tend to exhibit preferential memory for negative information and/or reduced retrieval of positive material when challenged with stress or negative affect (e.g., Gilboa and Gotlib 1997; Hedlund and Rude 1995; Teasdale and Dent 1987). Prospective studies suggest that these memory biases interact with negative life events to predict subsequent changes in depressive symptoms (e.g., Bellew and Hill 1991; Reilly-Harrington et al 1999). These mood-congruent memory biases in depression are particularly evident for information related to the self, as opposed to negative words in general (Bradley and Mathews 1983; Dozois and Dobson 2001; Teasdale and Dent 1987). This may be due to a more elaborate or organized network of negative information tied to the concept of self and dysphoric mood in depression-vulnerable individuals (Ingram 1984). Taken together, this evidence underscores the importance of examining the interaction of self-referent mood-congruent processing in individuals vulnerable to depression.

It is not yet clear, however, what factors and what neural mechanisms modulate mood-congruent memory biases in depression-vulnerable individuals. This is a critical gap in our understanding of vulnerability factors; certainly, knowledge of the neurobiological bases of memory biases in depression could yield valuable information about neurocognitive markers in MDD and potentially enhance our ability to identify individuals who are at particular risk for depression relapse. One potential candidate is the amygdala, a subcortical anatomical structure in the medial temporal lobe. Substantial animal research and neuroimaging studies with healthy individuals have implicated the amygdala in rapid detection of emotionally salient information and encoding of that information into long-term memory (for reviews, see Cahill 2003; Hamann 2001; McGaugh 2004). That is, greater amygdala response to emotionally arousing stimuli is associated with enhanced memory for those stimuli. The amygdala has also been frequently implicated in the maintenance of mood disorders (Whalen et al 2002). Increased amygdala activity has been found not only in currently depressed individuals (Drevets 1999; Siegle et al 2002) but also in individuals who have remitted from MDD (Bremner et al 2003; Drevets et al 1992). The integration of these research domains, however (i.e., the function of the amygdala in emotional memory and mood disorders), has not received attention. Because memory biases are one of the

From the Department of Psychology (WR, PRG, IHG), Stanford University, Stanford, California; and VA San Diego Healthcare System and Department of Psychiatry (LTE, GGB, JRM), University of California, San Diego, California.

Address reprint requests to Dr. Wiveka Ramel, Department of Psychology, Stanford University, Jordan Hall, Bldg 420, Stanford, CA 94305-2130; E-mail: wiveka@psych.stanford.edu.

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most reliable cognitive distortions in MDD and because the amygdala is a possible neural substrate implicated in the neural circuit that maintains these biases and potentially prolongs the disorder, it is important that we begin this integration.

The current study used functional magnetic resonance imaging (fMRI) to examine whether amygdala response modulates mood-congruent memory of negative words in individuals who are vulnerable to depression. Specifically, we hypothesized a stronger relation between amygdala response during self-referent encoding/evaluation of negative words and recall of negative self-referent words only after a sad mood induction in remitted depressed (RD) individuals than in never depressed (ND) control participants. This relation was not predicted during self-referent encoding and retrieval of negative words in euthymic mood. The hypothesis was based on the assumption that evaluation of negative self-descriptive words would be especially salient for individuals with a history of recurrent MDEs during a transient mood challenge. The proposed mechanism for this effect is activation of a depressogenic cognitive-affective network via an amygdala-modulated emotional arousal system that contributes to deeper encoding of negative self-referent words and subsequently enhanced retrieval of these words for RD compared with ND individuals.

Methods and Materials

Participants

Fourteen RD and 14 ND participants were matched on age, gender, years of education, and handedness (Table 1). The Structured Clinical Interview for DSM-IV (SCID) (First et al 1997) was administered by trained raters (interrater reliability, $\kappa = 1.00$; Gotlib et al 2004) to determine diagnostic status. Participants were excluded if they met criteria for a psychotic disorder, mania, hypomania, bipolar disorder, or substance/alcohol abuse in the last 6 months or reported ever being treated for substance/alcohol abuse. Never depressed control participants did not meet any DSM-IV criteria on the SCID. Participants were also excluded if they reported current psychotropic medication, daily cigarette use, a history of learning disabilities, English as their second language, neurological cardiovascular disorders, brain surgery, electroconvulsive or radiation treatment, brain hemorrhage, tumor, stroke, seizures, epilepsy, diabetes, hypothyroidism or hyperthyroidism, or head trauma with loss of consciousness greater than 5 minutes. Due to potential effects on cerebral blood flow, participants were asked not to consume any alcohol, recreational drugs, and pain killers (e.g., ibuprofen or aspirin) during the 24-hour period before their magnetic resonance (MR) scan or to ingest caffeinated fluid or food 5 hours prior to the scan.

Inclusion/Exclusion Criteria for RD Participants. Remitted depressed individuals were required to have experienced a minimum of two past MDEs, with the most recent episode occurring within the past 10 years. Remitted depressed individuals were considered remitted from their depression if they reported no signs of depressive illness during the past 8 weeks prior to assessment (i.e., no more than two symptoms experienced to more than a mild degree). Remitted depressed individuals who exhibited subsyndromal depression were considered not fully remitted and were thus excluded from the study. These conservative diagnostic criteria adhere to the guidelines recommended by the National Institute of Mental Health (NIMH) Collaborative Program on the Psychobiology of Depression for definition of depression recovery (Keller et al 1992; Winokur et al 1993). In addition, RD individuals were required to obtain scores in the minimal symptom range (<14) on the Beck Depression Inventory-II (BDI-II) (Beck et al 1996) and in the asymptomatic range (<7) on the 17-item Hamilton Depression Rating Scale (HDRS-17) (Hamilton 1960). The BDI-II and HDRS-17 criteria meet the Frank et al (1991) definition for fully remitted depressed patients.

Procedures

Approvals for procedures used in this study were obtained from Internal Review Boards at the University of California San Diego, San Diego State University, and Stanford University. Potential participants were recruited through web-based community listings, posters, and outpatient psychiatry clinics at Stanford University. Following an initial telephone screening interview, potentially eligible participants came to the laboratory, provided informed consent, and completed a clinical assessment consisting of a structured diagnostic interview and a battery of psychiatric questionnaires. The questionnaires included the Emotion Regulation Questionnaire (ERQ) (Gross and John 2003), NEO-Five Factor Inventory, short form (NEO-FFI) (Costa and McCrae 1992), Response Style Questionnaire (RSQ) (Nolen-Hoeksema and Morrow 1991), and State Trait Anxiety Inventory (STAI) (Spielberger et al 1983).

