Neural Substrates of Increased Memory Sensitivity for Negative Stimuli in Major Depression

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Background: Although memory biases for negatively valenced stimuli have been reliably associated with depression and have been postulated to play a critical role in the maintenance of this disorder, the neural bases of these biases have received little attention. In this study, we tested a model of heightened memory sensitivity for negative information in depression in which neural mechanisms that normally facilitate memory for affective material are over-recruited during encoding of negative material in depression.

Methods: We used functional magnetic resonance imaging to examine amygdala activity and functional connectivity with the hippocampus and caudate-putamen during successful encoding—as assessed by a recognition memory probe 1 week after scanning—of negative, neutral, and positive pictures by 14 depressed and 12 nondepressed individuals.

Results: Depressed individuals demonstrated greater memory sensitivity than nondepressed participants to negative but not to neutral or positive stimuli. The right amygdala was more active and showed greater functional connectivity with the hippocampus and caudate-putamen in depressed than in control participants during encoding of subsequently remembered negative but not neutral or positive stimuli. The degree of memory-related right amygdala responsivity in the depressed participants was significantly correlated with depressive severity.

Conclusions: These findings support the formulation that, in remembering negative information better than nondepressed persons, depressed individuals over-recruit a neural network involved more generally in enhancing memory for affective stimuli and that the degree to which they over-recruit this system is related to the severity of clinical symptomatology.

Key Words: Amygdala, caudate, depression, hippocampus, memory, putamen

Cognitive theories of depression (1) posit that negative cognitions, derived from dysfunctional self schemas, play a central role in the etiology and course of this disorder. These dysfunctional schemas are hypothesized to bias information processing in depression, with depressed individuals selectively attending to and remembering affectively negative material. Indeed, there is strong evidence that depressed individuals are characterized by negative biases in memory, demonstrating better memory than nondepressed individuals for negative material (2–4). Importantly, several theorists have proposed that selective memory for negative information in depression contributes to the duration and severity of depressive episodes (5,6).

Despite these consistent findings, we know little about the neural underpinnings of enhanced memory for negatively valenced stimuli in depressed relative to nondepressed individuals. Both lesion and functional neuroimaging studies confirm that the amygdala plays an important role in bolstering memory for emotional material. Cahill *et al.* (7,8), for example, reported that the generally better recall of affectively valenced than of neutral information is sharply attenuated in patients with lesions confined to the amygdala. Furthermore, with functional magnetic resonance imaging (fMRI), Canli found amygdala responsivity to predict subsequent memory performance for affective stimuli both across individuals (9) and across trials (10).

Several investigators have posited that the amygdala facilitates memory for emotional stimuli through modulation of the hippocampus, a structure crucial for episodic memory encoding (11). Packard *et al.* (12), for example, showed that amygdala stimulation after training facilitated hippocampal-mediated learning in rats and was not blocked by anesthetizing the amygdala before a retention test, indicating that the resulting pro-mnemonic effects were not due to lasting changes within the amygdala itself. These findings of amygdala facilitation of hippocampal-dependent learning are echoed in neuroimaging studies of humans by investigators reporting a significant correlation between activation of the amygdala and hippocampus during successful encoding of affective stimuli (13,14).

The amygdala has also been found to facilitate learning that is dependent on the putamen and caudate (12,15), a structure complex centrally involved in skill learning (16). Packard and Teather (15), for example, found that amygdala stimulation after training in rats facilitates caudate-putamen–mediated learning and, furthermore, that these memory-bolstering effects are blocked by anesthetizing the caudate-putamen after training but not by pre-test amygdala anesthetization. Moreover, given that the amygdala and caudate-putamen comprise nodes of the affective division of the cortico-striatal-pallidal-thalamic (CSPT) loop (17), a circuit involved in the maintenance of information in working memory (18), investigators have posited that the amygdala-caudate-putamen system subserves emotionally-mediated working memory.

The formulation that overactive amygdala-caudate-putamen and/or amygdala-hippocampus systems underlie enhanced memory for negative information in depression is also consistent with findings that depressed individuals have been characterized by greater responsivity to negative stimuli in the amygdala (19–22), hippocampus (19), and caudate-putamen (19) than nondepressed persons. The relevance of amygdala reactivity to memory in depression has been shown by Roberson-Nay *et al.* (23), who found that, unlike their nondepressed peers, depressed adolescents showed greater amygdala reactivity when

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viewing faces that they subsequently remembered versus faces that they subsequently forgot.

The present study was designed to test a model of enhanced memory for negative stimuli in depression in which the neural mechanisms that are involved in bolstering encoding of emotionally valenced material in general are recruited more during encoding of negative material by depressed individuals. More specifically, we test a model in which amygdala activity and consequent modulation of the hippocampus and/or the caudate-putamen is increased during successful encoding of negative stimuli in depression. On the basis of the published reports reviewed in the preceding text, we hypothesize that depressed individuals will exhibit better memory than nondepressed individuals for negative material as well as greater amygdala activation during successful encoding of negative material. Finally, we predict that amygdala activation during successful encoding of negative stimuli will be more strongly correlated with activation in the hippocampus and caudate-putamen in depressed than in nondepressed participants.

