

Negative Autobiographical Memory in Depression Reflects Elevated Amygdala-Hippocampal Reactivity and Hippocampally Associated Emotion Regulation

Bruce P. Doré, Odile Rodrik, Chelsea Boccagno, Alexa Hubbard, Jochen Weber, Barbara Stanley, Maria A. Oquendo, Jeffrey M. Miller, M. Elizabeth Sublette, J. John Mann, and Kevin N. Ochsner

ABSTRACT

BACKGROUND: Dysregulated autobiographical recall is observed in major depressive disorder (MDD). However, it is unknown whether people with MDD show abnormalities in memory-, emotion-, and control-related brain systems during reactivity to and regulation of negative autobiographical memories.

METHODS: We used functional magnetic resonance imaging to identify neural mechanisms underlying MDD-related emotional responses to negative autobiographical memories and the ability to downregulate these responses using a cognitive regulatory strategy known as reappraisal. We compared currently depressed, medication-free patients with MDD ($n = 29$) with control participants with no history of depression ($n = 23$).

RESULTS: Relative to healthy control participants, medication-free MDD patients reported greater negative emotion during recall but relatively intact downregulation success. They also showed elevated amygdala activity and greater amygdala-hippocampal connectivity. This connectivity mediated the effect of MDD on negative emotional experience. When reappraising memories (vs. recalling from an immersed perspective), the MDD and control groups showed comparable recruitment of the prefrontal, parietal, and temporal cortices, and comparable downregulation of the amygdala and anterior hippocampus. However, MDD patients showed greater downregulation of the posterior hippocampus, and the extent of this downregulation predicted successful reduction of negative affect in MDD patients only.

CONCLUSIONS: These data suggest amygdala-hippocampal connectivity and posterior hippocampal downregulation as brain mechanisms related to elevated emotional reactivity and atypical emotion regulation in MDD.

Keywords: Autobiographical memory, Emotion, Emotion regulation, fMRI, Hippocampus, Major depressive disorder
<https://doi.org/10.1016/j.bpsc.2018.01.002>

Major depressive disorder (MDD) is a prevalent disorder characterized by disturbances in mood and cognition (1). Many lines of research converge to indicate that autobiographical memory represents an area of core dysfunction in this disorder (2–4). Beyond providing a representation of past events, memory provides a foundation for self-identity, social interaction, and decision making, all of which are disrupted in MDD (5–8). Moreover, previous work suggests that disruptions in the character of autobiographical memories can predict future depressive symptoms (9). However, little is known about MDD-related disturbances in the neural mechanisms underlying the emotional impact of negative autobiographical memories or the ability to control this impact via emotion regulation.

One reason for this gap in knowledge is that prior studies have typically examined responses to normative stimuli (e.g., static facial expressions, valenced words, images of distressing

situations drawn from standardized stimulus sets), and not autobiographical memories. Neural models developed in nondepressed adults implicate the amygdala in the bottom-up generation of emotion, and a set of prefrontal, parietal, and lateral temporal regions in the top-down regulation of emotion (10,11). Studies have suggested that these models may generalize to negative autobiographical memories, with additional involvement of regions, like the hippocampus, that are involved in episodic memory retrieval and that interact with regions involved in emotional arousal (12–15).

A growing consensus in this research area is that people with MDD are able to successfully regulate negative affect within standardized image-based emotion regulation tasks (showing comparable effect sizes and no significant behavioral differences in comparison with healthy control participants), but they do so by engaging neural mechanisms that differ from

Mechanisms of Negative Memory in MDD

those engaged by nondepressed people (16–22). However, it is unknown whether people with MDD show differential recruitment of memory-, emotion-, and control-related brain systems during recall and regulation of negative autobiographical memories.

We sought to address these gaps in knowledge with a functional magnetic resonance imaging (fMRI) study investigating reactivity to and regulation of emotional responses to negative autobiographical memories, comparing currently depressed, medication-free patients with MDD to control participants with no history of depression. Guided by a model of the processing systems underlying reactivity and regulation in nondepressed people, we asked three targeted questions about people with MDD, as compared with healthy control participants: 1) Do people with MDD differ from control participants in the emotional impact of negative autobiographical memories? 2) Do people with MDD differ from control participants in their ability to downregulate this impact? and 3) Do people with MDD differ in the neural mechanisms underlying reactivity to and regulation of negative autobiographical memories?

METHODS AND MATERIALS

Participants

Participants were 29 (15 women) people with DSM-IV MDD (mean age = 31.6 years, SD = 9.9 years) and 23 (12 women) healthy control participants (mean age = 32.6 years, SD = 8.5 years), recruited as part of a larger multimodal study of MDD and suicide risk (see Table 1). Participants were eligible for assignment to the MDD group if they were 18 to 60 years of age; had no active medical illness; were currently in a major depressive episode as part of MDD as determined via the Structured Clinical Interview for DSM-IV; had a score of at least 16 on the 17-item Hamilton Depression Rating Scale; were not diagnosed with any of the following Axis I psychiatric conditions: bipolar disorder, psychotic disorders, current drug or alcohol abuse (within 2 months) or dependence (within 6 months), and anorexia or bulimia nervosa (within the past year); and were able to discontinue psychiatric medications and other psychotropic drugs for at least 21 days before the scan. Participants were not excluded from the MDD group on the basis of comorbid diagnosis of an anxiety disorder. Participants were eligible for assignment to the control group if they were 18 to 60 years of age, had no active medical illness, had

Table 1. Characteristics of the Participants in the MDD and Control Groups

	MDD Group	Control Group
Age, Years, Mean (SD)	31.6 (9.9)	32.6 (8.5)
Sex, Female, %	52	52
Education, Years, Median (Range)	15.3 (12–20)	16 (12–18)
HDRS Score, Median (Range)	20.2 (16–27)	1.5 (0–11)
% Ever Used Antidepressant	38	
Years Since Last Antidepressant, Median (Range)	12 (3–29)	
% With Comorbid Anxiety Disorder	34	

HDRS, Hamilton Depression Rating Scale; MDD, major depressive disorder.

no lifetime history of Axis I or Axis II psychiatric illness, had no first- or second-degree relatives with a history of a major depressive episode, and were not taking any psychiatric medications or psychotropic drugs. In addition, all participants were screened to confirm that they could read and speak fluently in English, had normal or corrected-to-normal vision, and had no conditions that contraindicated MRI. Study procedures were approved by institutional review boards at Columbia University and the New York State Psychiatric Institute.

