

# Reduced capacity to sustain positive emotion in major depression reflects diminished maintenance of fronto-striatal brain activation

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**Anhedonia, the loss of pleasure or interest in previously rewarding stimuli, is a core feature of major depression. While theorists have argued that anhedonia reflects a reduced capacity to experience pleasure, evidence is mixed as to whether anhedonia is caused by a reduction in hedonic capacity. An alternative explanation is that anhedonia is due to the inability to sustain positive affect across time. Using positive images, we used an emotion regulation task to test whether individuals with depression are unable to sustain activation in neural circuits underlying positive affect and reward. While up-regulating positive affect, depressed individuals failed to sustain nucleus accumbens activity over time compared with controls. This decreased capacity was related to individual differences in self-reported positive affect. Connectivity analyses further implicated the fronto-striatal network in anhedonia. These findings support the hypothesis that anhedonia in depressed patients reflects the inability to sustain engagement of structures involved in positive affect and reward.**

anhedonia | emotion regulation | nucleus accumbens

Anhedonia, the loss of pleasure or interest in previously rewarding stimuli, is a hallmark of clinical depression (1). Anhedonia and/or a persistently depressed mood are required by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) for the diagnosis of major depressive disorder (MDD). While the exact biological bases of anhedonia are not known, research suggests that anhedonia may result, in part, from disruption of systems implicated in reward and motivation, which likely include the nucleus accumbens (NAcc) (2–4) and the frontostriatal network (5). Furthermore, human and nonhuman work suggest that the prefrontal cortex (PFC) influences activity in the striatum and can modulate reward-related firing in the NAcc in a top-down manner (5–8). Indeed, a recent review of the rodent literature by DeArco and Mora (5) makes a strong case for modulation of NAcc activity by efferent PFC neurons. This network has been proposed as one pathway by which anhedonia is instantiated (2, 3).

One hypothesis regarding the etiology of anhedonia is that depressed patients suffer from reduced hedonic capacity, defined as the total amount of positive affect that is possible for one to experience (9, 10). While many current depression researchers subscribe to the notion of reduced hedonic capacity, behavioral and physiological studies of individuals with anhedonia have been mixed as to whether anhedonic individuals actually show a reduction in their capacity to experience pleasure. Many studies have shown that individuals with depression or non-depressed individuals with the trait of anhedonia have decreased facial electromyography (EMG) zygomatic responses (11), reduced startle attenuation (12), and reduced self-reported experience of positive affect to positive stimuli (13). Other studies, however, have been unable to replicate these findings (14–16). Neuroimaging studies of individuals with anhedonia are also inconclusive. For instance, some

studies show that depressed individuals or those with trait-like anhedonia display a lack of increase in NAcc activity when presented with pleasurable stimuli (17, 18). Yet, other studies have not found group differences in NAcc activity in MDD (19–22).

Such inconsistencies suggest the possibility that MDD reflects more than a simple reduction in the capacity to experience pleasure. As was proposed by Myerson (9), anhedonia may not be solely due to a tonic reduction in the capacity to experience pleasure, but an inability to sustain positive affect and reward responsiveness over time. The notion of sustainability of positive affect was more recently discussed by Tomarken and Keener (23) who hypothesized that the inability to sustain positive affect in depression may result from disordered positive emotion regulation. They suggested that effective up-regulation and down-regulation of positive emotion is necessary to experience positive affect over time. Indeed, in healthy individuals there is evidence suggesting that the regulation of positive affect involves biasing signals directed from PFC to the NAcc (6, 7). Collectively, this suggests the hypothesis that depressed individuals will exhibit difficulties using PFC to sustain NAcc activity over time, particularly when that activity occurs in the context of attempts to up-regulate or enhance positive affect.