Between 1 to 2 weeks later (mean interval = 9.3 days, SD = 8.1 days), eligible participants attended a scanning session, with the majority (82%) being scanned in the evening (6:00 PM to 10:00

Table 1. Demographic and Matching Characteristics of the Sample

	Remitted Depressed			Never Depressed		
Variable	Mean (SD)	*n*	%	Mean (SD)	*n*	%
Total Sample		14			14	
Age	36.79 (8.07)			36.43 (10.86)		
Years of Education	17.39 (2.56)			17.21 (2.40)		
Females		10	71.4		10	71.4
Handedness (Mean = EHI, *n* = Right-Handed)	4.41 (.70)	13	92.9	4.07 (.83)	13	92.9
Caucasian		12	85.7		8	57.1
African American		0	0		2	14.3
Asian		1	7.1		1	7.1
Married		3	21.4		4	28.6
Divorced		2	14.3		3	21.4
Shipley Vocabulary (T-score)	58.29 (5.00)			60.50 (5.05)		

There were no significant between-group differences on any of the demographic variables.
EHI, Edinburgh Handedness Inventory.

PM). Before the scan, participants completed questionnaires and interviews assessing mood (BDI-II and HRSD), affective state (Positive and Negative Affect Schedule-State version [PANAS-S]) (Watson et al 1988), and sleepiness (Stanford Sleepiness Scale [SSS]) (Hoddes et al 1973), and practiced the scanner task with nonexperimental word stimuli. Participants were scanned as they completed a Self-Referent Encoding/Evaluation Task (SRET) before and after a sad mood-induction procedure (MIP). Visual Analogue Scales (VAS) were used to assess current mood state four times during the scanning session. Participants rated their moods on three 9-point unipolar VAS measuring sadness, anxiety, and happiness dimensions anchored with 1 = neutral, 5 = moderate, and 9 = extreme. After each SRET, participants performed a free recall task while the scanner was offline. Following scanning, participants completed questionnaires about their affective state, scanning experience, and level of sleepiness and were debriefed and reimbursed. Care was taken to assure that participants' mood had returned to average levels before they left.

Information Processing Tasks

Self-Referent Encoding/Evaluation Task. The SRET (Derry and Kuiper 1981) is an information-processing measure of self-schema. Participants press a button indicating whether a word is self-descriptive (Yes/No). To maximize detection of signal magnitude across conditions, a blocked experimental design was chosen for this study (Liu et al 2001). Two independent but equivalent versions of the SRET (SRET1 and SRET2) were administered during MR scanning using E-PRIME software (Psychological Software Tools, Inc., Learning 2002; Research and Development Center, University of Pittsburgh, Pennsylvania). The two SRET versions were counter-balanced in order of presentation across participants. In each SRET, 36 positive, 36 negative, and 36 neutral words were presented in 18 blocks, with each block consisting of 6 words of the same valence. All of the neutral and two thirds (four blocks) of the positive and negative adjectives were derived from the Affective Norms for English Words (ANEW) (Bradley and Lang 1999) and were selected for equivalence of word length, frequency, and arousal across valence. The remaining one third (two blocks) of the negative and positive words were idiosyncratic words generated by the participants in an effort to increase the personal relevance of the SRETs. For the current report, the normed ANEW words and the idiosyncratic words were collapsed into a single unit of analysis.

Each word was presented for 3 seconds with no intertrial interval, making each word block 18 seconds long. As a baseline condition, each word block was followed by an asterisk fixation block, during which participants did not make any responses. The duration of the fixation blocks was jittered (range, 6 seconds to 18 seconds, mean = 12 seconds) to reduce anticipation of the subsequent word block onset. Total time for a SRET run was 9 minutes and 9 seconds. The blocks were presented in a fixed pseudorandomized order; two blocks of the same valence never followed each other and each SRET started and ended with neutral word blocks. Within each word block, the words of the same valence were randomly selected without replacement. During fMRI scanning, stimuli were back-projected onto a screen by an LCD projector and viewed by means of a mirror attached to the head coil. Each word or fixation asterisk was presented in the center of the screen in white capitalized letters against a black background.

Recall Task. Participants were informed prior to scanning that a recall task would follow each SRET. While in the scanner in the absence of MR data acquisition, participants were asked to recall as many words as possible (minimum 3 words and maximum 20 words) from the immediately preceding SRET over a period no longer than 5 minutes while a researcher (WR) recorded the recalled words. Requiring participants to report a minimum and maximum number of words is a procedure that has been used in prior research (Hertel and Rude 1991) to standardize the extent of effort and threshold for responding.

Mood-Induction Procedure

The MIP consisted of a combination of re-experiencing an autobiographical sad personal event and listening to somber music. This induction is one of the more effective strategies for evoking transient, dysphoric mood states (Martin 1990).

Approximately 1 week prior to scanning, eligible participants were asked to compose a detailed autobiographical script of a very sad personal experience. On a scale from 1 (neutral) to 9 (extremely sad), they were encouraged to describe an event that they rated 5 or higher. Participants also listened to the first minute of four music pieces on a compact disc with headphones and chose one that could best bring about sad affect. The music consisted of standard selections previously used in sad mood-induction studies.[1] While in the MR scanner, participants listened to approximately 7 minutes of the selected music piece while reading and re-experiencing the sadness of the event depicted in the autobiographical script, which was projected onto a screen. Because MR scanning was not occurring during this time, the participant could clearly hear the music through headphones. On completion, the participant was asked to make VAS ratings.

