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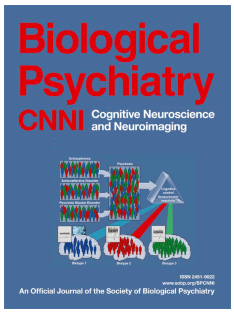

Negative autobiographical memory in depression reflects elevated amygdala-hippocampal reactivity and hippocampally-associated emotion regulation

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, Kevin N. Ochsner

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Negative autobiographical memory in depression reflects elevated amygdala-hippocampal reactivity and hippocampally-associated emotion regulation

Doré, Bruce P.[1], Rodrik, Odile[2], Boccagno, Chelsea[2], Hubbard, Alexa[3], Weber, Jochen[2], Stanley, Barbara[4,5], Oquendo, Maria A.[7], Miller, Jeffrey M.[4,5], Sublette, M. Elizabeth[4,5], Mann, J. John[4,5,6], Ochsner, Kevin N.[2]

[1]Annenberg School for Communication, University of Pennsylvania
[2]Department of Psychology, Columbia University
[3]Department of Psychology, New York University
[4]Division of Molecular Imaging and Neuropathology, New York State Psychiatric Institute
[5]Department of Psychiatry, Columbia University
[6]Department of Neurology, Columbia University
[7]Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania

Corresponding author:
Bruce Doré
Annenberg School for Communication, University of Pennsylvania
3620 Walnut St, Philadelphia, PA 19104
brucedore@gmail.com

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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 fMRI to identify neural mechanisms underlying MDD-related emotional responses to negative autobiographical memories and the ability to down-regulate these responses using a cognitive regulatory strategy known as reappraisal. We compared currently depressed, medication-free patients with MDD (n = 29) to control participants with no history of depression (n = 23).
Results: Relative to healthy controls, medication-free MDD patients reported greater negative emotion during recall but relatively intact down-regulation 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 (versus recalling from an immersed perspective), MDD and control groups showed comparable recruitment of prefrontal, parietal, and temporal cortex, and comparable down-regulation of amygdala and anterior hippocampus. However, MDD patients showed greater down-regulation of posterior hippocampus, and the extent of this down-regulation predicted successful reduction of negative affect in MDD patients only.
Conclusions: These data suggest amygdala-hippocampal connectivity and posterior hippocampal down-regulation as brain mechanisms related to elevated emotional reactivity and atypical emotion regulation in MDD.

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, or images of distressing situations drawn from standardized stimulus sets), and not autobiographical memories. Neural models developed in non-depressed 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 suggest 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 to healthy controls), but they do so by engaging neural mechanisms that differ from those engaged by non-depressed 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 non-depressed people, we asked three targeted questions about people with MDD, as compared to healthy controls. 1: Do people with MDD differ from controls in the emotional impact of negative autobiographical memories? 2: Do people with MDD differ from controls in their ability to down-regulate this impact? 3: Do people with MDD differ in the neural mechanisms underlying reactivity to and regulation of negative autobiographical memories?

Methods

Participants

Participants were 29 (15 female) people with DSM-IV MDD (mean age = 31.6, SD=9.9), and 23 (12 female) healthy controls (mean age = 32.6, SD=8.5), recruited as part of a larger multi-modal 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 old, had no active medical illness, were currently in a major depressive episode as part of major depressive disorder as determined via the Structured Clinical Interview for DSM-IV, scored at least 16 on the 17-item Hamilton Depression Rating Scale (HAMD), were not diagnosed with any of the following Axis I psychiatric conditions: bipolar disorder, psychotic disorders, and current drug or alcohol abuse (within 2 months) or dependence (within 6 months), anorexia or bulimia nervosa (within the past year), and were able to discontinue psychiatric medications and other psychotropic drugs for at least 21 days prior to the scan. Participants were not excluded from the MDD group on the basis of co-morbid diagnosis of an anxiety disorder. Participants were eligible for assignment

	MDD group	Control group
Age	31.6 (SD=9.9)	32.6 (SD=8.5)
Sex	52% Female	52% Female
Education	15.3 (range 12 to 20)	16 (range 12 to 18)
HAMD score	20.2 (range 16 to 27)	1.5 (range 0 to 11)
% ever used anti-depressant	38%	
years since last anti-depressant	12 (range 3 to 29)	
% with comorbid anxiety disorder	34%	