Image Acquisition

Data were collected with a 3T GE MR750 magnet (GE Healthcare, Waukesha, WI) using a 32-channel radiofrequency head coil. Structural volumes were acquired using a high-resolution T1-weighted sagittal three-dimensional BRAVO sequence yielding 1-mm isotropic voxel size. Functional volumes were acquired using a T2*-sensitive echo-planar imaging sequence with a repetition time of 2000 ms, an echo time of 25 ms, a 77° flip angle, and a 19.2-cm field of view consisting of 45 interleaved 3-mm slices acquired parallel to the anterior commissure-posterior commissure axis. Four runs of 119 repetition times were collected. Each run began with 8 seconds of fixation, and the corresponding four volumes were discarded.

Negative Autobiographical Memory fMRI Task

Scanner Recollection and Regulation Task. Before scanning, participants were tested to confirm that they could recall their memories when prompted with the cues they provided in the prescan session (see Supplement) and then were trained on a task that involved two types of trials—immerse and distance. On immerse trials, participants were asked to recall the situation from a first-person perspective and to allow their emotions to unfold naturally. On distance trials, participants were asked to recall the situation as if unfolding from a distance and to adopt the perspective of an external observer focusing on the facts. All participants successfully described the strategies and verbalized examples of their implementation to the experimenter.

In the scanner, participants completed this experimental task within four scanner runs of four trials each, for a total of eight immerse trials and eight distance trials (see Figure 1). The task consisted of a memory-cue period of recall (bring the memory to mind), a cued period of immerse or distance (apply the immersive recall or distancing reappraisal strategy, indexing reactivity and regulation, respectively), an interstimulus interval, a rating period (rate negative affect and vividness on a 5-point scale), and an intertrial interval. Each memory was allocated once to both the immersive recall and distancing reappraisal conditions, in a counterbalanced order. Between memory trials, participants completed an active perceptual baseline task consisting of making a behavioral response to indicate the direction of a visual arrow cue presented on the center of the screen for 20 seconds. The arrow cue randomly pointed left or right, staying on the screen for 3 seconds or until a response was made. This task was used to minimize self-reflection or autobiographical memory retrieval in the rest periods between trials (23). Stimuli were presented with E-Prime

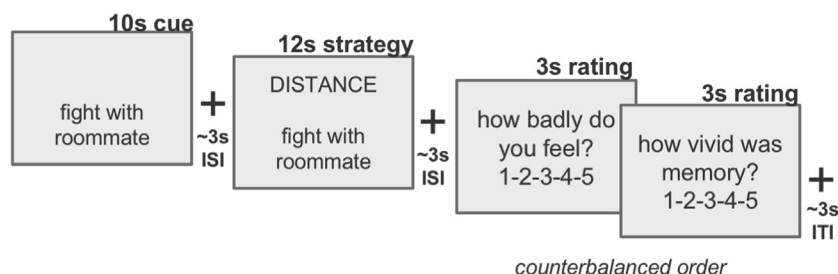


Figure 1. Negative autobiographical memory functional magnetic resonance imaging task. On each trial participants recalled a specific negative autobiographical memory, applied either a distancing reappraisal (here, distance) or immersive recall (immerse) strategy, and rated negative affect and memory vividness. ISI, interstimulus interval; ITI, intertrial interval.

version 1.2 (24), and participants made behavioral responses on a five-button response pad.

Behavioral Analysis

Analyses were conducted in R version 3.3.1 (25). Average ratings of vividness and negative affect collected during the scanner task were submitted to two separate 2 group (MDD vs. control) \times 2 condition (immerse vs. distance) mixed linear models. Ratings were also used to compute participant-specific scores for 1) overall negative affect during memory recall (i.e., the mean across immerse and distance conditions) and 2) the degree of reappraisal-evoked downregulation of negative affect (i.e., immerse mean – distance mean). Unstandardized regression coefficients were used to indicate effect sizes.

fMRI Analysis

Preprocessing/General Linear Model. Data preprocessing was conducted with SPM8 (Wellcome Department of Cognitive Neurology, University College London, London, United Kingdom) and consisted of slice-time correction, realignment, coregistration of functional and structural images, and normalization to the standard Montreal Neurological Institute brain by segmentation of the structural image and applying the parameters from this step during warping. Normalized images were resliced to 3-mm isotropic voxels and smoothed with a 6-mm kernel.

First-level (individual) general linear model analyses were implemented in NeuroElf version 1.1 (neuroelf.net). Memory cue, reactivity/regulation, and rating periods of each trial were modeled as boxcar functions convolved with the canonical hemodynamic response function. The arrows task was pooled into the implicit baseline of the model. Separate regressors were entered for immerse and distance trials. All analyses focused on brain signal estimated during the reactivity/regulation period (i.e., the period where participants were instructed to use immersive recall or distancing reappraisal) of each trial. Motion parameters and a high-pass temporal filter for 128 seconds were added as regressors of no interest.