Methods and Materials

Participants

Fourteen individuals diagnosed with major depressive disorder (MDD; 8 women) and 12 nondepressed control subjects (6 women) with no history of psychiatric disorder participated in this study. Participants were recruited from local psychiatric outpatient clinics as well as through website postings. Inclusion criteria optimized diagnostic homogeneity of our depressed and nondisordered samples and required that all participants: 1) were between the ages of 18 and 50; 2) had no reported history of brain injury, lifetime history of primary psychotic ideation, social phobia, panic disorder, mania, or post-traumatic stress disorder; 3) did not meet diagnostic criteria for current generalized anxiety disorder; 4) had no reported substance abuse within the previous 6 months; and 5) had no physical limitations that prohibited them from undergoing an fMRI examination. Nine of the depressed participants and none of the nondepressed participants were taking antidepressant medication at the time of the study; medicated depressed individuals were required to have maintained a steady antidepressant dosage for 1 month before being scanned.

All depressed participants met criteria for a DSM-IV diagnosis of MDD on the basis of the Structured Clinical Interview for DSM (SCID) (24); none of the control participants met criteria for any current or past Axis I disorder. In addition, all participants completed the Beck Depression Inventory-II (BDI-II) (25). Depressed individuals with comorbid panic disorder or social phobia were excluded from participation in the study. Informed consent was obtained from all participants, and each participant was paid $25/hour. All aspects of this study complied with the ethical standards for treatment of human participants from the American Psychiatric Association.

Picture Encoding Task

Participants viewed stimuli in the scanner through a projector-directed mirror. The stimuli were selected from the International Affective Picture System (IAPS) (26). A schematic of the in-scanner picture encoding task, adapted from a procedure used by Canli *et al.* (10), is presented in Figure 1. Each trial lasted 14 sec and was composed of: 1) picture presentation for the first 2000 ms; 2) picture intensity rating (1 – not intense, 2 – somewhat intense, 3 – quite intense, 4 – extremely intense); and 3) affective valence rating of the picture (1 – negative, 2 – neutral, 3 – positive). A response indicator light in the console room of the scanner was monitored to ensure that participants maintained attention to the task; in addition, in-scanner behavioral data were checked after scanning to ensure there were no missed trials. For the remainder of the trial, participants viewed a fixation cross. Responses were made with a four-button fMRI response box developed at The Lucas Center at Stanford University. Stimulus presentation, timing, and recording of behavioral data during scanning as well as subsequent memory assessment were controlled by a Dell PC running E-prime v1.2 (Psychology Software Tools; http://www.pstnet.com/eprime).

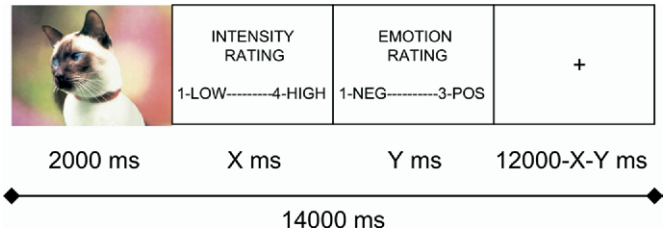

Figure 1. Schematic of individual functional magnetic resonance imaging memory encoding trials.

Each participant viewed 70 negative (mean normed valence: 2.60; range: 1.3–3.9), 70 neutral (mean normed valence: 5.05; range: 4.3–5.8), and 70 positive (mean normed valence: 7.30; range: 6.7–8.3) pictures, for a total of 210 14-sec trials completed over five 588-sec scanning runs. Stimuli were presented in random order to each participant. Two sets of IAPS stimuli were used for this study. One set was used for the in-scanner encoding portion of the study, and the other set, of equal size and matched for normed intensity and valence, served as foil stimuli for subsequent incidental recognition memory testing; the stimulus set designated as "target" or "foil" varied randomly across participants.

Incidental Recognition Memory Task

One week after the scan, participants returned to the lab to complete the incidental recognition memory portion of the study. The 210 IAPS pictures they had seen the previous week during scanning and 210 foil IAPS pictures were used as stimuli. On each trial, participants first saw a fixation cross presented for 1000 ms that alerted them to the coming memory probe. An IAPS picture probe was then presented along with a key indicating how they should respond. To optimize variability in our memory measure to reflect the real variation that is present in recognition of previously seen stimuli as well as to afford us the opportunity to account for this variability in our behavioral and neural analyses, we used a three-point recognition memory probe. Participants were to press "1" if they assessed the picture as previously unseen, "2" if the picture seemed merely familiar, and "3" if participants remembered having seen the picture.