Accordingly, we used functional magnetic resonance imaging (fMRI) data acquired from a sample of depressed ( $n = 27$ ) and control ( $n = 19$ ) individuals during an instructed emotion regulation paradigm to test whether depression reflects a deficit in the ability to sustain activity in structures involved in reward, motivation and positive affect over a 37-min scan session. Participants were instructed to use cognitive appraisal to “enhance” or “suppress” their emotional response to positive and negative images, or to simply “attend” to the stimuli in the absence of cognitive reappraisal. To investigate changes across the scan session, we modeled time in two ways. In our primary analyses, we split the 37-min scan session into two halves and examined the change in activation across those two halves. Secondary analyses treated time continuously across the six scan runs and examined the slope of change in activity across time. Thus, we were able to test several specific predictions. We first

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**Table 1. Significant activations at  $P < 0.05$  (corrected) for the weighted Group  $\times$  Time interaction for enhance vs. suppress**

Location	Cluster maximum			No. of voxels	Cluster volume, mm <sup>3</sup>	F value	P value
	x	y	z				
L insula/transverse temporal gyrus	-53	-17	14	99	792	16.62	$9.8 \times 10^{-5}$
R thalamus	1	-13	9	70	560	17.31	$7.2 \times 10^{-5}$
L nucleus accumbens	-9	12	0	65	520	18.78	$3.8 \times 10^{-5}$

Data correspond to a  $P$  value threshold of 0.005 ( $k > 50$  voxels). L, left; R, right; the  $x$ ,  $y$ ,  $z$  coordinates use the Talaraich system.  $F$  and  $P$  values correspond to the peak.

was not specific to our choice of control condition. We also performed this contrast in a map-wise fashion; for other significant regions, see Table S1. In addition, we performed the above two analyses in which time was modeled continuously (as a function of run) with an amplitude modulator. Within the NAcc cluster found in the first step and using the “enhance” vs. “suppress” contrast, the depressed group showed a significantly greater linear reduction across time than the controls (at  $P < 0.005$ ) in the NAcc, providing further evidence that NAcc activity habituates in a linear fashion across time in depressed patients. In an analysis using the “enhance” vs. “attend” contrast, a similar pattern emerged, albeit at a lower threshold ( $P < 0.025$ ). These results corroborate our findings based on splitting the session into halves and suggest that the decreased engagement of NAcc by the depressed patients occurred in a linear fashion.

As a way of integrating these results, we performed a follow-up trend analysis using the NAcc cluster from the first analysis to examine whether the reduction in NAcc activity across time was linearly related to the amount of positive affect putatively produced by condition (defined as the greatest decrease across scan session for the “enhance,” followed by the “attend” condition, and the least decrease during the “suppress” condition). Using change in activity from first half to second half as the dependent variable, the Group  $\times$  Condition (“enhance,” “attend,” “suppress”) interaction was significant [ $F_{(2, 42)} = 5.01$ ;  $P = 0.01$ ]. Simple effects tests showed that for the MDD group, change in NAcc activity was linearly related to regulation instruction [ $F_{(1, 76)} = 6.77$ ;  $P = 0.01$ ] such that the greatest change in NAcc activity occurred in the condition which putatively engendered the most positive affect; for the control group, change in NAcc activity was not linearly related to regulation instruction [ $F_{(1, 55)} < 1$ ;  $P = 0.54$ ; see Fig. 3].

To examine change in NAcc activity across time in the absence of effortful emotion regulation), we investigated whether the mean activity in the NAcc cluster defined in the first analysis also evinced a significant Group  $\times$  Half (first and second half) interaction in the “attend” vs. baseline contrast. The NAcc cluster did show a significant interaction [ $F_{(1, 43)} = 6.71$ ;  $P = 0.013$ ] and follow up  $t$  tests showed that the depressed group showed a specific reduction in NAcc activity in the second half of the experiment [ $t_{(25)} = 3.325$ ;  $P = 0.003$ ]; controls showed no change [ $t_{(18)} = -0.63$ ;  $P = 0.536$ ; see Table S2 for whole brain effects].