Second-level (group) random-effects analyses were implemented in NeuroElf using iteratively reweighted least-squares regression (26). All activation peaks are reported in Montreal Neurological Institute space. We defined anatomical regions of interest for the amygdala (left: $-23, -5, -18$; right: $23, -4, -18$; 5324 mm^3) and hippocampus (left: $-25, -22, -14$; right: $23, -21, -15$; $11,263 \text{ mm}^3$) using maximum 25% probability volumes from the Harvard-Oxford atlas. For region-of-interest

analyses, small-volume correction was applied to achieve a corrected p value of $< .05$, using Gaussian random field theory to estimate the independent resolution elements in each region of interest. For whole-brain analyses, we used permutation-based thresholding implemented in NeuroElf to achieve a whole-brain familywise error-corrected p value of $< .05$, with a cluster-defining threshold of $p < .002$.

Functional Connectivity. We applied psychophysiological interaction (PPI) analysis to examine connectivity between the amygdala and hippocampus, using anatomical left and right hippocampus as seeds in two separate PPI models. Regressors were entered for the seed-region time series and for the interaction of the seed-region time series with the experimental conditions (PPI term). In a group-level analysis we contrasted the PPI map for immerse + distance across MDD patients versus control participants to estimate the main effect of group on connectivity. We also conducted a mediation analysis (using the *mediation* package in R, with 10,000 bootstrap samples), testing amygdala-hippocampal connectivity as a mediator of the effect of MDD diagnosis on negative affect elicited by negative memories (27). For this analysis, we used connectivity estimates extracted from a region of the right amygdala that showed a conjunction effect such that its connectivity with both left hippocampus and right hippocampus was correlated with negative affect ratings, across all subjects (height thresholded at $p < .01$; 594 mm^3).

RESULTS

Behavioral Results

Patients with MDD showed elevated negative affect during memory recall in the scanner task but were able to downregulate negative affect. First, we considered self-reports of negative affect made during the scanner task. There was a main effect of group, such that MDD patients reported higher levels of negative affect than did healthy control participants (CTL) ($b_{\text{MDD-CTL}} = 0.47$; 95% confidence interval [CI], 0.08 to 0.86; $p = .02$) (see Figure 2A, left). There was also a main effect of condition, such that participants reported less negative affect during distancing reappraisal (DIST) versus immersive recall (IMM) ($b_{\text{DIST-IMM}} = -0.79$; 95% CI, -0.96 to -0.61 ; $p < .001$), with downregulation of negative affect shown by MDD patients ($b = -0.74$; 95% CI, -0.94 to -0.53 ; $p < .001$) as well as control participants ($b = -0.85$; 95% CI, -1.17 to -0.53 , $p < .001$), and no condition by group interaction ($b_{\text{group} \times \text{cond}} = -0.11$; 95% CI, -0.46 to 0.25 ; $p = .55$). This pattern of results indicates that

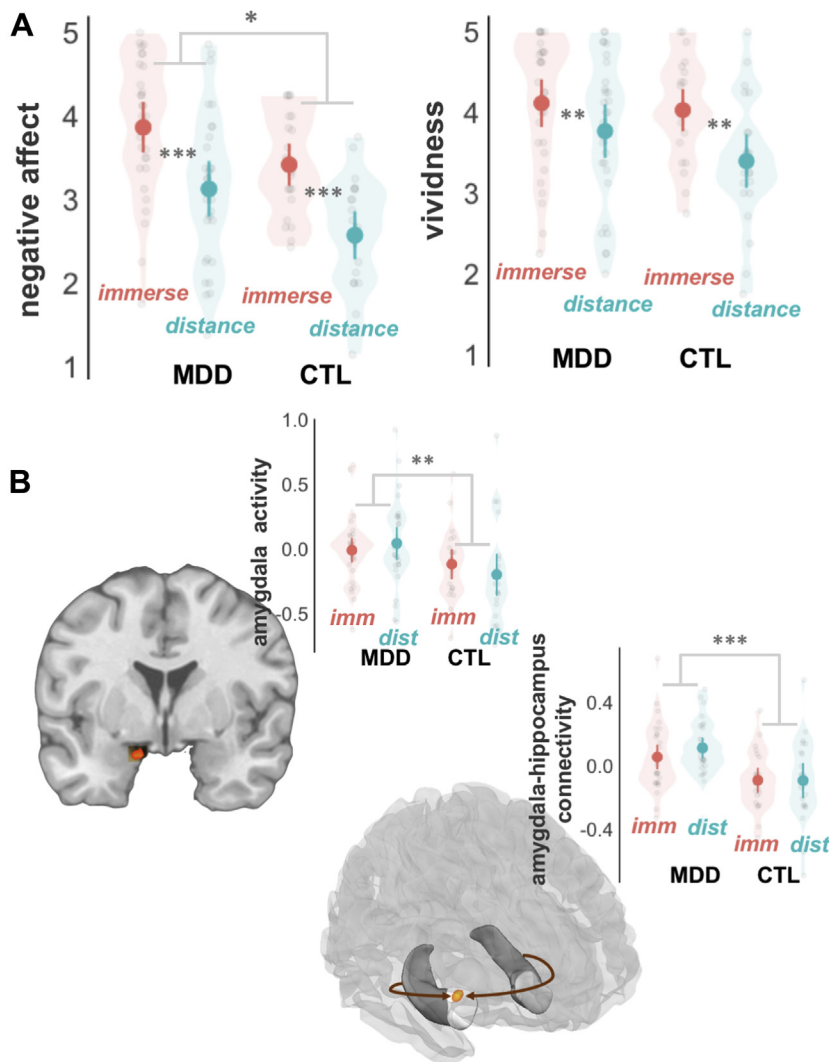


Figure 2. (A) Behavioral ratings. Negative affect ratings showed a main effect of group, such that the major depressive disorder (MDD) group reported higher levels of negative affect than the healthy control group (CTL), and a main effect of condition, such that distancing (dist) reappraisal decreased negative affect relative to immersive (imm) recall. Vividness ratings showed a main effect of condition. (B) Amygdala activity and amygdala-hippocampal connectivity. A main effect of group was apparent on activity within the left amygdala, and on connectivity of the right amygdala with both the left and right hippocampus (conjunction small-volume corrected $p < .05$, displayed at $p < .01$, uncorrected). Graphs show group means with 95% confidence interval, probability density plot, and participant means. * $p < .05$, ** $p < .01$, *** $p < .001$.

patients with MDD showed elevated negative affect to autobiographical memories but were able to downregulate this affect using distancing reappraisal.