FMRI Data Acquisition

Blood-oxygen level-dependent (BOLD) data were acquired with a 1.5-T General Electric Signa MR scanner (Milwaukee, Wisconsin). After scout scanning, two iterations of high-order shimming were performed over the whole brain. Next, BOLD data were acquired with a single channel, whole-head imaging coil from 24 axial slices with a spiral pulse sequence (27) (repetition time [TR] = 83 msec/slice, echo time [TE] 40 msec, flip angle = 70°, field of view [FOV] = 24 cm, acquisition time =

2000 msec/frame, number of frames = 299/run). Axial slices had 3.75-mm^2 in-plane and 4-mm through-plane resolution (with 1-mm between-slice distance). A high-resolution structural scan (115 slices, 1-mm^2 in-plane and 1.5-mm through-plane resolution, TE = minimum, flip angle = 15°, FOV = 22 cm) was performed after BOLD scanning runs. Head movement was minimized by using a bite-bar formed with each participant's dental impression.

Analyses: Recognition Memory Data

For each participant, memory sensitivity was calculated for each of the three valence categories. Individual trials from recognition memory testing were categorized as "Hits" if participants had seen the probe picture during scanning and indicated this during testing of recognition memory by assigning it a rating of "3." Trials were categorized as "False Alarms" if participants had not seen the probe picture during the scan but assigned it a rating of "3," indicating that they thought they had seen the picture. Hit and False Alarm rates were calculated for each subject for each valence category by dividing the number of hits and false alarms, respectively, by the total number of "3" (i.e., "picture seen") responses for a particular valence category. These rates were then used to compute sensitivity indexes (d'). Given the reliable finding that depressed individuals do not remember information, in general, as well as their nondepressed counterparts (28), we controlled for variance introduced by this general memory effect in our estimates of valence-specific memory sensitivity by dividing each participant's valence-specific (negative and positive) d' by their d' for neutral information. A two-way (group repeated over valence) analysis of variance (ANOVA) was conducted on these resultant memory sensitivity indexes.

Analyses: BOLD Data

Preprocessing. The BOLD images were slice-time corrected by using the axial slice with the greatest degree of intersection with the core nuclei of the amygdalae as the reference slice. Images were then motion corrected with a Fourier interpolation algorithm from the AFNI imaging analysis suite (National Institutes of Health; http://afni.nimh.nih.gov/). Data for which sudden movement did not exceed 1 mm were not corrected further. Scans for which sudden movement fell between 1 mm and 3 mm were corrected with a despiking algorithm from AFNI that replaced data from individual high-motion acquisitions with outlier insensitive estimates. Data were then spatially smoothed with a Gaussian kernel (full width at half maximum = 4 mm) and high-pass filtered with a frequency criterion of 1 cycle/min, and then converted to units of percent signal change. Finally, the BOLD data were warped to a common template space (29) to allow comparison between diagnostic groups.

Comparing Memory-Related Amygdala Reactivity Across Valence and Diagnosis. Indexes of amygdala activity for remembered relative to forgotten stimuli were obtained for positive, negative, and neutral stimuli for each participant. Response amplitude differences for subsequently remembered versus forgotten stimuli were calculated as follows: 1) for each valence, δ functions were computed according to the rule that a picture-viewing event that generated a rating of "3" (picture was seen) during the recognition memory task received a value of 1, and a picture-viewing event that generated a rating of "1" (picture was not seen) during recognition memory testing was given a value of −1; 2) resulting δ functions for each participant for each valence were convolved with a γ function to render memory-relevant covariates for fitting with amygdala BOLD timecourses; and 3) a least-squares data-fitting procedure (AFNI's 3dDeconvolve) was conducted on the memory covariates individually, first accounting for nuisance covariates.

To compare the resulting indexes of amygdala responsivity to subsequently remembered versus forgotten stimuli as a function of group and valence, two-way (group repeated over valence) ANOVAs were conducted on a voxel-wise basis within the amygdalar region of interest (ROI). The statistical threshold was set at $p = .05$, corrected, for this analysis and analyses subsequently described. Statistical significance of these comparisons was calculated with the AFNI program AlphaSim, which estimates null hypothesis distributions via multiple Monte Carlo simulations. Probability values for any pairwise contrasts in which the direction of effect was predicted by our hypotheses were calculated as one-tailed; otherwise, p values were calculated as two-tailed.

Calculating Psychophysical Interaction Between Amygdala Seed Regions and the Hippocampus and Caudate-Putamen. We used a procedure similar to that described by Heekeren *et al.* (30) to calculate the degree of psychophysical interaction between amygdala seed regions and the hippocampus and caudate-putamen. This approach differs from resting-state connectivity analyses in that it permits the calculation of context-dependent correlations in BOLD signal between structures in order to detect task- or performance-dependent co-activity. We implemented this procedure as follows. First, for each participant, an amygdala timecourse was extracted and nuisance covariates were removed. Next, for each valence condition, the resulting "clean" amygdala timecourse was multiplied, on a timepoint × timepoint basis, by a γ function-convolved δ function contrasting successful and unsuccessful encoding events. The fit of the resulting task × amygdala timecourse with voxel timecourses within hippocampal and caudate-putamen ROIs was then calculated. A two-way (group repeated over valence) ANOVA was conducted on the resulting fit coefficients at each hippocampus and caudate-putamen voxel.