Image Acquisition

Magnetic resonance imaging was performed on a General Electric 1.5 Tesla Signa magnet with a T2*-weighted gradient-echo spiral in/out pulse sequence sensitive to blood oxygenation level-dependent (BOLD) contrast (Glover and Law 2001). Head movement was minimized with tight padding as well as a bite bar. Functional images (366 volumes per functional run) were obtained from 21 sequential axial slices (repetition time [TR] = 1500 milliseconds, echo time [TE] = 30 milliseconds, flip angle = 75°, field of view [FOV] = 24 cm, matrix = 64 × 64, single shot, in-plane resolution = 3.75 × 3.75 mm, and slice thickness = 5mm). A high-resolution, T1-weighted spoiled-GRASS (gradient-recalled acquisition in the steady state) pulse sequence was used to acquire structural images in the sagittal plane at the end of each MR scanning session (TR = 9.0 ms, TE = 1.2 ms, in-plane resolution = .9375 mm, and slice thickness = 1.5 mm).

fMRI Data Preprocessing and Statistical Analyses of Functional Images

Analysis of Functional NeuroImages (AFNI) (Cox 1996) was used for preprocessing and statistical analysis of these data. For each functional run, the first 9 seconds were removed to allow for magnetic stabilization, slice acquisition time was interpolated to the middle time point of each TR, volumes were registered to an empirically determined optimal base image, outliers were interpolated, voxels were spatially smoothed using an isotropic Gaussian kernel of full-width half-maximum (FWHM) 3.75 mm^3, and high-pass filtering removed low-frequency noise. No brain

[1]The music selections were *Russia under the Mongolian Yoke* from the film *Alexander Nevsky*, composed by Prokofiev, played at half speed; *Adagio for Strings* from the film *Platoon,* composed by Samuel Barber; *Drive Home* from the film *Field of Dreams,* composed by James Horner; and *Adagio* by Albinoni.

volumes with movement greater than ±1.25 mm in the x, y, or z direction were detected. Visual inspection of each time series resulted in the elimination of a total of 22 brain volumes across three participants (2 ND and 1 RD). There was no evidence of stimulus-correlated motion within or between groups.

AFNI's 3dDeconvolve program was used to conduct linear regression analyses. Stimulus vectors for each condition were convolved with a gamma variate model of the hemodynamic response function. The model estimated components of the MR time series associated with 1) baseline, linear, and quadratic trends; 2) three translation and three rotation motion correction variables; 3) BOLD signal for each condition (i.e., negative, positive, and neutral words); and 4) general linear contrast of negative versus positive words (a separate regression analysis contrasted each valence vs. fixation blocks). Statistical maps were resampled into 3.75 mm^3 isotropic voxels and spatially normalized into Talairach and Tournoux (1988) atlas space before group analyses. Anatomical region of interest (ROI) masks of left and right amygdala were drawn based on structural probability maps defined in the Talairach Daemon (Lancaster et al 2000). Examination of individual participant brain maps confirmed that the boundaries of the amygdala were included in the anatomical ROI masks. Fit coefficient values were averaged over all the voxels in the amygdala ROI.

Results

Clinical Characteristics

As shown in Table 2, mean MDE in the clinical sample was 4.6 (range 2–12, median = 3.5) and mean time since last MDE was about 3 years (range 3.5 months to 8 years). Only one RD participant met criteria for a current anxiety disorder (panic disorder without agoraphobia), and four had prior histories of an anxiety disorder (two with social phobia, one with panic disorder, and one with posttraumatic stress disorder). Seventy-nine percent of RD participants reported previous antidepressant treatment (primarily selective serotonin and/or norepinephrine reuptake inhibitors and bupropion) with a mean of 26 months (range 3–87 months) since treatment termination. Eighty-six percent had received psychotherapy treatment. No participants were currently being treated with psychotropic medications or psychotherapy. Both RD and ND participants presented with minimal depressive symptomatology as defined by the BDI-II and HRSD-17 and did not differ significantly. However, RD participants endorsed significantly higher levels of trait anxiety (STAI), neuroticism (NEO-FFI), expressive suppression (ERQ), and ruminative tendencies (RSQ) than did ND participants. Immediately prior to scanning, RD participants reported higher negative affect (NA) on the PANAS-S than did ND participants [RD = 13.3, ND = 10.9, $t(26) = 2.43$, $p < .05$]. Although not clinically significant, this difference was statistically controlled for in the primary analyses. The groups did not differ on NA immediately after scanning or in positive affect and sleepiness at prescanning or postscanning.

Mood Manipulation

To assess the effect of the mood induction on VAS mood ratings, a three-factor analysis of covariance (ANCOVA) was conducted with one between-subject factor (Group: ND and RD), two within-subject factors (Emotion: sad, happy, and anxious; and Time: pre-SRET1/VAS1, pre-MIP/VAS2, post-MIP/VAS3, and post-SRET2/VAS4), and PANAS-S NA as a covariate. Type 1 error rate for multiple pairwise follow-up comparisons was controlled using Tukey honestly significant difference (HSD). The analysis yielded a significant interaction of Emotion and Time [$F(6,20) = 4.98$, $p < .003$, η_p^2 (partial eta squared) = .60], with no significant main ($p = .17$) or interaction (all p's $> .11$) effect for Group. As shown in Figure 1, both groups demonstrated significantly increased sadness ratings and decreased happiness ratings at the most critical time points, that is, from pre-MIP to post-MIP, while anxiety ratings remained constant throughout the experiment. Exam-

Table 2. Clinical and Personality Characteristics of the Sample

	Remitted Depressed			Never Depressed		
Variable	Mean (SD)	*n*	%	Mean (SD)	*n*	%
No. of Previous MDEs	4.57 (3.13)				0	
Months Since Last MDE	37.07 (31.41)					
Age at First MDE	17.57 (7.36)					
Current Anxiety Disorder		1	7.1		0	
Anxiety Disorder in Remission		4	28.6		0	
Mood Disorder Family History		11	78.6		2	14.3
Previous AD Treatment[a]		11	78.6		1	7.1
Previous Psychotherapy Treatment[a]		12	85.7		5	35.7
Previous CBT Treatment[a]		5	35.7		0	
Depressive Symptoms (BDI-II)	3.86 (4.42)			1.86 (2.80)		
Depressive Symptoms (HRSD-17)	1.79 (1.48)			.93 (.83)		
Cognitive Reappraisal (ERQ)	29.57 (7.54)			31.36 (4.38)		
Expressive Suppression (ERQ)[a]	16.71 (5.08)			13.07 (4.18)		
Extraversion (NEO-FFI)	38.86 (5.89)			43.79 (7.26)		
Neuroticism (NEO-FFI)[a]	36.64 (7.42)			23.57 (6.67)		
Rumination (RSQ)[a]	43.21 (12.36)			33.86 (8.20)		
Trait Anxiety (STAI)[a]	39.00 (9.86)			28.64 (6.80)		

MDE, major depressive episode; AD, antidepressant; CBT, cognitive behavioral therapy; BDI-II, Beck Depression Inventory; Second Edition; HRSD-17, 17-item Hamilton Rating Scale for Depression; ERQ, Emotion Regulation Questionnaire; NEO-FFI, NEO Five-Factor Inventory; RSQ, Response Style Questionnaire; STAI, State Trait Anxiety Inventory.