Turning to vividness ratings, there was a main effect of condition, such that participants reported less vivid recall during distancing reappraisal than during immersive recall ($b_{\text{DIST-IMM}} = -0.47$; 95% CI, -0.66 to -0.27 ; $p < .001$) (see Figure 2A, right). However, there was no main effect of group ($b_{\text{MDD-CTL}} = 0.23$; 95% CI, -0.17 to 0.63 ; $p = .27$) or condition by group interaction ($b_{\text{group} \times \text{cond}} = -0.29$; 95% CI, -0.67 to 0.10 ; $p = .15$).

fMRI Results

Patients with MDD showed elevated amygdala activity and amygdala-hippocampal connectivity. We first considered main effect differences in the brain activity of MDD patients versus healthy control participants apparent when collapsing across

distancing reappraisal and immersive recall. MDD patients (vs. control participants) showed greater activity within the right amygdala ($-12, 0, -21$; $b_{\text{MDD-CTL}} = 0.18$; 95% CI, 0.06 to 0.30 ; small-volume corrected [SVC] $p < .05$) (see Figure 3B, top left). Follow-up whole-brain analyses revealed no other regions showing a main effect of group.

We next ran a functional connectivity analysis to ask whether this increased negative affect reported by people with MDD could be explained by enhanced connectivity between the amygdala, which is involved in the generation of negative affect, and the hippocampus, which is involved in episodic memory recall. This revealed that MDD patients showed increased functional connectivity of the left hippocampus with a region of the right amygdala ($24, 3, -12$; $b_{\text{MDD-CTL}} = 0.16$; 95% CI, 0.05 to 0.27 ; SVC $p < .05$) and of the right hippocampus with an overlapping region of the right amygdala ($24, -6, -18$; $b_{\text{MDD-CTL}} = 0.17$; 95% CI, 0.07 to 0.27 ; SVC $p < .05$) (significant conjunction of these connectivity effects

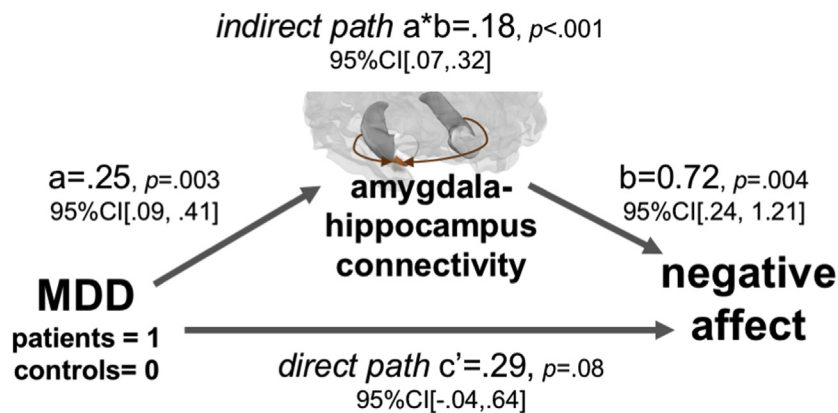


Figure 3. Mediation model. Major depressive disorder (MDD)-associated elevation in negative affect was mediated by greater amygdala-hippocampus connectivity, consistent with a model in which elevated negative affective responses to personal memories in MDD are brought about via elevated connectivity between the amygdala and hippocampus. CI, confidence interval.

shown in Figure 2B, bottom right). This pattern indicates that MDD patients showed greater amygdala activity and greater amygdala-hippocampal connectivity during negative autobiographical memory recall.

Elevated negative affect in MDD was mediated by amygdala-hippocampal connectivity. We used a mediation analysis to assess the whether the data were consistent with a causal model whereby the elevated negative affect seen in MDD patients is mediated by elevated amygdala-hippocampal connectivity.

To do this, we extracted estimates of amygdala-hippocampus connectivity from a cluster within the right amygdala (33, 6, -24) for which connectivity with hippocampus was correlated with higher negative affect across all subjects. In the mediation model, the predictor variable was group (MDD patients = 1, control participants = 0), the outcome variable was average negative affect, and the mediator variable was amygdala-hippocampus connectivity. The results of this model (see Figure 3) indicated that the effect of MDD on elevated negative affect was mediated by increased amygdala-hippocampal connectivity (indirect path $a*b = 0.18$; 95% CI, 0.07 to 0.32; $p < .001$). When controlling for amygdala-hippocampal connectivity, the effect of MDD on negative affect decreased in magnitude and dropped to trend-level significance (direct path $c' = 0.29$; 95% CI, -0.04 to 0.64; $p = .08$). Although these variables were not experimentally manipulated, this pattern of results is consistent with a model in which elevated negative affective responses to personal memories in MDD are brought about via greater connectivity between the amygdala and hippocampus.

MDD patients and control participants showed comparable recruitment of the prefrontal, parietal, and temporal cortices, and comparable downregulation of the amygdala and anterior hippocampus for distancing reappraisal relative to immersive recall. Our initial analyses revealed mechanisms underlying negative affect, but they did not consider the neural mechanisms underlying downregulating this affective impact via distancing reappraisal. To address this, we tested main effects of distancing reappraisal versus immersive recall on brain activity, collapsing across MDD patients and control participants. For distancing reappraisal (vs. immersive recall), we found engagement of the right dorsolateral prefrontal cortex, bilateral

posterior parietal cortex, and bilateral lateral temporal cortex (familywise error-corrected $p < .05$) (see Figure 4, left). We also found downregulation (i.e., less activity during distancing reappraisal versus immersive recall) within the bilateral amygdala and bilateral anterior hippocampus (SVC $p < .05$) (see Figure 4, top and bottom right). Across these regions, patients with MDD and healthy control participants showed effects of comparable magnitude (see Figure 4). There were no significant differences in activity between the two groups in regions engaged during reappraisal (collapsing across activated regions; $b_{\text{group} \times \text{cond}} = 0.08$; 95% CI, -0.07 to 0.22; $p = .31$) or in downregulation of the amygdala and anterior hippocampal regions during reappraisal ($b_{\text{group} \times \text{cond}} = 0.02$; 95% CI, -0.12 to 0.08; $p = .70$; MDD patients showed directionally, but not significantly, larger effects than control participants). This pattern indicates that MDD patients and healthy control participants showed comparable recruitment of a network of control-related cortical regions and comparable downregulation of emotion- and memory-related subcortical regions when reappraising negative autobiographical memories.