Results

Participant Characteristics

Table 1 presents the demographic and clinical characteristics of the depressed and nondepressed participants. The two groups of participants did not differ with respect to age [$t(24) = 1.22$], education [$t(24) = .17$], or gender composition [$\chi^2(1,24) = .48$]; all $ps > .05$. As expected, the depressed participants had higher scores on the BDI-II than the nondepressed participants [$t(24) = 8.26$]; $p < .05$. Table 2 presents additional characteristics of our depressed sample, including antidepressant medication (if any) taken, medication dosage, length of medication period, number of depression-related hospital stays, duration of current depressive episode, time since first onset of depressive illness, and BDI score.

Table 1. Participant Demographic and Clinical Data

	Control	Depressed
Age	31.4 ± 10.2	36.5 ± 10.3
Education	15.43 ± 2.6	15.27 ± 1.7
% Female	50%	57%
BDI-II	.91 ± 1.4	27.6 ± 10.6

Mean ± SD.
BDI, Beck Depression Inventory.

Table 2. Depressed Participants: Pharmacological and Clinical Data

Participant	Medication and Daily Dosage	Duration of Medication	MDD-related Hospitalizations	Duration of Current Episode (months)	Yrs Since First Episode	BDI
MDD1	Venlafaxine (300 mg)	4 months	0	21	29	15
MDD2	none	—	NR	NR	NR	14
MDD3	Venlafaxine (450 mg)	2 yrs	1	1	2	24
MDD4	none	—	0	6	25	13
MDD5	Escitalopram; Bupropion (dosage NR)	1.5 yrs; 4 yrs	0	6	18	45
MDD6	Venlafaxine (150 mg)	3 yrs	0	5	20	34
MDD7	Duloxetine (40 mg), Bupropion (300 mg)	1 yr; 1 month	0	36	NR	25
MDD8	none	—	0	8	25	15
MDD9	Sertraline (100 mg)	3 months	0	2	2	41
MDD10	none	—	0	10	7	33
MDD11	none	—	0	4	15	39
MDD12	Venlafaxine (225 mg); Bupropion (300 mg)	5 months; 5 months	0	14	1	27
MDD13	Venlafaxine (150 mg)	2 yrs	0	28	11	33
MDD14	Venlafaxine (75 mg); Bupropion (100 mg)	1 yr; 1 month	0	16	5	28

MDD, major depressive disorder; BDI, Beck Depression Inventory; NR, not reported.

Intensity Ratings

A two-way (group repeated over valence) ANOVA conducted on stimulus intensity ratings recorded during scanning yielded only a significant main effect of valence [$F(2,21) = 80.5$, $p < .05$]. Paired samples t tests contrasting intensity ratings as a function of valence indicate that participants rated negative stimuli as more intense than both neutral [$t(25) = 14.23$] and positive [$t(25) = 6.41$] stimuli and positive stimuli as more intense than neutral stimuli [$t(25) = 5.39$]; all $ps < .05$ (see Figure 2 for graphs of these results).

Recognition Memory Performance

A two-way (group repeated over valence) ANOVA was conducted on memory sensitivity estimates. No main effects for group [$F(1,23) = 2.73$], valence [$F(1,23) = .47$], or their interaction [$F(1,23) = 2.73$] were obtained; all $ps > .05$. We then examined differences in specific means to test our a priori hypotheses concerning group performance as a function of valence. These analyses indicated that, whereas depressed participants exhibited greater memory sensitivity than nondepressed control subjects for negative stimuli [$t(24) = 1.88$, $p < .05$], the two groups did not differ in memory performance for positive stimuli [$t(24) = 1.17$, $p > .05$]. Within-groups contrasts yielded no difference in memory for negative relative to positive stimuli in the depressed group [$t(13) = .50$]. In contrast, the nondepressed participants remembered positive stimuli better than negative stimuli [$t(11) = 3.01$, $p < .05$]. These results are presented graphically in Figure 3.

Amygdala ROI Results

Two-way ANOVAs conducted on contrast estimates from the comparison of successful with unsuccessful encoding trials in left amygdala voxels yielded nonsignificant results [peak left amygdala voxel: group, $F(1,21) = 1.25$; valence, $F(2,21) = .23$; group × valence interaction, $F(2,21) = .65$; all $ps > .05$]. The same analysis conducted on voxels within the right amygdala yielded a nonsignificant effect for group [$F(1,21) = 1.86$, $p > .05$] and a significant main effect for valence [$F(2,21) = 4.92$, $p < .05$] that was qualified by a significant interaction of group and valence [$F(2,21) = 3.35$, $p < .05$] (all statistics reported from peak right amygdala voxel). Follow-up tests indicated that depressed participants exhibited greater right amygdala responsivity than nondepressed participants during successful relative to unsuccessful encoding for negative material [$t(24) = 2.49$, $p < .05$] but not for neutral [$t(24) = .86$, $p > .05$] or positive [$t(24) = .09$, $p > .05$] material. Importantly, this group difference in memory-related responsivity to negative material in the right amygdala was driven by greater amygdala reactivity in depressed than in nondepressed participants to subsequently remembered stimuli [$t(24) = 2.32$, $p < .05$] and not by decreased responsivity in depressed participants to subsequently forgotten stimuli [$t(24) = .09$, $p > .05$]. In addition, within the depressed group, right amygdala responsivity during successful relative to unsuccessful encoding was greater for negative than for both neutral [$t(13) = 3.82$, $p < .05$] and positive [$t(13) = 2.529$, $p < .05$] stimuli, which did not differ significantly from each other [$t(13) = .311$, $p > .05$]. In contrast, within the nondepressed group, memory-related