[a]Indicates a differences between the groups at $p < .05$. Previous psychotherapy treatment was defined broadly and included counseling in college, couples therapy, group therapy, as well as focused therapy addressing a clinical diagnosis.

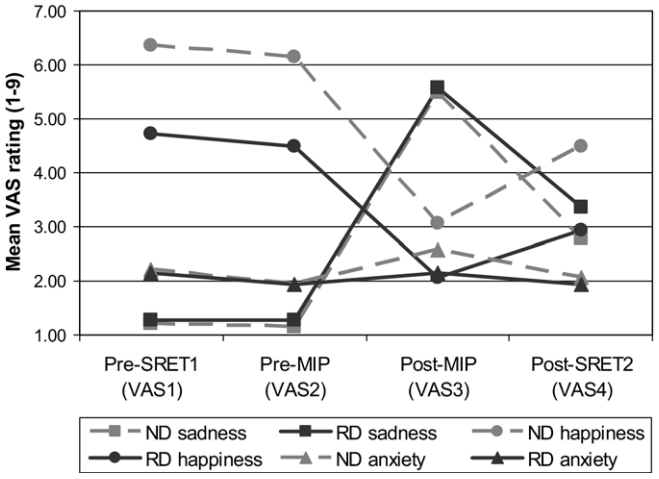

Figure 1. VAS ratings in ND and RD groups. Split-plot ANCOVA analysis indicated a significant Emotion by Time interaction [$F(6,20) = 4.98$, $p < .003$], with both groups reporting significantly increased sadness and decreased happiness ratings from pre-Mean to post-MIP, while anxiety ratings remained unchanged. The two groups differed significantly on happiness ratings at pre-SRET1 and post-SRET2 time points. Behavioral observation indicated that 5 RD participants and 2 ND participants (ns, $p = .39$) cried during the MIP. VAS, Visual Analogue Scales; MIP, mood-induction procedure; SRET, Self-Referent Encoding/Evaluation Task; RD, remitted depressed individuals; ND, never depressed control participants.

ining each emotion at each time point, between-group univariate contrasts did not yield any significant differences for the sadness or anxiety ratings. However, ND participants rated themselves significantly happier than did RD participants at pre-SRET1 [$F(1,25) = 4.66$, $p < .05$] and post-SRET2 [$F(1,25) = 4.41$, $p < .05$]. As is evident in Figure 1, the ND and RD groups reported very consistent changes in their mood ratings across the experiment, but ND participants' happiness ratings were higher than those of RD participants at the start and end points of the experiment.

Behavioral Results

SRET Recall. The groups did not differ significantly on mean total correct words recalled after SRET1 (ND = 10.00 vs. RD = 10.43), after SRET2 (ND = 9.29 vs. RD = 8.79), or from SRET1 to SRET2. Compared with RD participants, the ND participants reported a significantly higher number of intrusions (non-SRET recalled words) after SRET2 [ND = 2.43 vs. RD = 1.29, $t(26) = 2.17$, $p < .04$], but this difference was not specific to any valence. These results suggest that despite their significant psychiatric history, the RD participants in the current study did not show a general free recall deficit.

The primary outcome variable for SRET recall was the number of endorsed words in a valence category that was subsequently recalled divided by the total number of words endorsed (e.g., all endorsed and recalled negative SRET1 words were divided by total number of endorsed SRET1 words). This variable has the advantage of controlling for group differences in overall rates of endorsement (Symons and Johnson 1997) and will henceforth be referred to as proportion self-referent recall. Means and standard deviations for both the unadjusted (i.e., without division with total endorsement) and proportion self-referent recall by valence are shown in Table 3. Analyses of retrieval for each valence category revealed a significant reduction in recall of proportion self-referent positive words from pre-MIP to post-MIP for the RD participants [$F(12) = 5.77$, $p < .04$] but not for ND participants ($p = .47$).

fMRI Results

Amygdala and Recall of Negative Self-Referent Words. We hypothesized that recall of negative self-referent words would be significantly predicted by greater differential amygdala BOLD response to negative versus positive words in RD compared with ND post-MIP. Hierarchical linear regressions were conducted for each group at pre-MIP (SRET1) and at post-MIP (SRET2) with proportion negative self-referent recall as the dependent variable. The predictor variable was BOLD response (fit coefficient) from an anatomical ROI mask of bilateral amygdala for the contrast of negative versus positive words. This variable was entered in step 2 of the regression analysis after controlling for PANAS-S NA (entered in step 1). Negative and positive word blocks were used because they were the most balanced of our word conditions in terms of word selection (i.e., containing both normed ANEW words and idiosyncratically derived words) and arousal. To examine the contribution for each valence, we also conducted similar hierarchical regression analyses with negative words versus asterisk fixation block contrast or positive words versus fixation block contrast as the predictor variable. Fisher's r-to-Z transformation was used to compare the magnitude of correlations between groups.

Pre-MIP, there was no relation between recall and BOLD response in the amygdala for either group. Post-MIP, however, left and right amygdala response to negative versus positive words predicted proportion negative self-referent recall in RD participants [$F(2,10) = 8.86$, $p < .007$, adjusted $R^2 = .55$, R^2 change = .62] but not in ND participants ($F = .06$, $r = .13$), as

Table 3. Self-Referent Recalled SRET Words per Group and Valence

	Unadjusted Self-Referent Words Recalled				Proportion Self-Referent Words Recalled			
	Pre-MIP (SRET1)		Post-MIP (SRET2)		Pre-MIP (SRET1)		Post-MIP (SRET2)	
Valence Category	RD	ND	RD	ND	RD	ND	RD	ND
Negative Words	.64 (.84)	.64 (.93)	.71 (1.07)	.57 (.94)	.013 (.017)	.015 (.021)	.017 (.027)	.014 (.023)
Positive Words	3.79 (1.89)[a]	3.29 (1.64)	2.21 (2.55)[a]	2.29 (1.90)	.092 (.048)[a]	.080 (.038)	.052 (.052)[a]	.059 (.049)
Neutral Words	1.00 (1.04)	.50 (.65)	1.14 (1.41)	.64 (.75)	.026 (.028)	.012 (.015)	.028 (.034)	.017 (.019)

Proportion self-referent recalled words refer to the number of endorsed and subsequently recalled words within a valence category divided by the total number of endorsed words per SRET. Unadjusted self-referent recall has not been divided by endorsement ratings.