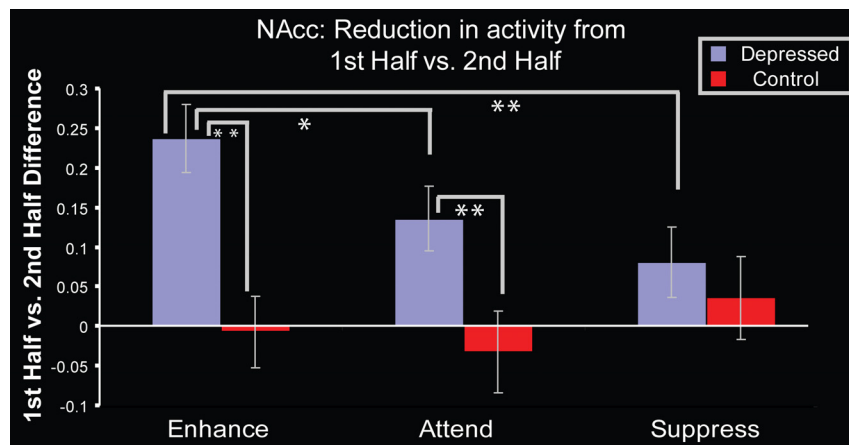
We further tested the hypothesis that sustainability of activity in the NAcc during the enhance condition can reliably differentiate between depressed patients and healthy controls. Given recent discussions in the neuroimaging literature (e.g., 25), we wish to emphasize that this analysis is meant to be descriptive in nature, with the intention of quantifying the consistency of this finding across participants, and not as a separate novel test. To do this, we performed a linear discriminant analysis to show that the ability to sustain NAcc activation was able to significantly classify depressed patients [81% of MDD group, and 68% of controls were correctly classified;  $F_{(1, 44)} = 13.22$ ;  $P = 0.001$ ]. By contrast, NAcc activation averaged across time was not predictive of group, [ $F_{(1, 44)} < 1$ ;  $P = 0.434$ ].

**Deficits in Sustaining Activity in the NAcc Is Specific to Positive Emotion.** We further examined whether the changes in NAcc activity in the depressed group were specific to trials on which positive stimuli were presented. To test this, we created an “enhance” vs. “suppress” and “enhance” vs. “attend” contrast map for each subject (for both the first and second half of the scan session) for trials on which negative stimuli were presented. We then performed a weighted ANOVA to examine whether decreased NAcc activity in the second half of the scan session occurred only during up-regulation of positive and not negative affect in the MDD group. As predicted, a cluster in the NAcc, overlapping the cluster found in the previous analysis was significant at  $P < 0.005$ , indicating that reductions found in NAcc across the scan session are specific to positive stimuli.

In addition, taking the mean percent signal change across the entire NAcc cluster found in the first analysis, we tested whether changes in NAcc activity across the scan session during the positive “attend” condition was also present during the “attend” condition when negative stimuli were presented. For the MDD group only, there was a significant Valence  $\times$  Half (first and second half) interaction [ $F_{(1, 25)} = 6.55$ ;  $P = 0.017$ ]. Follow-up paired  $t$  tests revealed that NAcc activity decreased across the scan session during the positive “attend” [ $t_{(25)} = 3.325$ ;  $P = 0.003$ ], but not the negative “attend” [ $t_{(25)} = 0.597$ ;  $P = 0.57$ ] condition.