Table 1. *Characteristics of the participants in the MDD and Control groups, including mean age, sex, median years of education, median Hamilton Depression Rating Scale (HAMD) score, percent of total group that has ever used an anti-depressant medication, median number of years*

since last use of anti-depressant medication, and percent of total group with a lifetime diagnosis of an anxiety disorder.

to the control group if they were 18 to 60 years old, had no active medical illness, no lifetime history of Axis I or Axis II psychiatric illness, 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 magnetic resonance imaging (MRI). Study procedures were approved by IRBs at Columbia University and New York State Psychiatric Institute.

Image acquisition

Data were collected with a 3T GE MR750 magnet using a 32-channel RF head coil. Structural volumes were acquired using a high-resolution T1-weighted sagittal 3D BRAVO sequence yielding 1mm isotropic voxel size. Functional volumes were acquired using a T2*-sensitive echo planar imaging (EPI) sequence with a repetition time (TR) of 2000ms, an echo time (TE) of 25ms, a 77° flip angle, and a 19.2cm FOV consisting of 45 interleaved 3mm slices acquired parallel to the AC-PC axis. Four runs of 119 TRs were collected. Each run began with 8s of fixation and the corresponding 4 volumes were discarded.

[Figure 1]

Negative autobiographical memory fMRI task

Scanner Recollection and Regulation Task. Before scanning, participants were tested to confirm they could recall their memories when prompted with the cues they provided in the pre-scan session (see Supplemental Materials), and then 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 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). It 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 inter-stimulus interval (ISI), a rating period (rate negative affect and vividness on a 5 point scale), and an inter-trial interval (ITI). Each memory was allocated once to both 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 20s. 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 1.2 (24), and participants made behavioral responses on a five-button response pad.

Behavioral analysis

Analyses were conducted in R v3.3.1 (25). Average ratings of vividness and negative affect collected during the scanner task were submitted to two separate 2 (Group: MDD vs. Control) X 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 down-regulation of negative affect (i.e., IMMERSE mean – DISTANCE mean). Unstandardized regression coefficients were used to indicate effect sizes.

fMRI analysis

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

First-level (individual) GLM analyses were implemented in NeuroElf v1.1 (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 v1.1 using iteratively re-weighted least squares regression (26). All activation peaks are reported in Montreal Neurological Institute (MNI) space. We defined anatomical regions of interest (ROIs) for the amygdala (L -23,-5,-18; R 23, -4, -18; 5324 mm^3) and hippocampus (L -25, -22, -14; R, 23, -21, -15; 11263 mm^3) using maximum 25% probability volumes from the Harvard-Oxford atlas. For ROI 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 ROI. For whole-brain analyses, we used permutation-based thresholding implemented in NeuroElf v1.1 to achieve a whole-brain family-wise error rate (FWE) corrected $p < 0.05$, with a cluster-defining threshold of $p < 0.002$.

Functional connectivity. We applied psychophysiological interaction (PPI) analysis to examine connectivity between 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 controls 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 $p<0.01$, 594 mm^3).

Results

Behavioral Results

Patients with MDD showed elevated negative affect during memory recall in the scanner task, but were able to down-regulate 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 controls, $b_{MDD\text{-}CTL} = 0.47$, 95%CI[.08, .86], $p=0.02$ (see Figure 2A, left). There was also a main effect of condition such that participants reported less negative affect during distancing reappraisal versus immersive recall, $b_{DIST\text{-}IMM} = -0.79$, 95%CI[-.96, -.61], $p<0.001$, with down-regulation of negative affect shown by MDD patients, $b = -0.74$, 95%CI[-.94, -.53], $p<0.001$, as well as controls, $b = -0.85$, 95%CI[-1.17, -.53], $p<0.001$, and no condition by group interaction, $b_{grpXcond} = -0.11$, 95%CI[-.46, .25], $p=0.55$. This

pattern of results indicates that patients with MDD showed elevated negative affect to autobiographical memories but were able to down-regulate 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, $b_{DIST-IMM}$ = -0.47, 95%CI[-0.66, -0.27], p<0.001 (see Figure 2A, right). However, there was no main effect of group, $b_{MDD-CTL}$ = 0.23, 95%CI[-0.17, 0.63], p=0.27, or condition by group interaction, $b_{grpXcond}$= -0.29, 95%CI[-0.67, 0.10], p=.15.