MIP, mood-induction procedure; ND, never depressed; RD, remitted depressed; SRET, self-referent encoding/evaluation task; PANAS-S, Positive and Negative Affect Schedule-State version.

[a]Indicates a difference within a group from pre-MIP to post-MIP at $p < .05$ after controlling for PANAS-S negative affect. There were no significant differences between groups within the SRETs.

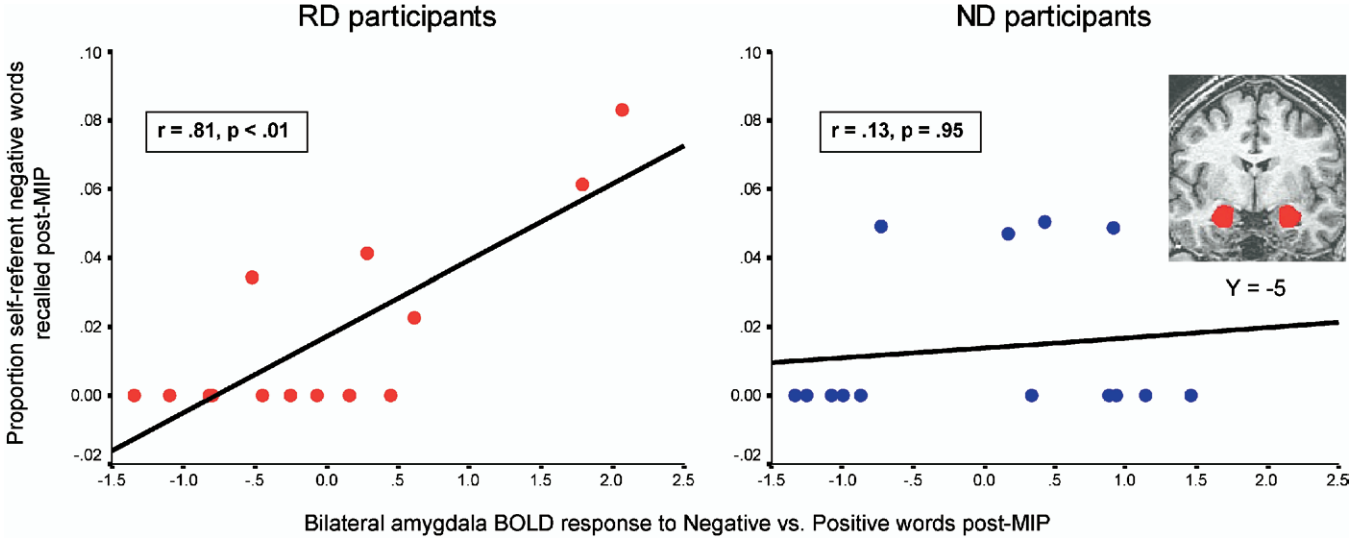

Figure 2. Scatterplots from hierarchical linear regression analyses predicting proportion self-referent negative recall post-MIP. Positive and Negative Affect Schedule-State version (PANAS-S) negative affect was entered in step 1 as a covariate and BOLD response to negative versus positive words in left amygdala and right amygdala, separately, were entered in step 2 as the independent variables. The regression analysis was significant for the remitted depressed (RD) [$F(2, 10) = 8.86, p < .007$] but not for the never depressed (ND) control group ($F = .06$). The magnitude of the correlations was significantly different between the groups ($Z = 2.33$, $p < .02$). MIP, mood-induction procedure; PANAS-S, Positive and Negative Affect Schedule-State version; BOLD, blood oxygenation level-dependent; RD, remitted depressed individuals; ND, never depressed control participants.

shown in Figure 2. Between-group comparison of the correlation coefficients revealed a significant difference ($Z = 2.34$, $p < .02$). In RD participants, right amygdala response was positively associated ($t = 3.87$, $p < .004$, sr^2 [semipartial variance] = .52), while left amygdala was negatively associated with negative self-referent recall ($t = -3.84$, $p < .004$, $sr^2 = .51$). Thus, increased signals in the right amygdala during encoding of negative words and in the left amygdala during encoding of positive words were associated with enhanced recall of negative self-referent words in RD participants post-MIP. The scatterplots highlight the low recall of negative self-referent words, with an average of .64 words (unadjusted) for both groups at both time points (range of 0–3 words), with the majority of subjects not recalling any self-referent negative words.[2] Of note, the groups did not differ significantly in number of negative self-referent words recalled (Table 2) or in number of individuals per group recalling one or more negative self-referent words post-MIP (5 RD and 4 ND), but the association with amygdala response was present only in the RD group.

Amygdala response also predicted negative self-referent recall post-MIP in RD participants when unadjusted negative self-referent recall was used as the dependent variable [$F(2,10) = 4.75$, $p < .05$]. When the mean number of total negative words recalled was regressed on amygdala response to negative versus positive words, no significant regressions emerged for either group at pre-MIP or post-MIP, suggesting the retrieval results were specific to negative self-referent recall. The amygdala-recall finding was not specific to the negative versus positive word contrast; it was also observed when negative words were contrasted to asterisk fixation blocks and used as the predictor variable [$F(2,10) = 4.55$, $p < .04$, adj. $R^2 = .34$), where it was driven by the right amygdala ($t = 3.02$, $p < .02$, $sr^2 = .46$). In contrast, no significant results were found when regressing negative self-referent word recall on BOLD response to positive words versus fixation blocks in the right or left amygdala.