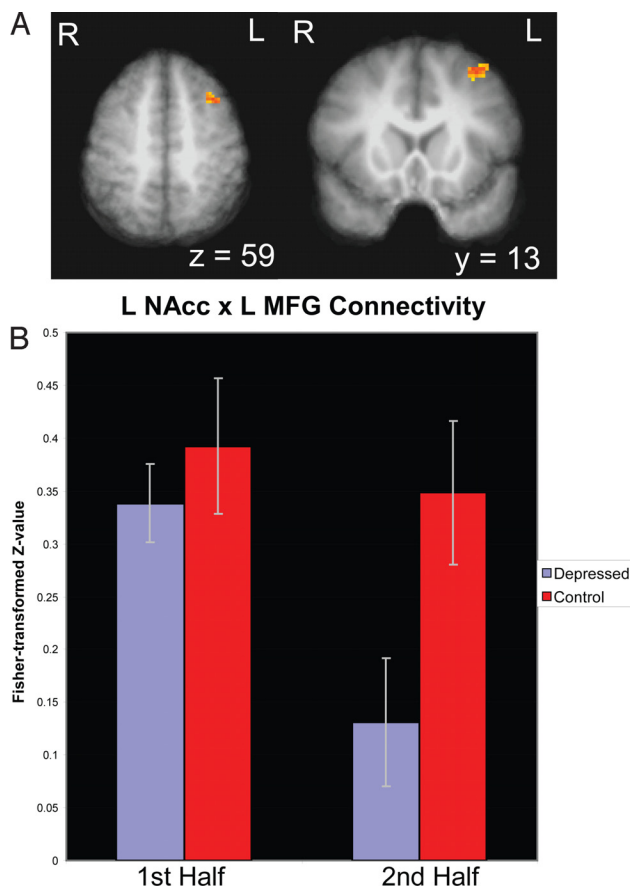
**Patients Who Fail to Sustain NAcc Activity Report Less Intense Positive Emotion.** We next used a highly reliable and well-validated measure of self-reported positive affect to assess whether the failure to sustain ventral striatal activity in depression is related to the conscious experience of positive emotion. To do this, we examined relations between overall, self-reported positive affect [as assessed by the PANAS (26)] with activity changes from the NAcc cluster across time. For the depressed group only, less decrease in NAcc activity across time in the enhance condition predicted greater overall self-reported positive affect ( $r = -0.46$ ;  $P = 0.019$ ; Fig. 1B). In the positive “enhance” condition, those depressed individuals with a sharper decline of activity in the NAcc across the two scan session halves reported experiencing less overall positive affect. This relationship was not driven by any outliers as confirmed by a Spearman’s rho test ( $\rho = -0.538$ ;  $P = 0.005$ ). These relations were valence-specific, as similar relations were not found for self-reported negative affect ( $r = 0.05$ ;  $P = 0.81$ ). These relations were also specific to the sustainability of activity in the NAcc, as aggregated activity across the scan session to the positive enhance condition was not related to self-reported positive affect ( $r = 0.05$ ;  $P = 0.82$ ). In fact, the correlation between self-reported positive affect and sustainability of NAcc activity was significantly greater than the correlation between self-reported positive affect and aggregated NAcc activity [ $t_{(25)} = -2.095$ ;  $P = 0.047$ ]. This provides further evidence that it is the specific ability to sustain activity in the NAcc across time that is related to general levels of self-reported positive affect.

**Difficulties Sustaining NAcc Activation Reflect Reduced Prefrontal Connectivity.** We then tested whether depressed individuals’ inability to sustain NAcc activity during the positive enhance condition



**Fig. 3.** For depressed patients, the greatest decrease in NAcc activity across time occurs to the enhance condition. Greater values indicate a greater decrease in activation from first to second half. Across the three conditions, the Group  $\times$  Condition interaction was significant [ $F_{(2, 42)} = 5.01$ ;  $P = 0.01$ ]; the MDD group also showed a significant linear trend across conditions [ $F_{(1, 76)} = 6.77$ ;  $P = 0.01$ ]; controls did not ( $F < 1$ ). Pairwise  $t$  tests for the MDD group were significant in the Enhance vs. Attend [ $t_{(25)} = 2.60$ ;  $P = 0.015$ ] and Enhance vs. Suppress [ $t_{(25)} = 3.09$ ;  $P = 0.005$ ] contrasts, there were no significant pairwise contrasts for the controls. Significant group differences were also found in the Enhance [ $t_{(43)} = -3.86$ ;  $P < 0.001$ ] and Attend [ $t_{(43)} = -2.59$ ;  $P = 0.01$ ] conditions such that the MDD group showed a greater decrease in NAcc activity from first to second half than controls. Error bars indicate SEM. \*,  $P < 0.05$ ; \*\*,  $P < 0.01$ .