[Figure 2]

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 controls apparent when collapsing across distancing reappraisal and immersive recall. MDD patients (versus controls) showed greater activity within right amygdala (-12, 0, -21), $b_{MDD-CTL}$ = 0.18, 95%CI[0.06, 0.30], SVC p<0.05 (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 left hippocampus with a region of right amygdala (24, 3, -12), $b_{MDD-CTL}$ = 0.16, 95%CI[0.05, 0.27], SVC p<0.05, and of right hippocampus with an overlapping region of right amygdala (24, -6, -18), $b_{MDD-CTL}$ = 0.17, 95%CI[0.07, 0.27], SVC p<0.05 (significant conjunction of these connectivity effects 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.

[Figure 3]

To do this, we extracted estimates of amygdala-hippocampus connectivity from a cluster within 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, controls = 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, 0.32], p<0.001. 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, 0.64], p=0.08. Although these variables were not experimentally manipulated, this pattern of results is consistent with a model whereby elevated negative affective responses to personal memories in MDD are brought about via greater connectivity between amygdala and hippocampus.

MDD patients and controls showed comparable recruitment of prefrontal, parietal, and temporal cortex, and comparable down-regulation of 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 down-regulating 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 controls. For distancing reappraisal (versus immersive recall), we found engagement of right dorsolateral PFC, bilateral posterior parietal cortex, and bilateral lateral temporal cortex (FWE p<0.05) (see Figure 4,

[Figure 4]

left). We also found down-regulation (i.e., less activity during distancing reappraisal versus immersive recall) within bilateral amygdala and bilateral

anterior hippocampus (SVC p<0.05) (see Figure 4, top and bottom right). Across these regions, patients with MDD and healthy controls 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), $b_{groupXcond}$ = 0.08, 95%CI[-0.07, 0.22], p=0.31, or in down-regulation of amygdala and anterior hippocampal regions during reappraisal, $b_{groupXcond}$ = -0.02, 95%CI[-0.12, 0.08], p=0.70 (MDD patients showed directionally, but not significantly, larger effects than controls). This pattern indicates that MDD patients and healthy controls showed comparable recruitment of a network of control-related cortical regions and comparable down-regulation of emotion- and memory-related subcortical regions when reappraising negative autobiographical memories.

MDD patients (but not controls) showed down-regulation of posterior hippocampus that predicted down-regulation of negative affect. Next, we asked whether MDD patients showed different effects of distancing reappraisal compared with healthy controls within the hippocampus. We saw an interaction within the hippocampus, with a peak in the left posterior hippocampus (MNI coordinates -30, -39, -3), $b_{groupXcond}$ = -0.10, 95%CI[-0.16, -0.04], SVC p<0.05, where MDD patients, but not controls, showed reappraisal-related down-regulation of activity (see Figure 5, left panel). We did not observe an interaction of group and condition within the amygdala (SVC p>.20), nor for any clusters surviving correction in a whole-brain analyses (FWE p>.10).

Finally, we asked whether down-regulation of this posterior hippocampal region was predictive of reappraisal success for MDD patients but not controls.

[Figure 5]

We reasoned this would be the case if this effect reflected a distinct pathway to down-regulating negative affect active for the MDD group (but not controls). Indeed, posterior hippocampal down-regulation correlated with reappraisal-evoked down-regulation of negative affect for the MDD group, b=0.07, 95%CI[0.01, 0.12], p=0.02, but not controls, b=-0.03, 95%CI[-0.07, 0.02], p=0.27, with a significant difference between these two effects, b=0.10, 95%CI[0.03, 0.17], p=0.009 (see Figure 5, right panel). Moreover, the relationship between down-regulation of posterior hippocampus and down-regulation of negative affect held when additionally including age and gender as covariates within the mediation model, b=.09, 95%CI[0.01, 0.17], p=0.03. These data indicate that down-regulation of memory-evoked negative affect in patients with MDD was associated with a distinct brain pathway that entailed down-regulation of 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 down-regulate this negative affect via distancing reappraisal. In terms of brain 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 controls showed comparable engagement of lateral PFC, posterior parietal, and lateral temporal cortex and comparable down-regulation of amygdala and anterior hippocampus, but the MDD group showed down-regulation of posterior hippocampus, and the extent of this down-regulation correlated with down-regulation 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 amygdala and hippocampus; and 2) down-regulation of these emotional responses involves a pathway, not engaged by healthy controls, that entails down-regulation of posterior hippocampus (in addition to down-regulation of amygdala and anterior hippocampus also shown by controls). Notably, although people with MDD engaged this additional pathway, they achieved down-regulation of negative emotion that was comparable in magnitude to that of controls.