Characteristics of RD Participants with Amygdala-Modulated Mood-Congruent Recall

Examining the scatterplot in Figure 2, five data points distributed from .02 to .08 on the Y–axis appear to be responsible for the amygdala and negative word recall correlation in RD participants. In post hoc analyses, the five RD participants with amygdala-modulated negative recall were contrasted with the remaining nine RD participants who did not show amygdala-modulated negative recall on the variables listed in Tables 1 and 2 (i.e., demographics, personality, psychiatric symptom and history) as well as affective state. Table 4 shows means and frequencies on indices with notable group differences. Of the five participants with amygdala-modulated negative recall, all were female, and four had a comorbid current ($n = 1$) or past ($n = 3$) anxiety disorder in contrast to only one among the remaining nine RD participants ($p < .05$). The five RD participants reported significantly longer time since their last MDE, earlier age of MDD onset, as well as higher depressive symptoms (BDI-II) and rumination (RSQ), driven by the brooding subscale, than the other nine RD participants. The groups did not differ on number of past MDEs, depressive symptoms as measured by HDRS-17, neuroticism or extraversion (NEO-FFI), trait anxiety (STAI), negative or positive state affect (PANAS-S), or VAS ratings.

Discussion

The current study is the first to demonstrate that amygdala BOLD response modulates mood-congruent retrieval biases in a psychiatrically vulnerable population. By integrating biological and psychological constructs, this study provides valuable information regarding a possible neural marker of a well-established cognitive-affective process that places some individuals at an

[2]Negative self-referent recall residuals from the regression analysis were examined both for the entire sample and for each group. Skewness, kurtosis, and statistical tests of normality (Kolmogorov-Smirnov, Shapiro-Wilk) all indicated that there were no violations of the normal distribution assumption of the residuals.

Table 4. Characteristics Differing Between RD Participants With and Without Amygdala-Modulated Mood Congruent Negative Self-Referent Recall

	5 RD with Amygdala-Modulated Negative Self-Referent Recall				9 RD Without Amygdala-Modulated Negative Self-Referent Recall				
Variable	Mean (SD)	Range	*n*	%	Mean (SD)	Range	*n*	%	Cohen's *d*
Months Since Last MDE[a]	64.00 (34.81)	6–96			22.11 (17.09)	3.5–49			1.77
Age at First MDE[a]	11.80 (2.86)	8–15			20.78 (7.17)	13–35			1.72
DSM-IV Anxiety Disorder[a]			4	80.0			1	11.1	
Depressive Symptoms (BDI-II)[a]	7.20 (3.63)	2–11			2.00 (3.77)	0–11			1.44
Expressive Suppression (ERQ)[b]	20.20 (2.05)	18–22			14.78 (5.29)	7–21			1.25
Rumination (RSQ)[a]	52.20 (16.69)	34–79			38.22 (5.52)	30–47			1.36

MDE, major depressive episode; BDI-II, Beck Depression Inventory, Second Edition; ERQ, Emotion Regulation Questionnaire; RSQ, Response Style Questionnaire.

[a]Indicates a difference between the groups at $p < .05$.

[b]Indicates a difference between the groups at $p = .05$.

increased risk for depressive relapse. The results indicate that in a subset of a carefully screened and characterized sample of asymptomatic and nonmedicated individuals who were fully remitted from recurrent MDEs, bilateral amygdala response was associated with a negative recall bias following a sad mood induction. This association was not observed when the RD participants were in a euthymic mood, and it was not evident in individuals without a psychiatric history regardless of mood state. Moreover, the relation was specific to self-referent negative word recall and was not observed with recall of all negative words.

That amygdala response during encoding of valenced words in transient sad mood contributes to recall of negative self-referent words in a subgroup of RD participants may be related to several mechanisms, including increased emotional arousal (McGaugh 2004), enhanced elaboration or rehearsal of information related to the self (cf. depth of processing theory, Craik and Tulving 1975), or a combination of increased emotional arousal and extended elaboration. As revealed by the regression scatterplots, the amygdala-modulated negative recall was produced by five RD participants whose demographic and psychiatric characteristics (notably, female gender, comorbid anxiety disorder, early MDD onset, increased rumination, and depressive symptoms) have been implicated in more protracted courses of MDD as well as relapse/recurrence (Belsher and Costello 1988; Nolen-Hoeksema and Morrow 1991). There were only five RD participants in the entire sample who had a comorbid anxiety disorder, and the fact that four of them were among the participants with the amygdala-modulated negative recall argues for the role of the amygdala in arousal, as this is a key feature in anxiety disorders (Clark et al 1994). Given the high rates of comorbidity between lifetime anxiety disorders and major depressive disorder (59.2%; Kessler et al 2003), one would expect an overlap in brain regions mediating emotional responses in individuals with depressive and anxious predispositions. In this respect, the amygdala appears to be a viable candidate, as it has been implicated in neuroimaging studies with both anxious and depressed patient samples (e.g., Davidson and Irwin 1999). The RD participants with comorbid current or past anxiety disorder may be particularly likely to react with a sense of threat or worry to potent self-referent words, and this heightened arousal may increase the likelihood of amygdala-modulated emotional memory formation. A limit to this formulation is that these five RD participants did not endorse higher trait anxiety or positive/negative state affect at prescanning or postscanning, but low statistical power necessitates further investigation of this hypothesis.

The relation between amygdala and recall revealed hemispheric laterality. This finding indicated that the combination of increased BOLD signal in right amygdala to negative words and increased signal in left amygdala to positive words predicted negative self-referent recall post-MIP in the RD group. When negative word blocks were contrasted to baseline fixation blocks, the right amygdala relation was replicated, yielding additional validation for this association. As reviewed by Hamann (2001), although the amygdala has been more frequently linked with negative emotion and memory, a growing number of studies have implicated the amygdala in a corresponding role for retrieval of positive stimuli. As indicated by the Hamann (2001) review, the amygdala might modulate encoding and retrieval of both positive and negative self-referent information. This suggests that it is emotional arousal, rather than valence, that is the primary factor engaging the amygdala.

Several previous neuroimaging studies have found support for sex-related lateralization of amygdala function in long-term memory modulation of emotionally arousing stimuli (reviewed in Cahill 2003). These studies report predominantly increased right amygdala responses among male participants and predominantly increased left amygdala responses among female participants to arousing negative stimuli. Given that the present results implicated bilateral amygdala activation, with the right amygdala demonstrating increased response to negative words in a sample of female participants, they are partly inconsistent with the prior literature. It is likely, however, that other individual differences (e.g., psychiatric status), as well as baseline metabolism and brain structure, are considerations in this context. Indeed, neither functional (Abercrombie et al 1998; Drevets 1999; Drevets et al 1992; Siegle et al 2002) nor structural (Sheline 2003) imaging studies of major depression have demonstrated consistent hemispheric differences in amygdala.