MDD patients (but not control participants) showed downregulation of the posterior hippocampus that predicted downregulation of negative affect. Next, we asked whether MDD patients showed different effects of distancing reappraisal compared with healthy control participants within the hippocampus. We saw an interaction within the hippocampus, with a peak in the left posterior hippocampus (Montreal Neurological Institute coordinates -30, -39, -3; $b_{\text{group} \times \text{cond}} = -0.10$; 95% CI, 0.16 to 0.04; SVC $p < .05$) where MDD patients, but not control participants, showed reappraisal-related downregulation of activity (see Figure 5, left panel). We observed an interaction of group and condition neither within the amygdala (SVC $p > .20$), nor for any clusters surviving correction in a whole-brain analyses (familywise error-corrected $p > .10$).

Finally, we asked whether downregulation of this posterior hippocampal region was predictive of reappraisal success for MDD patients but not control participants. We reasoned this would be the case if this effect reflected a distinct pathway to downregulating negative affect active for the MDD group (but not for the control participants). Indeed,

Mechanisms of Negative Memory in MDD

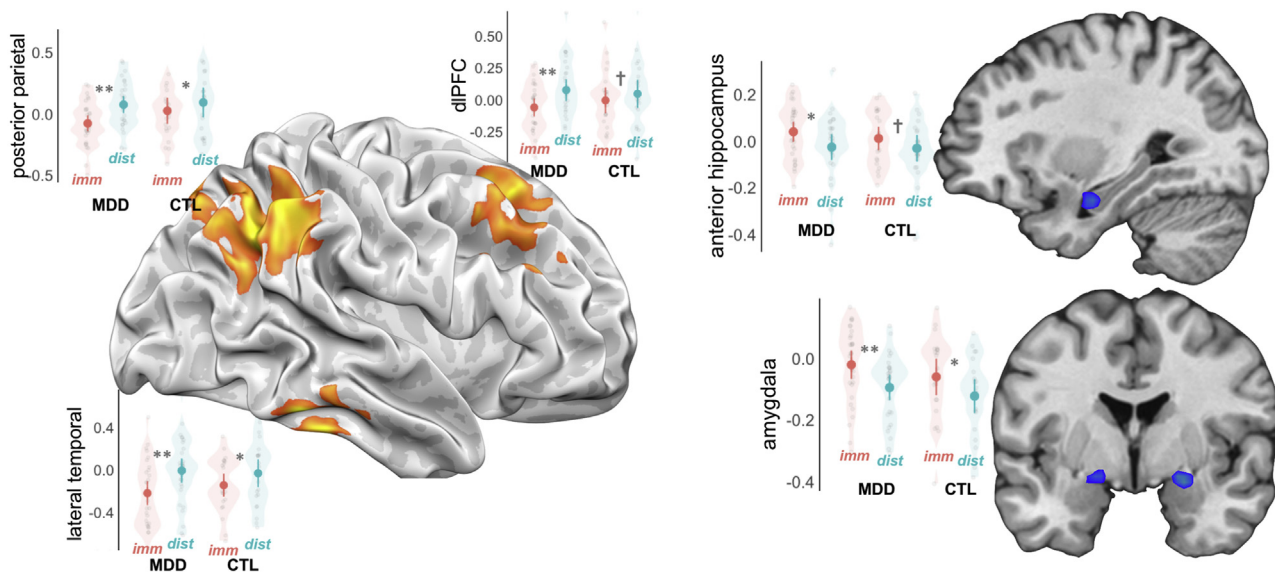


Figure 4. Reappraisal-related brain activity. The major depressive disorder (MDD) group and healthy control group (CTL) showed comparable engagement of the dorsolateral prefrontal cortex (dIPFC), posterior parietal cortex, and lateral temporal cortex (familywise error-corrected $p < .05$) during reappraisal, and comparable downregulation of the bilateral amygdala and anterior hippocampus (small-volume corrected $p < .05$, displayed at $p < .01$ uncorrected). Graphs show group means with 95% confidence interval, probability density plot, and participant means. † $p < .10$, * $p < .05$, ** $p < .01$. dist, distance; imm, immerse.

posterior hippocampal downregulation correlated with reappraisal-evoked downregulation of negative affect for the MDD group ($b = 0.07$; 95% CI, 0.01 to 0.12; $p = .02$) but not for control participants, $b = -0.03$; 95% CI, -0.07 to 0.02; $p = .27$), with a significant difference between these two effects ($b = 0.10$; 95% CI, 0.03 to 0.17; $p = .009$) (see Figure 5, right panel). Moreover, the relationship between downregulation of the posterior hippocampus and downregulation of negative affect held when additionally including age and sex as covariates within the mediation model ($b = 0.09$; 95% CI, 0.01 to 0.17; $p = .03$). These data indicate that downregulation of memory-evoked negative affect in patients with MDD was associated with a distinct brain

pathway that entailed downregulation of the posterior hippocampus.