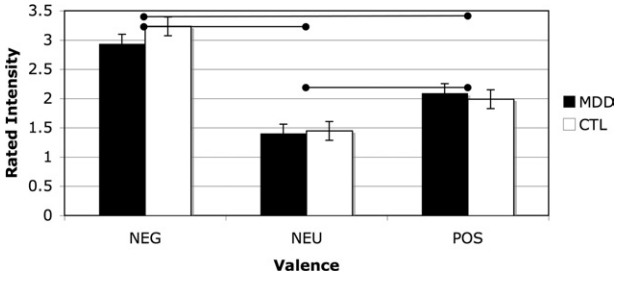

Figure 2. Mean intensity ratings with standard error bars for positive (POS), neutral (NEU), and negative (NEG) stimuli in depressed (MDD) and control (CTL) groups. Mean values connected by bars are significantly different.

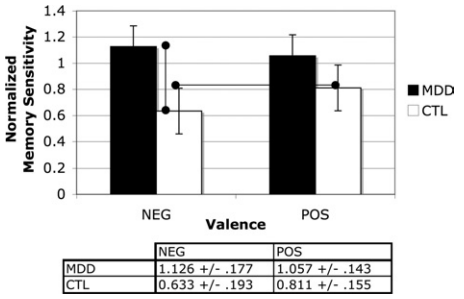

Figure 3. Mean normalized memory sensitivity scores across levels of group and valence factors. Abbreviations as in Figure 2.