Many human and animal studies support the notion of an anterior-posterior functional dissociation within the hippocampus, with more anterior regions implicated in the expression of fear and anxiety, and more posterior implicated in the reinstatement of richly detailed spatial and relational information (28-31). In light of this dissociation, our data suggest that in order to down-regulate memory-evoked negative affect, people with MDD modulate activity in 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 non-depressed 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 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 amygdala showing connectivity with hippocampus was relatively ventral compared to 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 controls 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 non-depressed controls could be driven to reappraise in a manner more comparable to what was shown by people with MDD here (i.e., to robustly down-regulate 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 down-regulation of activity in specific hippocampal subregions. That is, despite the observation that people with MDD and healthy controls 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 in order 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 autobiographical memories. However, we did not study reactivity to or regulation of positive or neutral memories – therefore, we don't 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 in order to ask how instructed reactivity and regulation differs from natural recall in people with MDD versus matched control participants. Finally, future studies using 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.

Conclusion

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 down-regulate this negative impact, they do so via a distinct pathway that entails modulating a region of posterior hippocampus not modulated by controls. 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.

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Figure Legends

Figure 1. Negative autobiographical memory fMRI 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, inter-trial interval

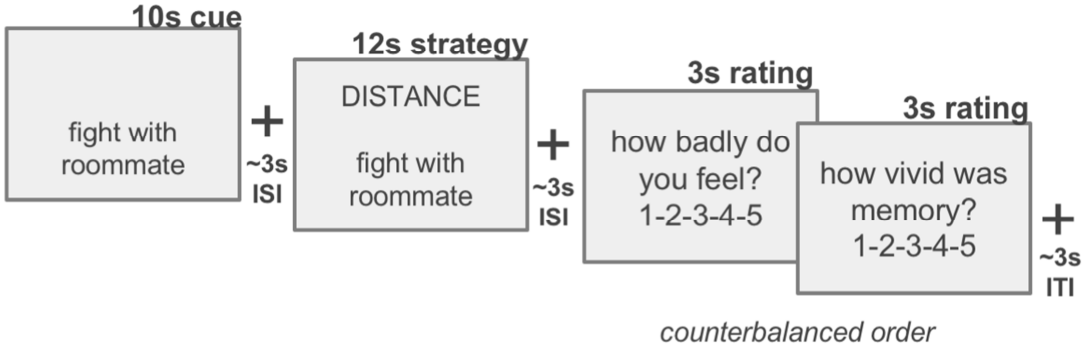
Figure 2. A) Behavioral ratings. Negative affect ratings showed a main effect of group, such that the MDD group reported higher levels of negative affect than the healthy control group (CTL), and a main effect of condition, such that distancing reappraisal decreased negative affect relative to immersive 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 left amygdala, and on connectivity of right amygdala with both left and right hippocampus (conjunction SVC $p<0.05$, displayed at $p<0.01$, uncorrected). (Graphs show group means with 95%CI, probability density plot, and participant means; †$p<0.10$ *$p<0.05$, **$p<0.01$, ***$p<0.001$)

Figure 3. Mediation model. MDD-associated elevation in negative affect was mediated by greater amygdala-hippocampus connectivity, consistent with a model whereby elevated negative affective responses to personal

memories in MDD are brought about via elevated connectivity between amygdala and hippocampus.

Figure 4. Reappraisal-related brain activity. The MDD group and healthy control group (CTL) showed comparable engagement of dlPFC, posterior parietal and lateral temporal cortex (FWE $p<0.05$) during reappraisal, and comparable down-regulation of bilateral amygdala and anterior hippocampus (SVC $p<0.05$, displayed at $p<0.01$ uncorrected). (Graphs show group means with 95%CI, probability density plot, and participant means; †$p<0.10$ *$p<0.05$, **$p<0.01$, ***$p<0.001$.