DISCUSSION

Emotion dysregulation and autobiographical memory dysfunction are observed in major depression. Here we report a study of the neural mechanisms underlying regulation of responses to negative autobiographical memories in MDD. Relative to healthy control participants, currently depressed patients with MDD showed elevated negative affect during memory recall but comparable ability to downregulate this negative affect via distancing reappraisal. In terms of brain

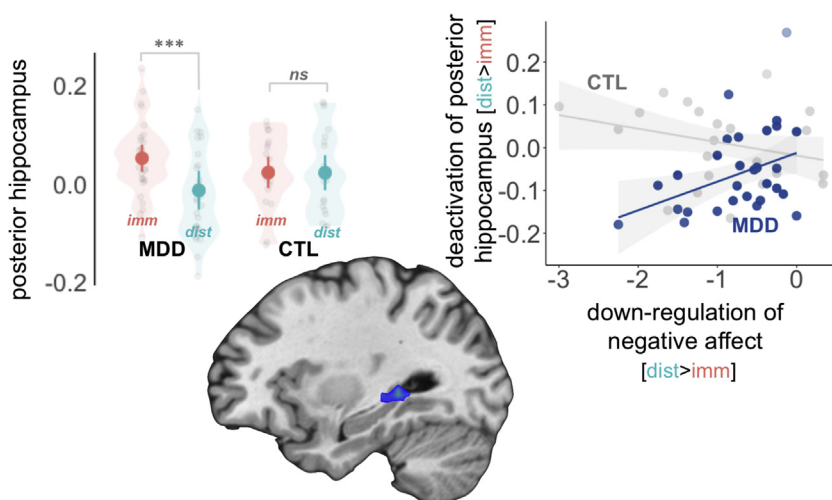


Figure 5. Major depressive disorder (MDD) patients showed downregulation of the posterior hippocampus. The [MDD > control participants (CTL)] [distance (dist) > immerse (imm)] interaction contrast revealed downregulation of the posterior hippocampus for the MDD group only (small-volume corrected $p < .05$, displayed at $p < .01$ uncorrected), and it tracked with downregulation of negative affect. Left panel: group means with 95% confidence interval, probability density plot, and participant means; right panel: scatter plot with robust regression lines and 95% confidence intervals. *** $p < .001$. ns, not significant.

activity, MDD patients showed elevated activity in the amygdala and increased functional connectivity of amygdala with hippocampus, which mediated the relationship between MDD diagnosis and elevated negative affect. In terms of the brain mechanisms of emotion regulation, the results revealed a broadly similar pattern across MDD and control groups, except for one key difference. Patients and control participants showed comparable engagement of the lateral prefrontal cortex, posterior parietal, and lateral temporal cortex and comparable downregulation of the amygdala and anterior hippocampus, but the MDD group showed downregulation of posterior hippocampus, and the extent of this downregulation correlated with downregulation of negative affect (for the MDD group only).

Implications for Neural Mechanisms of MDD-Related Emotion Disturbance

These findings provide evidence for a model of MDD whereby 1) elevated emotional responses to negative autobiographical memories are related to underlying interactions of the amygdala and hippocampus and 2) downregulation of these emotional responses involves a pathway, not engaged by healthy control participants, that entails downregulation of the posterior hippocampus (in addition to downregulation of the amygdala and anterior hippocampus also shown by control participants). Notably, although people with MDD engaged this additional pathway, they achieved downregulation of negative emotion that was comparable in magnitude to that of control participants.

Many human and animal studies support the notion of an anteroposterior functional dissociation within the hippocampus, with more anterior regions implicated in the expression of fear and anxiety, and more posterior regions implicated in the reinstatement of richly detailed spatial and relational information (28–31). In light of this dissociation, our data suggest that to downregulate memory-evoked negative affect, people with MDD modulate activity in the posterior hippocampus regions that support episodic memory reinstatement. This finding converges with a growing body of literature suggesting that people with MDD are able to regulate emotional experience in lab-based tasks, but they do so by engaging neural mechanisms that differ from those engaged by nondepressed people (16–22). Here, it may be that people with MDD tend to regulate their affective responses to negative memories by dampening activity within a region that supports the reinstatement of specific details of the remembered negative experience. This pattern of data corresponds with a growing body of studies suggesting that people with MDD show relatively spared regulation abilities but aberrant regulatory tendencies (32).

Implications for Translating the Basic Science of Emotion Regulation

Where brain models of emotion regulation have previously highlighted the importance of interacting brain systems for top-down control and bottom-up generation of emotion, the results of this study extend these models in several ways. First, our results indicate a role for amygdala-hippocampus interactions in reactivity to negative autobiographical memories, which converges with basic research indicating that amygdala-hippocampus

connectivity at encoding facilitates memory for emotionally evocative laboratory stimuli in healthy individuals (33–35) and in people with MDD (36). Moreover, our data suggest that affective differences apparent in MDD may not reflect an inability to use a top-down strategy for emotion regulation when instructed to, but instead use a combination of elevated responses to negative autobiographical memories (5,37,38) and a tendency to implement a top-down strategy for emotion regulation using atypical circuitry (32,39). Notably, the region of the amygdala showing connectivity with the hippocampus was relatively ventral compared with peaks typically reported in reappraisal studies (10). This peak could represent connectivity with the basolateral amygdala. However, the spatial resolution of fMRI limits any strong inference about differential roles for particular amygdalar subregions on the basis of these results.

Future studies could extend this work by determining whether specific cognitive training, psychotherapy, or drug treatments can normalize elevated negative affective responses and/or brain activity apparent during reappraisal of personal memories. Prospective and/or developmental studies could ask whether amygdala and hippocampal responses to negative autobiographical memories have relevance for who will become depressed in the future, or who will respond to specific treatments (39–41). Moreover, such studies could ask to what extent observed differences in brain activity between people with MDD and healthy control participants are related to differences in affect initially experienced during aversive life events versus effects of depression on the recall of these events. Longitudinal studies that track brain activity and emotional responses to negative life experiences over time (i.e., instead of asking participants to recall the initial impact of a remembered event) could illuminate the role of amygdala-hippocampus interactions in the early versus lasting emotional impact of negative life experiences. Moreover, such studies could shed light on how differences in the kinds of life experiences that people with MDD tend to experience and remember may affect the brain responses they have during memory recall and regulation.