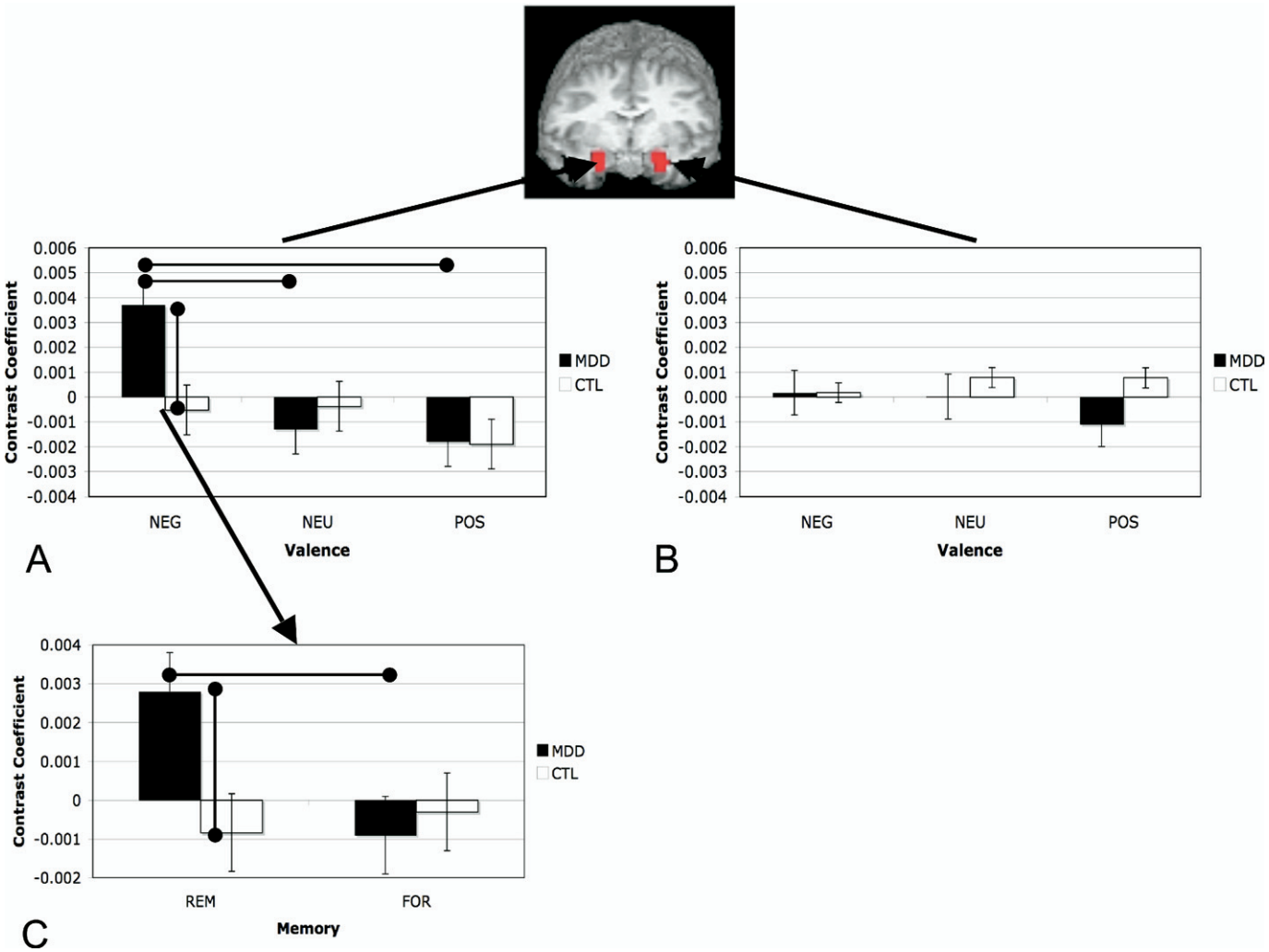

Figure 4. Mean contrast coefficient values from remembered (REM) versus forgotten (FOR) contrast across valence and group variables in peak left amygdala (**A**; −19, −4, −12) and right amygdala (**B**; 17, −5, −12) voxels, and REM versus fixation and FOR versus fixation for negative stimuli in each group **(C)**. Other abbreviations as in Figure 2.

right amygdala responsivity did not differ as a function of stimulus valence [all $t(11) < 1.60$, all $ps > .05$]. These results are presented graphically in Figure 4. Finally, although the subsample sizes are relatively small, it is important to note that Kruskal-Wallis tests—a nonparametric test appropriate for use with small samples that is more sensitive to between-group differences than ANOVA statistics (31)—yielded no significant differences between medicated and unmedicated MDD participants in memory-related right amygdala responsivity for negative, neutral, or positive stimuli; all $ps > .05$.

Psychophysical Interaction Results

Psychophysical Interaction of Amygdala With Hippocampus. Two-way (group repeated over valence) ANOVAs were conducted on indexes of psychophysical interaction with the amygdala at each hippocampal voxel. No effects of group or valence or the interaction of these factors were sufficiently large to satisfy the statistical correction imposed by examining all voxels within this ROI. To decrease the magnitude of the correction factor to our significance threshold, we examined a smaller set of anterior hippocampal voxels found to correlate with the amygdala during effective encoding of affective stimuli (13). Although omnibus tests of group and valence effects and their interaction were not statistically significant [$F(1,21) = .91$, $F(2,21) = .93$, $F(2,21) = 1.17$, respectively, at peak voxel], exploratory between-group contrasts revealed that the degree of psychophysical interaction of the amygdala with the hippocampus was greater in the depressed than in the nondepressed participants during successful encoding of negative [$t(24) = 1.84$, $p < .05$] but not of neutral [$t(24) = .44$, $p > .05$] or positive [$t(24) = 1.05$, $p > .05$] stimuli. No significant within-group effects of valence were obtained; all $ps > .05$. These results are presented in Figure 5.

Psychophysical Interaction of Amygdala With Caudate-Putamen. Analyses of the correlation of memory-related activity in the right amygdala with activation in voxels comprising ipsilateral caudate and putamen showed significant main effects within the right putamen for both group [$F(1,24) = 11.54$, $p < .05$] and valence [$F(2,24) = 3.83$, $p < .05$]; the interaction of group and valence, however, was not significant [$F(2,24) = 2.67$, $p < .05$]. Follow-up tests showed a greater memory-related correlation between the right amygdala and right putamen for depressed than for nondepressed participants for negative [$t(24) = 3.55$, $p < .05$] but not for neutral [$t(24) = 1.22$, $p > .05$]