Figure 5. MDD patients showed down-regulation of posterior hippocampus. The [MDD > Controls] [Distance> Immerse] interaction contrast revealed down-regulation of posterior hippocampus for the MDD group only (SVC $p<0.05$, displayed at $p<0.01$ uncorrected), and it tracked with down-regulation of negative affect. (Left panel: group means with 95%CI, probability density plot, and participant means; Right panel: scatter plot with robust regression lines and 95% confidence bands.)



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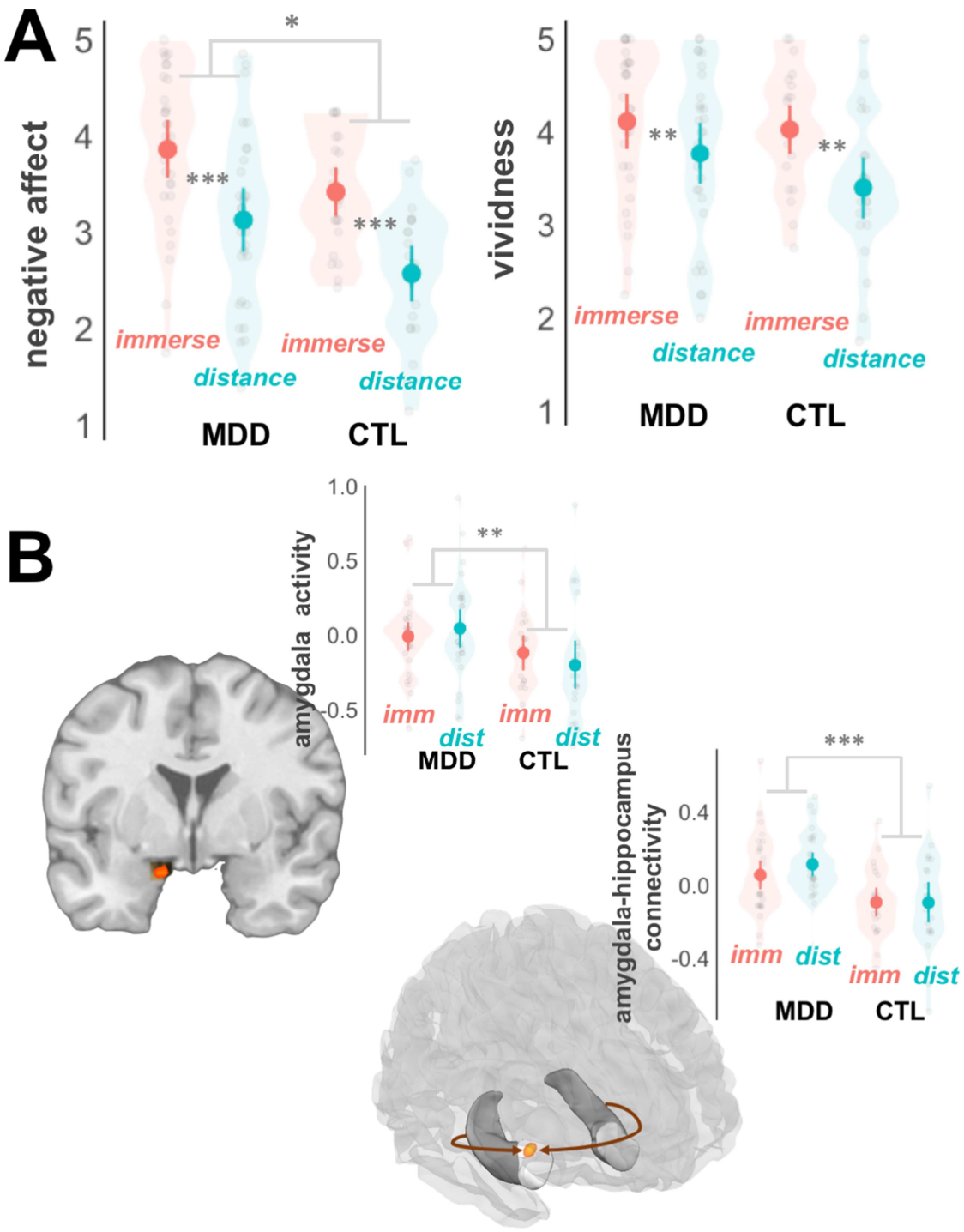
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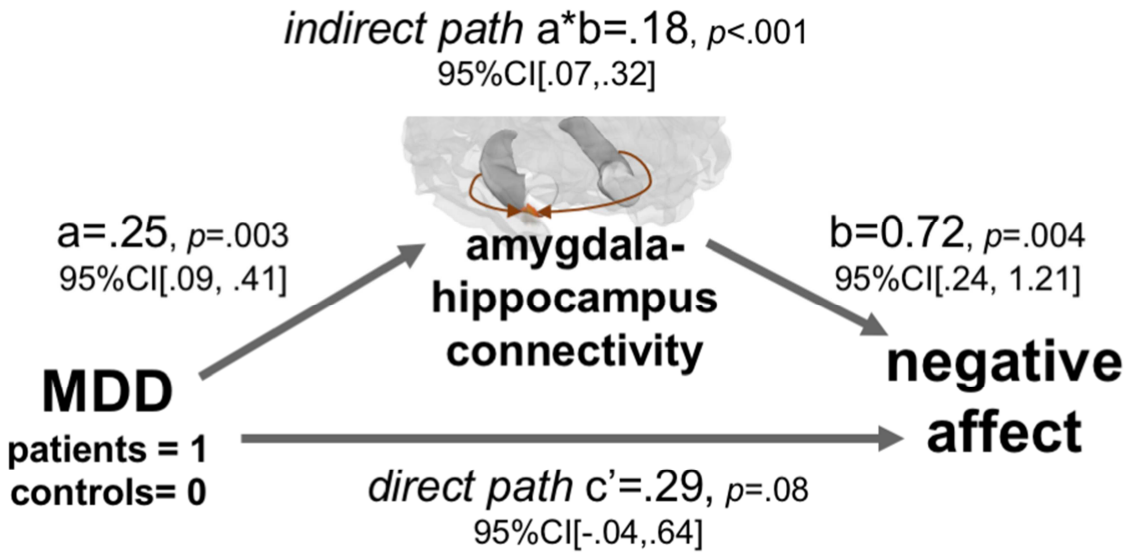
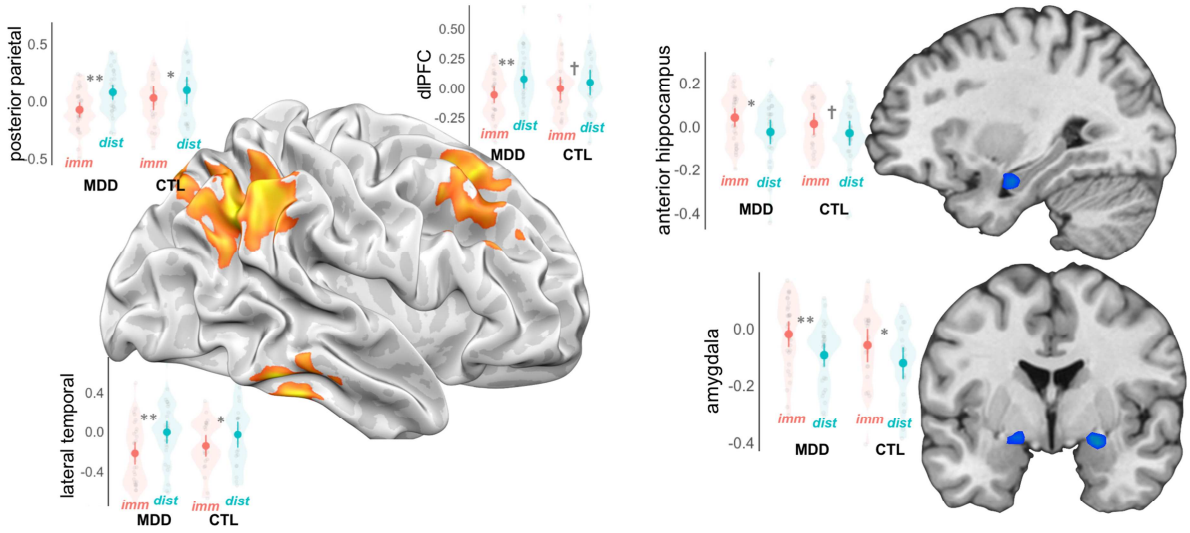
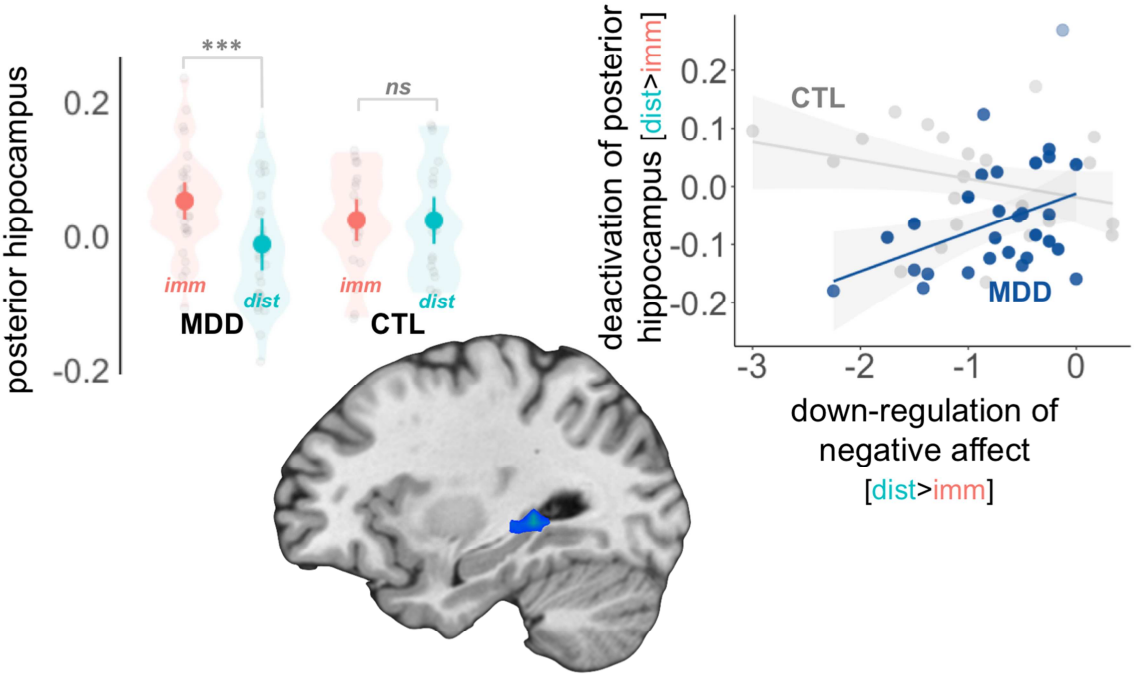