reflected a failure to engage regions of PFC implicated in emotion regulation. To this end, we performed a connectivity analysis using the significant cluster in left NAcc as the seed region. Consistent with our prediction, a prefrontal cluster [BA 8; peak  $x, y, z$ :  $-37, 13, 59$ ; in the left middle frontal gyrus (MFG)] (Fig. 4 and Table S1) showed a significant Group  $\times$  Time interaction ( $P < 0.05$ ; small volume corrected), such that a reduction in connectivity with the NAcc across time was specific to the depressed group. This suggests that the reductions in activity in the NAcc may be driven, in part, by disordered connectivity with the left MFG.



**Fig. 4.** Connectivity analysis indicating reduction of LNacc/L MFG connectivity as a function of time ( $P < 0.05$ , small volume corrected;  $k > 15$  voxels). Error bars indicate SEM.

**Analyses Controlling for Task Engagement.** It was possible that depressed individuals' inability to sustain positive affect simply reflects nonspecific group differences in task engagement or motivation to regulate. If so, depressed individuals would be expected to show parallel differences in measures sensitive to motivation and workload, such as reaction time (RT) or pupil dilation. In particular, over the scan session, one would predict that depressed individuals would be slower to indicate the valence of the image, reflecting their diminished engagement or greater fatigue. A two-way Group  $\times$  Time (first vs. second half) ANOVA of RT to the positive images revealed no significant interaction ( $F < 1$ ). There was also no Group  $\times$  Time interaction when RT to all images was used ( $F < 1$ ). Another objective measure of motivation is that of changes in pupil dilation, which reflect total cognitive effort (27, 28). A two-way Group  $\times$  Time (first vs. second half) ANOVA of pupil dilation occurring during the enhance condition revealed no significant interaction ( $F < 1$ ), suggesting that changes in NAcc activity in the depressed group are specific to affect and not to motivation or attention.

## Discussion

Anhedonia is a hallmark symptom of MDD and elucidating the core neural signatures and processes of anhedonia is necessary for a more complete understanding and treatment of the disorder (29). Given that the NAcc and fronto-striatal network have been implicated in reward processing (30–32) and positive emotion regulation (7), we hypothesized these networks to be involved in the disordered regulation of positive affect characteristic of anhedonia. In addition, due to inconsistencies in the depression literature, we tested the hypothesis that anhedonia reflects, in part, an inability to sustain positive affect across time.

FMRI results supported our hypotheses. First, while attempting to up-regulate positive emotion, individuals with MDD showed a specific decrease in activation in the NAcc across time, while control subjects maintained their level of activation. Depressed participants were also unable to sustain elicitation of NAcc engagement when simply attending to their emotional response to positive images. Furthermore, depressed patients displayed the greatest decreases in NAcc activity across time in those conditions which putatively engendered the most positive affect. The implication of this finding is that it is more difficult for depressed patients to sustain NAcc engagement in contexts during which the maintenance and/or up-regulation of positive affect is expected. Second, we demonstrated that the amount of decrease in NAcc activity across time predicted overall self-reported positive affect. Lastly, a connectivity analysis revealed that the inability to sustain activity of NAcc may result from a breakdown in connectivity with left MFG. Collectively, these results suggest that disordered positive emotion regu-

lation may result from an inability to sustain activity in the fronto-striatal network which leads to abnormalities in reward processing and reductions in positive affect.