The amygdala-modulated negative self-referent recall in the RD group was not paralleled by a significant increase in recall of these words following the mood-induction, suggesting a dissociation between neural and behavioral results. In the behavioral analyses, however, we did find a significant reduction in recall of positive self-referent words in the RD participants from before mood induction to after mood-induction. Given different statistical power contexts and units of analyses in neuroimaging and behavioral experiments, incompletely overlapping patterns of results are to be expected and may reflect different sensitivities in measurement techniques. The behavioral finding of reduced positive self-referent word recall in the RD participants speaks to the efficacy of the mood-induction in inducing a mood-congruent response in this group, as this can be characterized by both increases in negative responses and decreases in positive responses compared with control participants (for examples of the

latter, see Gilboa et al 1997; Hedlund and Rude 1995; McCabe et al 2000). It is likely that this cognitive-affective change identified behaviorally reflects a similar or related mechanism as the finding observed in the fMRI analyses. Both suggest a mood-induced bias in affective information processing that is specific to individuals vulnerable to depression; behaviorally, this was expressed with reduced recall of mood-incongruent words, and neurally, this was identified with increased amygdala-modulated mood-congruent recall.

It is important to note some limitations of the present study. First, the amygdala-modulated negative self-referent recall was limited to a small sample of RD participants with specific psychiatric characteristics, restricted demographics, and high educational attainment. Replication is necessary before firmer conclusions can be drawn about the role of the amygdala in emotional memory in individuals at risk for mood disorders. Methodological concerns include the possibility that demand characteristics influenced the mood-induction results, although evidence challenges the notion that explicit mood-induction can be accounted for by demand effects (Martin 1990). Because the retrieval results are limited by a restricted range in the number of words recalled and a blocked SRET design, an analysis of the relation between BOLD signal to individual items and subsequent memory is precluded. Future studies would benefit from using a larger sample, an event-related design, and incorporating recognition memory. It will also be important to extend the analysis of the neural basis of emotional memory to other areas of the brain associated with memory, emotion, and self-referent processing, such as the hippocampus, anterior cingulate, and medial prefrontal cortex.

In conclusion, the results from the current study suggest that the amygdala modulates mood-congruent and self-referent memory biases during transient sad mood in individuals who are vulnerable to depression relapse. While this finding does not speak to a causal role of the amygdala in the development of cognitive vulnerability to depression, it provides preliminary evidence that amygdala may be part of a diathesis-stress neural mechanism modulating a mood-memory association in individuals with a history of recurrent MDEs. A longitudinal study is necessary to evaluate whether the amygdala-modulated negative recall is associated with greater risk of depressive relapse.

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Abercrombie HC, Schaefer SM, Larson CL, Oakes TR, Lindgren KA, Holden JE, et al (1998): Metabolic rate in the right amygdala predicts negative affect in depressed patients. *Neuroreport* 9:3301–3307.

Beck AT (1967): *Depression: Clinical, Experimental, and Theoretical Aspects*. New York: Harper and Row.

Beck AT, Steer RA, Brown GK (1996): *Beck Depression Inventory-Second Edition Manual*. San Antonio, TX: The Psychological Corporation.

Bellew M, Hill AB (1991): Schematic processing and the prediction of depression following childbirth. *Pers Individ Dif* 12:943–949.

Belsher G, Costello CG (1988): Relapse after recovery from unipolar depression: A critical review. *Psychol Bull* 104:84–96.

Bradley B, Mathews A (1983): Negative self-schemata in clinical depression. *Br J Clin Psychol* 22:173–181.

Bradley MM, Lang PJ (1999): *Affective Norms for English Words (ANEW): Technical Manual and Affective Ratings*. Gainsville FL: The Center for Research in Psychophysiology, University of Florida.

Bremner JD, Vythilingam M, Ng CK, Vermetten E, Nazeer A, Oren DA, et al (2003): Regional brain metabolic correlates of alpha-methylparatyrosine-induced depressive symptoms: Implications for the neural circuitry of depression. *JAMA* 289:3125–3134.

Cahill L (2003): Sex-related influences on the neurobiology of emotionally influenced memory. *Ann N Y Acad Sci* 985:163–173.

Clark LA, Watson D, Mineka S (1994): Temperament, personality, and the mood and anxiety disorders. *J Abnorm Psychol* 103:103–116.

Consensus Development Panel (1985): NIMH/NIH Consensus Development Conference statement. Mood disorders: Pharmacologic prevention of recurrences. *Am J Psychiatry* 142:469–476.

Costa PT, McCrae RR (1992): Normal personality assessment in clinical practice: The NEO Personality Inventory. *Psychol Assess* 4:5–13.

Cox RW (1996): Software for analysis and visualization of functional magnetic resonance neuroimages. *Comput Biomed Res* 29:162–173.

Craik FI, Tulving E (1975): Depth of processing and the retention of words in episodic memory. *J Exp Psychol Gen* 104:268–294.

Davidson RJ, Irwin W (1999): The functional neuroanatomy of emotion and affective style. *Trends Cogn Sci* 3:11–21.

Derry PA, Kuiper NA (1981): Schematic processing and self-reference in clinical depression. *J Abnorm Psychol* 90:286–297.

Dozois DJ, Dobson KS (2001): Information processing and cognitive organization in unipolar depression: Specificity and comorbidity issues. *J Abnorm Psychol* 110:236–246.

Drevets WC (1999): Prefrontal cortical-amygdalar metabolism in major depression. *Ann N Y Acad Sci* 877:614–637.

Drevets WC, Videen TO, Price JL, Preskorn SH, Carmichael ST, Raichle ME (1992): A functional anatomical study of unipolar depression. *J Neurosci* 12:3628–3641.

First MB, Gibbon M, Spitzer RL, Williams JBW (1997): *Structured Clinical Interview for DSM-IV Axis I Disorders, Non-Patient Edition (SCID-NP, version 2.0)*. New York: Biometrics Research Department, New York Psychiatric Institute.