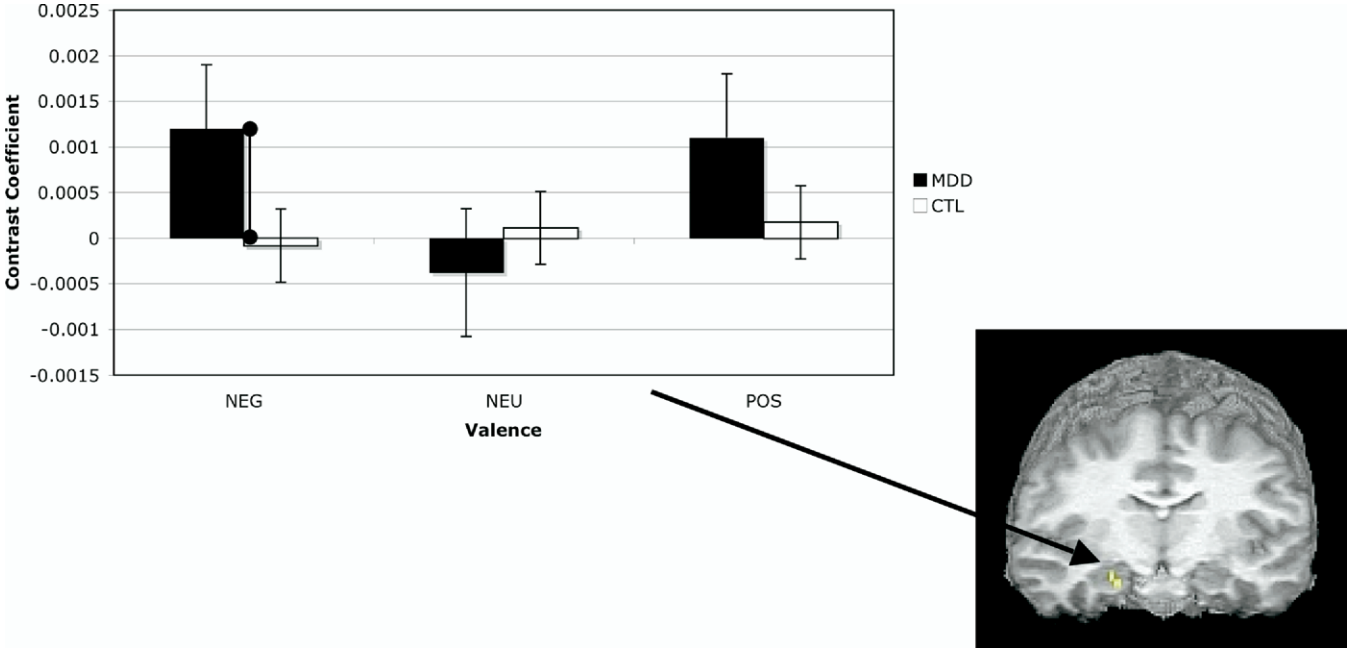

Figure 5. Mean contrast coefficients from analysis of psychophysical interaction between right amygdala and right hippocampus for each level of group and valence. Values shown are from peak hippocampal voxel (22, −11, −12). Abbreviations as in Figure 2.

or positive [$t(24) = .59$, $p > .05$] stimuli. Further comparisons indicated that, within the depressed group, the amygdala-putamen correlation was greater for negative than for positive stimuli [$t(13) = 3.55$, $p < .05$] but not for negative relative to neutral stimuli [$t(13) = 1.56$, $p > .05$] or for neutral relative to positive stimuli [$t(13) = 1.69$, $p > .05$], although the latter two comparisons did approach statistical significance. Within the nondepressed group, the memory-related amygdala-putamen correlation was lower for negative [$t(11) = 1.99$ $p < .05$] and positive [$t(11) = 2.77$, $p < .05$] stimuli than for neutral stimuli; correlations for positive and negative stimuli did not differ from each other [$t(11) = 2.78$, $p < .05$]. These results are presented in Figure 6.

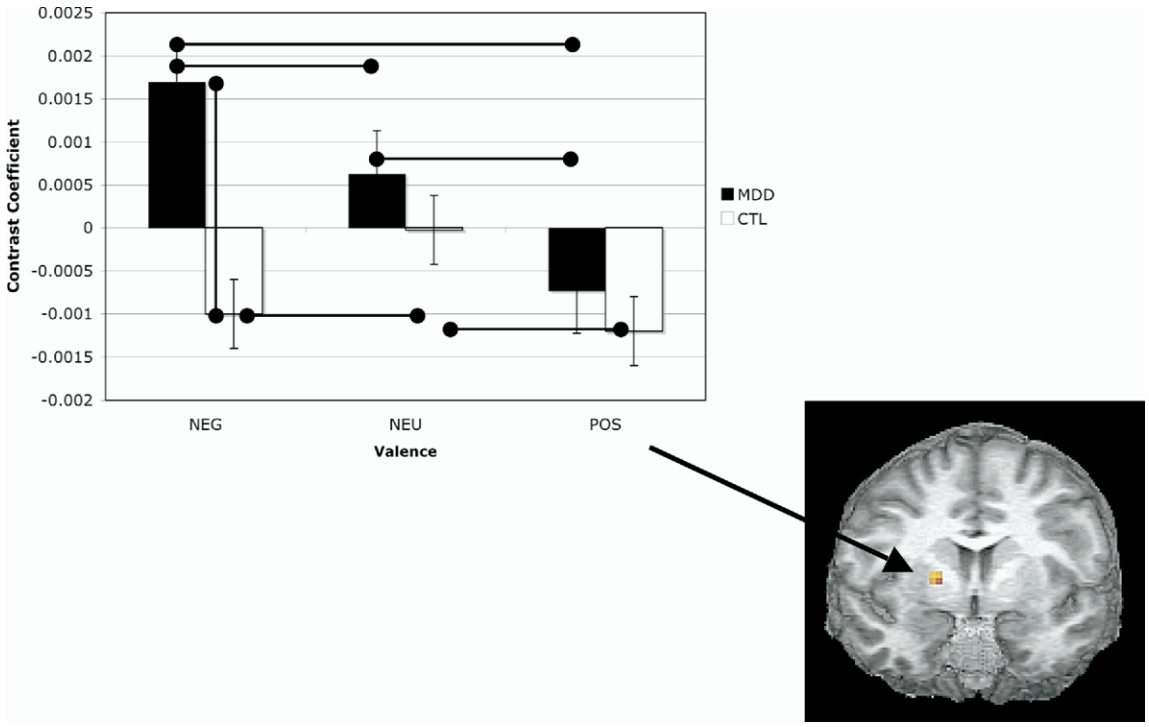

Figure 6. Mean contrast coefficients from analysis of psychophysical interaction between right amygdala and right caudate-putamen for each level of group and valence. Values shown are from peak caudate-putamen voxel (17, 5, 6). Abbreviations as in Figure 2.