Our laboratory previously published data from these same patients examining the neural correlates of cognitive emotion regulation in response to negatively valenced stimuli (33). In comparison to controls, the MDD patients displayed abnormalities in distinct networks when regulating negative as opposed to positive affect. However, both studies found abnormalities in the PFC. The fact that in depression, the PFC appears to be abnormally engaged in both positive and negative emotion regulation contributes to a growing body of work that suggests that depressed patients may have difficulty recruiting prefrontal resources to regulate subcortical structures involved in affect.

Researchers working at the nonhuman level work have found that the NAcc responds differentially to the anticipation vs. consumption of reward (34), suggesting that differentiating these phases of reward processing in depression is theoretically important. A recent publication by Pizzagalli and colleagues (35) sheds light on this issue. Patients engaged in a monetary incentive delay task in which they pressed a button in response to a target stimulus. Group differences in basal ganglia activity were weak during the anticipation period, but robust group differences were found in the caudate and NAcc during the consummatory phase of the trial. While a rich nonhuman literature underscores the complexity of the NAcc in reward processing (34), the findings of Pizzagalli and colleagues suggest that the inability to sustain NAcc activity found here may result from specific deficits in the consummatory phase of reward processing—which rely heavily on the ventral striatum. Indeed, previous research suggests that NAcc activity tracks the hedonic value of outcomes (36, 37). It may be the case, therefore, that depressed patients have difficulty sustaining the engagement of the NAcc in response to tasks that require both the effortful heightening and maintaining of positive affect.

The clinical implications of our findings suggest that a treatment regimen which attempts to increase the depressed patient's ability to sustain engagement of the NAcc may ameliorate anhedonic symptoms. Because NAcc activation has been linked to reward and motivation, training depressed individuals to sustain engagement with tasks which may activate the NAcc might be able to be used in clinical practice. Indeed, the behavioral therapy model for depression explicitly instructs depressed patients to increase the length of time spent performing rewarding activities (38). Because outcome studies have supported the clinical efficacy of the behavioral model (39), we would predict that one component of recovery from depression may be the ability to sustain engagement of the brain circuits implicated in reward and motivation.

Additionally, because both positive and negative stimuli were presented, it is important to be clear about the implications of these findings. Our study examines the ability of depressed patients to sustain engagement of the NAcc while enhancing positive affect in response to positive images embedded within a stream of stimuli that included both positive and negative images. This is a very important point, particularly with regard to the ecological validity of these findings. Namely, in everyday life, individuals do not generally encounter uninterrupted positive stimuli. Negative experiences often intermix with positive ones, and the ability of individuals to heighten and maintain positive affect in the face of negative stimuli is vitally important for health and well-being.

Lastly, an important issue that requires further delineation is distinguishing the neural substrates underlying the symptoms of anhedonia versus those of decreased motivation and psychomotor retardation seen in depression. A large nonhuman literature has suggested that the NAcc is involved in motivated, goal-directed behavior in addition to its contribution to reward processing (40, 41). Yet it is not entirely clear to what degree disordered firing in the NAcc could also be relevant to other MDD symptoms of psychomotor retardation and reduced motivation. An important

challenge for future work will be to disentangle the role of the NAcc in specific symptomatology associated with MDD including anhedonia, psychomotor retardation, and decreased motivation.

In conclusion, our findings suggest that individuals with depression suffer from an inability to sustain reward-related activity that is reflected in the fronto-striatal network across time, and that this deficit is associated with reduced positive affect. These findings are consistent with the hypothesis that the hallmark symptoms of anhedonia in MDD are based on an inability to sustain positive affect. These data offer an interpretation for the symptom of anhedonia in depression. The findings also underscore the need for future studies to investigate the temporal dynamics of positive affect in depression and underscore the important role of affective chronometry in understanding the mechanistic bases of affective style (42).