Negative Autobiographical Memory in Depression Reflects Elevated Amygdala-Hippocampal Reactivity and Hippocampally-Associated Emotion Regulation

Supplemental Information

*Pre-scan collection of memories***.** In an initial pre-scan session, participants were asked to recall 8 negative memories of experiences that occurred in the last six months, each consisting of a single event that occurred at a particular time and place and that made them feel negative emotions. If participants had difficulty identifying a memory, the experimenter told them that interactions with family, friends and work can elicit negative emotions. They were also asked to create brief phrases that could be used as memory cues for the fMRI task (i.e., to prompt recall of these memories). All participants were able to identify and generate cues for 8 specific negative autobiographical memories of experiences occurring in the past six months. That is, although prior research has often reported that people with MDD are more likely than controls to report overgeneral memories (i.e., statements about categories of events) when cued with standardized word stimuli we designed our procedure to elicit memories of specific experiences, which could be vividly recalled in response to personalized memory cues. After identifying a memory, participants rated (1-not at all to 10-very) how vividly they could recall the memory, how negative they felt during the original experience, and how negative they felt now, while recalling the memory.

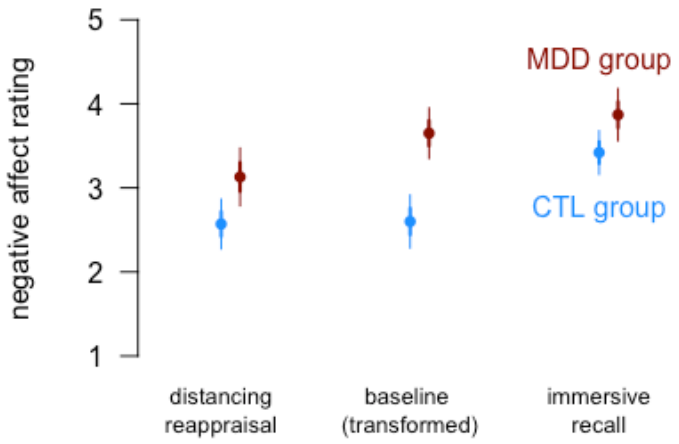
Patients with MDD showed elevated negative affect during the pre-scan session. We first examined self-reports of vividness, recalled initial negative affect (i.e., how

negative participants remembered feeling during the actual event remembered), and current negative affect (i.e., how negative participants felt when currently recalling the memory) made during the pre-scan memory collection session. Consistent with the notion that autobiographical memories of negative life experiences are particularly impactful for people with depression, in the pre-scan session MDD patients recalled higher initial negative emotion, $b_{MDD\text{-}CTL}$ = 0.77, 95%CI [0.22,1.31], p=0.007, reported higher current negative emotion, $b_{MDD\text{-}CTL}$ = 2.47, 95%CI [1.44, 3.51], p<0.001, and reported (at trend-level) higher vividness, $b_{MDD\text{-}CTL}$ = 0.58, 95%CI [-0.07,1.23], p=0.07, associated with their memories.

Moreover, there was a group by time (recalled initial versus experienced current affect) interaction, $b_{grpXtime}$ = -1.71, 95%CI [-2.86, -0.55], p=0.004, such that healthy controls showed a larger difference between recalled initial negative affect (mean=7.85, 95%CI [7.25, 8.45]) and current negative affect (mean=4.58, 95%CI [3.97, 5.18]), $b_{initial\text{-}current}$ = -3.27, 95%CI [-4.13,-2.42], p<0.001, than MDD patients showed between recalled initial negative affect (M=8.62, 95%CI [8.06, 9.17]) and current negative affect (M=7.05, 95%CI [6.50, 7.61]), $b_{initial\text{-}current}$ = -1.57, 95%CI [-2.35,-0.78], p<0.001. These data indicate that MDD patients reported greater negative affect in the pre-scan session than did healthy controls, and this group difference was especially pronounced for the current emotional impact of negative autobiographical memories.

Comparison of negative affect reported in the baseline session with negative affect reported within the scanner task. We conducted an additional exploratory analysis that sought to compare the negative affect reported by participants in the pre-scan baseline session to the negative affect reported within the scanner task. However, there are

several caveats worth noting that complicate this comparison. First, the memory recall conditions differ substantially: in the pre-scan the memory is recalled over an extended period of time in the context of a discussion with an experimenter, whereas in the scanner, the memory is recalled for a shorter amount of time in a more controlled setting. Second, it is likely that negative affect associated with the memories could decrease from the pre-scan session to the scanner (e.g., due to habituation). Third, the pre-scan ratings were collected on a 1-10 scale and the in-scanner ratings were collected on a 1- 5 scale. In order to compare the pre-scan and in-scanner negative affect ratings, we used a linear transformation to transform the pre-scan ratings (10-point scale) onto a 5-point space (to conform to the 5-point scale used in the scanner task). Next, we plotted these estimates of negative affect across experimental condition (see Supplementary Figure S1). Although this procedure is inexact, these data are consistent with two hypotheses that could be investigated in follow-up studies: 1) baseline negative affect is higher than negative affect reported during distancing reappraisal but lower than negative affect reported during immersive recall, but 2) this pattern seems to interact with diagnostic group, in that for healthy controls, baseline negative affect is more similar to the distancing reappraisal condition but for people with MDD, baseline negative affect is more similar to the immersive recall condition. However, it is also possible that it was the 10-point scale (rather than the psychological context of the baseline interview) that evoked a larger group difference in the baseline ratings.



Supplementary Figure S1. Mean ratings of negative affect across experimental condition (with standard error and 95% confidence interval). The distancing reappraisal and immersive recall ratings were collected on a 5-point scale within the scanner task; the baseline ratings were collected on a 10-point scale within the pre-scan interview and transformed onto a 5-point space.