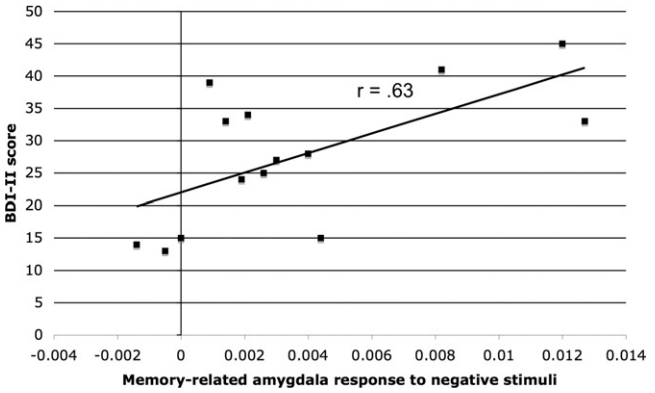

Figure 7. Scatter plot showing positive correlation between Beck Depression Inventory-II score in depressed participants and memory-related right amygdala responsivity to negative stimuli.

Correlation of Depressive Severity With Amygdala Responsivity

Finally, the severity of depression within the MDD group, as assessed by BDI-II scores, was significantly correlated with memory-related right amygdala activation in response to negative stimuli [$r(13) = .63$, $p < .05$] (see Figure 7) but not in response to neutral [$r(13) = .12$, $p > .05$] or to positive [$r(13) = -.09$, $p > .05$] stimuli.

Discussion

The present study was designed to test a neural model of enhanced memory for negative stimuli in depression. We report behavioral data that replicate previous findings showing better memory for negative information in diagnosed depressed than in nondepressed individuals. We also demonstrate that, compared with their nondepressed counterparts, depressed individuals are characterized by increased activity in the right amygdala during successful encoding of negative but not of neutral or positive stimuli. Finally, we find that during successful encoding only of negative stimuli was activity in the right amygdala correlated with activity in both ipsilateral caudate-putamen and hippocampus more strongly in depressed than in nondepressed participants. Taken together, these findings provide support for a neural model of enhanced memory for negative material in depression in which, as they encode negative information, depressed persons over-activate a neural system that subserves encoding of affective material more generally.

This fMRI study is the first to examine the neural substrates of the negative memory bias that has been found in behavioral studies with depressed adults. The present data advance our understanding of depression by elucidating the neural substrates of a consistently reported negative memory bias in this disorder, a process postulated to contribute to the severity of depressive episodes, (5,6). Indeed, this formulation is supported by the finding that severity of depression was significantly correlated with amygdala activity during encoding of negative stimuli that were remembered 1 week later.

An important aspect of the present findings concerns the specificity of amygdala responsivity and connectivity in depression. Activation differences between depressed and control participants were found for the encoding of subsequently remembered negative but not positive stimuli, despite the fact that positive stimuli also were rated as more intense than neutral stimuli. Thus, the amygdala responsivity exhibited by depressed participants in response to successfully encoded negative material was not simply reflecting an intensity effect. Moreover, these results do not seem to be related to medication status. Comparisons of amygdala responsivity in medicated and unmedicated MDD participants yielded no significant effects. Although the relatively small subsamples in these comparisons dictate that we use caution in interpreting these results, they are nonetheless consistent with the formulation that medicated and unmedicated depressed participants do not differ in memory-related amygdala responsivity.

It is noteworthy that, whereas Canli *et al.* (9,10) reported greater amygdala activity during effective encoding of affective stimuli in unselected participant samples, the nondepressed participants in the present study did not exhibit this pattern of activation. This discrepancy might be due to the fact that the nondepressed participants in the present study were selected to have no current or past Axis I disorder and, consequently, were more likely than the samples studied by Canli *et al.* to be characterized by lower levels of psychopathology or distress. This is an important consideration in selecting criteria for control groups in psychopathology research, and investigators might examine this formulation more explicitly and systematically in future research.

Investigators working to elucidate the neural substrates of the negative memory bias in depression could expand the neural model presented here by examining the neural underpinnings of both encoding and retrieval processes. It will also be important to design studies that will permit inferences about causality and directionality of influence to be incorporated into neural models of depressotypic processes. For example, the advent of real-time neurofeedback techniques, in which participants can learn to modulate activity in structures such as the amygdala (32) in making corresponding changes to thought and behavior, holds promise that the role of the amygdala in the increased memory sensitivity for negative information in depression might be more clearly elucidated.

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