Frank E, Prien RF, Jarrett RB, Keller MB, Kupfer DJ, Lavori PW, et al (1991): Conceptualization and rationale for consensus definitions of terms in major depressive disorder. Remission, recovery, relapse, and recurrence. *Arch Gen Psychiatry* 48:851–855.

Gilboa E, Gotlib IH (1997): Cognitive biases and affect persistence in previously dysphoric and never-dysphoric individuals. *Cogn Emotion* 11:517–538.

Gilboa E, Roberts JE, Gotlib IH (1997): The effects of induced and naturally occurring dysphoric mood on biases in self-evaluation and memory. *Cogn Emotion* 11:65–82.

Glover GH, Law CS (2001): Spiral-in/out BOLD fMRI for increased SNR and reduced susceptibility artifacts. *Magn Reson Med* 46:515–522.

Gotlib IH, Kasch KL, Traill S, Joormann J, Arnow BA, Johnson SL (2004): Coherence and specificity of information-processing biases in depression and social phobia. *J Abnorm Psychol* 113:386–398.

Gross JJ, John OP (2003): Individual differences in two emotion regulation processes: Implications for affect, relationships, and well-being. *J Pers Soc Psychol* 85:348–362.

Hamann S (2001): Cognitive and neural mechanisms of emotional memory. *Trends Cogn Sci* 5:394–400.

Hamilton M (1960): A rating scale for depression. *J Neurol Neurosurg Psychiatry* 23:56–62.

Hedlund S, Rude SS (1995): Evidence of latent depressive schemas in formerly depressed individuals. *J Abnorm Psychol* 104:517–525.

Hertel PT, Rude SS (1991): Depressive deficits in memory: Focusing attention improves subsequent recall. *J Exp Psychol Gen* 120:301–309.

Hoddes E, Zarcone V, Smythe H, Phillips R, Dement WC (1973): Quantification of sleepiness: A new approach. *Psychophysiology* 10:431–436.

Ingram RE (1984): Toward an information-processing analysis of depression. *Cognit Ther Res* 8:443–478.

Ingram RE, Miranda J, Segal ZV (1998): *Cognitive Vulnerability to Depression*. New York: Guilford.

Keller MB, Lavori PW, Mueller TI, Endicott J, Coryell W, Hirschfeld RM, et al (1992): Time to recovery, chronicity, and levels of psychopathology in major depression. A 5-year prospective follow-up of 431 subjects. *Arch Gen Psychiatry* 49:809–816.

Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR, et al (2003): The epidemiology of major depressive disorder: Results from the National Comorbidity Survey Replication (NCS-R). *JAMA* 289:3095–3105.

Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE (2005): Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry* 62: 593–602.

Lancaster JL, Woldorff MG, Parsons LM, Liotti M, Freitas CS, Rainey L, et al (2000): Automated Talairach atlas labels for functional brain mapping. *Hum Brain Mapp* 10:120–131.

Liu TT, Frank LR, Wong EC, Buxton RB (2001): Detection power, estimation efficiency, and predictability in event-related fMRI. *Neuroimage* 13:759–773.

Martin M (1990): On the induction of mood. *Clin Psychol Rev* 10:669–697.

McCabe SB, Gotlib IH, Martin RA (2000): Cognitive vulnerability for depression: Deployment of attention as a function of history of depression and current mood state. *Cognit Ther Res* 24:427–444.

McGaugh JL (2004): The amygdala modulates the consolidation of memories of emotionally arousing experiences. *Annu Rev Neurosci* 27:1–28.

Murray CJ, Lopez AD (1997): Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. *Lancet* 349:1436–1442.

Nolen-Hoeksema S, Morrow J (1991): A prospective study of depression and posttraumatic stress symptoms after a natural disaster: The 1989 Loma Prieta Earthquake. *J Pers Soc Psychol* 61:115–121.

Reilly-Harrington NA, Alloy LB, Fresco DM, Whitehouse WG (1999): Cognitive styles and life events interact to predict bipolar and unipolar symptomatology. *J Abnorm Psychol* 108:567–578.

Shea MT, Elkin I, Imber SD, Sotsky SM, Watkins JT, Collins JF, et al (1992): Course of depressive symptoms over follow-up. Findings from the National Institute of Mental Health Treatment of Depression Collaborative Research Program. *Arch Gen Psychiatry* 49:782–787.

Sheline YI (2003): Neuroimaging studies of mood disorder effects on the brain. *Biol Psychiatry* 54:338–352.

Siegle GJ, Steinhauer SR, Thase ME, Stenger VA, Carter CS (2002): Can't shake that feeling: Event-related fMRI assessment of sustained amygdala activity in response to emotional information in depressed individuals. *Biol Psychiatry* 51:693–707.

Spielberger CD, Gorush RL, Lushene RE, Vagg PR, Jacobs GA (1983): *Manual for the State-Trait Anxiety Inventory (Form Y)*. Palo Alto, CA: Consulting Psychologist Press.

Symons CS, Johnson BT (1997): The self-reference effect in memory: A meta-analysis. *Psychol Bull* 121:371–394.

Talairach J, Tournoux P (1988): *Co-planar Stereotaxic Atlas of the Human Brain*. New York: Thieme Medical Publisher.

Teasdale JD (1988): Cognitive vulnerability to persistent depression. *Cogn Emotion* 2:247–274.

Teasdale JD, Dent J (1987): Cognitive vulnerability to depression: An investigation of two hypotheses. *Br J Clin Psychol* 26:113–126.

Watson D, Clark LA, Tellegen A (1988): Development and validation of brief measures of positive and negative affect: The PANAS scales. *J Pers Soc Psychol* 54:1063–1070.

Whalen PJ, Shin LM, Somerville LH, McLean AA, Kim H (2002): Functional neuroimaging studies of the amygdala in depression. *Semin Clin Neuropsychiatry* 7:234–242.

Williams JMG, Watts FN, MacLeod C, Mathews A (1997): *Cognitive Psychology and Emotional Disorders, 2nd ed*. Chichester, England: Wiley.

Winokur G, Coryell W, Keller M, Endicott J, Akiskal H (1993): A prospective follow-up of patients with bipolar and primary unipolar affective disorder. *Arch Gen Psychiatry* 50:457–465.