From another angle, it is possible that nondepressed control participants could be driven to reappraise in a manner more comparable to what was shown by people with MDD here (i.e., to robustly downregulate posterior hippocampus) if given specific training or instructions, which could deepen our understanding of these mechanisms by identifying specific styles of emotion regulation that rely on downregulation of activity in specific hippocampal subregions. That is, despite the observation that people with MDD and healthy control participants achieved similar behavioral success in emotion regulation, our data suggest that they differed in the mechanisms they engaged to achieve this success, and future studies could use modified experimental paradigms to try to reveal more dramatic differences in behavioral performance. More generally, knowing how people react to and control memory representations of distressing autobiographical experiences is a crucial step in translating current neural models of emotion regulation to better understand daily life emotion disturbances seen in MDD and other clinical disorders.

We sought to understand whether people with MDD show differential recruitment of memory-, emotion-, and control-related brain systems during recall and regulation of negative

Mechanisms of Negative Memory in MDD

autobiographical memories. However, we did not study reactivity to or regulation of positive or neutral memories—therefore, we do not have an empirical basis for generalizing these findings to situations where people with MDD are asked to reflect on or control their emotional responses during recall of positive or unemotional life experiences. Moreover, follow-up work could also compare the brain mechanisms of instructed reactivity and regulation strategies to more spontaneous recall conditions to ask how instructed reactivity and regulation differs from natural recall in people with MDD versus matched control participants. Finally, future studies should use larger samples of memories and participants to more precisely estimate the effects we describe here and detect smaller magnitude effects. Related, efforts to aggregate and meta-analyze existing data could help estimate the magnitude of MDD-related impairment in reappraisal success, even if it is small and variable.

Conclusions

Although distressing life experiences come and go, they exert an impact on memory that can continue to have effects over time. Our data suggest that this impact is elevated for people with MDD, who show underlying differences in amygdala reactivity and amygdala-hippocampal connectivity. Moreover, although people with MDD are able to downregulate this negative impact, they do so via a distinct pathway that entails modulating a region of posterior hippocampus not modulated by control participants. These findings identify brain mechanisms underlying autobiographical memory disturbance in MDD and provide direction for future work into the role of these mechanisms in depressive etiology.

ACKNOWLEDGMENTS AND DISCLOSURES

The study was supported by Conte Grant No. MH090964.

JMM's family previously owned stock in Johnson & Johnson, and he currently serves as a coinvestigator on a research study funded by Johnson & Johnson, both unrelated to the current manuscript. JJM receives royalties for commercial use of the Columbia-Suicide Severity Rating Scale from the Research Foundation for Mental Hygiene. All other authors report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

From the Annenberg School for Communication (BPD) and Department of Psychiatry (MAO), Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania; and the Departments of Psychology (OR, CB, JW, KNO), Psychiatry (BS, JMM, MES, JJM), and Neurology (JJM), Columbia University; Department of Psychology (AH), New York University; and Division of Molecular Imaging and Neuropathology (BS, JMM, MES, JJM), New York State Psychiatric Institute, New York, New York.

Address correspondence to Bruce P. Doré, Ph.D., Annenberg School for Communication, University of Pennsylvania, 3620 Walnut St, Philadelphia, PA 19104; E-mail: brucedore@gmail.com.

Received Jul 13, 2017; revised and accepted Jan 4, 2018.

Supplementary material cited in this article is available online at <https://doi.org/10.1016/j.bpsc.2018.01.002>.

REFERENCES

- Otte C, Gold SM, Penninx BW, Pariante CM, Etkin A, Fava M, *et al.* (2016): Major depressive disorder. *Nat Rev Dis Primers* 2:16065.
- Beck AT, Bredemeier K (2016): A unified model of depression: Integrating clinical, cognitive, biological, and evolutionary perspectives. *Clin Psychol Sci* 4:596–619.
- Nolen-Hoeksema S (2000): The role of rumination in depressive disorders and mixed anxiety/depressive symptoms. *J Abnorm Psychol* 109:504–511.
- Segal ZV (1988): Appraisal of the self-schema construct in cognitive models of depression. *Psychol Bull* 103:147–162.
- Williams JMG, Barnhofer T, Crane C, Herman D, Raes F, Watkins E, Dalgleish T (2007): Autobiographical memory specificity and emotional disorder. *Psychol Bull* 133:122–148.
- Treadway MT, Bossaller NA, Shelton RC, Zald DH (2012): Effort-based decision-making in major depressive disorder: A translational model of motivational anhedonia. *J Abnorm Psychol* 121:553–558.
- Nezlek JB, Hampton CP, Shean GD (2000): Clinical depression and day-to-day social interaction in a community sample. *J Abnorm Psychol* 109:11–19.
- Sowislo JF, Orth U (2013): Does low self-esteem predict depression and anxiety? A meta-analysis of longitudinal studies. *Psychol Bull* 139:213–240.
- Liu Y, Yu X, Yang B, Zhang F, Zou W, Na A, *et al.* (2017): Rumination mediates the relationship between overgeneral autobiographical memory and depression in patients with major depressive disorder. *BMC Psychiatry* 17:103.
- Buhle JT, Silvers JA, Wager TD, Lopez R, Onyemekwu C, Kober H, *et al.* (2014): Cognitive reappraisal of emotion: A meta-analysis of human neuroimaging studies. *Cereb Cortex* 24:2981–2990.
- Ochsner KN, Silvers JA, Buhle JT (2012): Functional imaging studies of emotion regulation: A synthetic review and evolving model of the cognitive control of emotion. *Ann N Y Acad Sci* 1251:E1–E24.
- Davachi L, DuBrow S (2015): How the hippocampus preserves order: The role of prediction and context. *Trends Cogn Sci* 19:92–99.
- Holland AC, Kensinger EA (2010): Emotion and autobiographical memory. *Phys Life Rev* 7:88–131.
- Kross E, Davidson M, Weber J, Ochsner K (2009): Coping with emotions past: The neural bases of regulating affect associated with negative autobiographical memories. *Biol Psychiatry* 65:361–366.
- Silvers JA, Hubbard AD, Chaudhury S, Biggs E, Shu J, Grunebaum MF, *et al.* (2016): Suicide attempters with borderline personality disorder show differential orbitofrontal and parietal recruitment when reflecting on aversive memories. *J Psychiatr Res* 81:71–78.
- Smoski MJ, LaBar KS, Steffens DC (2014): Relative effectiveness of reappraisal and distraction in regulating emotion in late-life depression. *Am J Geriatr Psychiatry* 22:898–907.
- Smoski MJ, Keng S-L, Ji JL, Moore T, Minkel J, Dichter GS (2015): Neural indicators of emotion regulation via acceptance vs reappraisal in remitted major depressive disorder. *Soc Cogn Affect Neurosci* 10:1187–1194.
- Beauregard M, Paquette V, Lévesque J (2006): Dysfunction in the neural circuitry of emotional self-regulation in major depressive disorder. *Neuroreport* 17:843–846.
- Belden AC, Pagliaccio D, Murphy ER, Luby JL, Barch DM (2015): Neural activation during cognitive emotion regulation in previously depressed compared to healthy children: Evidence of specific alterations. *J Am Acad Child Adolesc Psychiatry* 54:771–781.
- Dillon DG, Pizzagalli DA (2013): Evidence of successful modulation of brain activation and subjective experience during reappraisal of negative emotion in unmedicated depression. *Psychiatry Res* 212:99–107.
- Ehring T, Tuschen-Caffier B, Schnulle J, Fischer S, Gross JJ (2010): Emotion regulation and vulnerability to depression: Spontaneous versus instructed use of emotion suppression and reappraisal. *Emotion* 10:563–572.
- Erk S, Mikschl A, Stier S, Ciaramidaro A, Gapp V, Weber B, Walter H (2010): Acute and sustained effects of cognitive emotion regulation in major depression. *J Neurosci* 30:15726–15734.
- Stark CE, Squire LR (2001): When zero is not zero: The problem of ambiguous baseline conditions in fMRI. *Proc Natl Acad Sci U S A* 98:12760–12766.
- Schneider W, Eschman A, Zuccolotto A (2002): E-prime, Version 1.1. Pittsburgh, PA: Psychology Software Tools.

25. R Development Core Team (2017): R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing.
26. Wager TD, Keller MC, Lacey SC, Jonides J (2005): Increased sensitivity in neuroimaging analyses using robust regression. *Neuroimage* 26:99–113.
27. Tingley D, Yamamoto T, Hirose K, Keele L, Imai K (2014): Mediation: R package for causal mediation analysis. Available at: <https://dspace.mit.edu/handle/1721.1/91154?show=full>. Accessed February 23, 2017.
28. Fanselow MS, Dong H-W (2010): Are the dorsal and ventral hippocampus functionally distinct structures? *Neuron* 65:7–19.
29. Pitkänen A, Pikkarainen M, Nurminen N, Ylinen A (2000): Reciprocal connections between the amygdala and the hippocampal formation, perirhinal cortex, and postrhinal cortex in rat: A review. *Ann N Y Acad Sci* 911:369–391.
30. Satpute AB, Mumford JA, Naliboff BD, Poldrack RA (2012): Human anterior and posterior hippocampus respond distinctly to state and trait anxiety. *Emotion* 12:58–68.
31. Strange BA, Witter MP, Lein ES, Moser EI (2014): Functional organization of the hippocampal longitudinal axis. *Nat Rev Neurosci* 15:655–669.
32. Liu DY, Thompson RJ (2017): Selection and implementation of emotion regulation strategies in major depressive disorder: An integrative review. *Clin Psychol Rev* 57:183–194.
33. Dolcos F, LaBar KS, Cabeza R (2004): Interaction between the amygdala and the medial temporal lobe memory system predicts better memory for emotional events. *Neuron* 42:855–863.
34. Murty VP, Ritchey M, Adcock RA, LaBar KS (2010): fMRI studies of successful emotional memory encoding: A quantitative meta-analysis. *Neuropsychologia* 48:3459–3469.
35. Phelps EA, Sharot T (2008): How (and why) emotion enhances the subjective sense of recollection. *Curr Dir Psychol Sci* 17:147–152.
36. Hamilton JP, Gotlib IH (2008): Neural substrates of increased memory sensitivity for negative stimuli in major depression. *Biol Psychiatry* 63:1155–1162.
37. Victor TA, Furey ML, Fromm SJ, Ohman A, Drevets WC (2010): Relationship between amygdala responses to masked faces and mood state and treatment in major depressive disorder. *Arch Gen Psychiatry* 67:1128–1138.
38. Young KD, Drevets WC, Bodurka J, Preskorn SS (2016): Amygdala activity during autobiographical memory recall as a biomarker for residual symptoms in patients remitted from depression. *Psychiatry Res* 248:159–161.
39. Joormann J, Gotlib IH (2010): Emotion regulation in depression: Relation to cognitive inhibition. *Cogn Emot* 24:281–298.
40. Phillips JL, Batten LA, Tremblay P, Aldosary F, Blier P (2015): A prospective, longitudinal study of the effect of remission on cortical thickness and hippocampal volume in patients with treatment-resistant depression. *Int J Neuropsychopharmacol* 18:pyv037.
41. Sumner JA, Griffith JW, Mineka S (2010): Overgeneral autobiographical memory as a predictor of the course of depression: A meta-analysis. *Behav Res Ther* 48:614–625.