## Materials and Methods

**Participants.** We examined a group of 27 medication-free, right handed adults satisfying the DSM-IV (1) criteria for unipolar major depressive disorder (age range, 19–53; mean age, 31.48 years; SD, 11.58; 12 males). These depressed individuals were compared with an age and sex-matched group of 19 right-handed controls (age range, 20–60 years; mean age, 31.84 years; SD, 14.65; 9 males; age difference between groups not significant;  $F < 1$ ). All subjects were recruited via the use of flyers posted in public places around the Madison, Wisconsin area. Depressed participants had depressive symptoms for at least 1 month before their screening visit and a score of at least 18 on the Hamilton Rating Scale for Depression (43) (HAM-D) at screen and the fMRI scan (mean HAM-D  $\pm$  SD depressed,  $20.6 \pm 2.39$ ; controls,  $1.2 \pm 1.6$ ). In addition to standard MRI compatibility criteria, subjects were screened for and excluded if they met DSM-IV criteria for alcohol or drug abuse or dependence, other DSM-IV Axis I or Axis II diagnoses, had a personal or family history of bipolar disorder or were using any medications that affect CNS function. Participants were also excluded if they had an anxiety disorder, ensuring that the sample represent a relatively “pure” MDD group. In addition to the HAM-D, both before and after the scan session, all participants except one depressed subject completed the extended version (48 total items) of the Positive Affect/Negative Affect scales (26) (PANAS-X) and was therefore removed from the analysis. The pre- and post-scan PANAS scores were then averaged to ensure reliable self-reported affect scores. Subjects participating in this study are the same as those who participated in (33). This research was approved by the University of Wisconsin-Madison Health Sciences Institutional Review Board, and all participants provided written informed consent.

**Task.** The experimental task was a variant of that used previously in our laboratory with normal subjects (27) and similar to the tasks used in other recent studies (44–46). Subjects were scanned while viewing a sequence of 72 emotionally positive and 72 negative pictures taken from the International Affective Picture System (IAPS) (47). A 1-s fixation cross coupled with a tone oriented subjects to the upcoming trial, after which each image was presented for 10 s, followed by a 6-s blank screen. To ensure participants remained attentive to the task, at the onset of each picture, subjects had to judge whether the image was positive or negative and respond with an appropriate button press on a two-button response pad. Four seconds into the presentation of each picture, an audio prompt instructed the participant to either increase (“enhance”) or decrease (“suppress”) their emotional response to the picture or to continue to “attend” to the picture. Participants were trained during a previous session while positioned inside a mock scanner on the use of cognitive re-appraisal strategies to re-evaluate the images as more or less emotional (27, 44). For the enhance condition, participants were trained to either imagine themselves or a loved one experiencing the situation being depicted or imagine a more extreme outcome than the one depicted (e.g., in response to a picture of a stunning natural scene, a participant might imagine being in that scene or one of their own choosing). Conversely, for the suppress condition, individuals were trained to either view the situation as fake or unreal or imagine that the situation being depicted had a different outcome than the one suggested (e.g., a couple in love were just actors and did not feel the way depicted in the image). Alternatively, on attend trials, participants were instructed to maintain their attention to the picture without changing their affective experience. Simulated scanner sounds and task instructions were presented using earbud headphones during this training session. The training was succeeded by follow-up queries to ensure that participants were using the strategies as instructed and reported being able to perform the task. See [SI Text](#) for additional detail.

In the fMRI session, there were 24 repetitions of each regulation condition and 12 repetitions of the attend condition for each picture valence, evenly distributed

over six scans, each lasting 380 s. The order of positive and negative images and the three regulation instructions was pseudorandomized such that each scan run contained at least one trial of each condition type. With regard to order of positive and negative trials, positive trials were preceded by other positive trials approximately as often as by negative trials (42% of the positive trials were preceded by a positive trial and 57% of the positive trials were preceded by a negative trial;  $\chi^2 = 1.37$ ;  $P = 0.241$ ), suggesting that the results are not due to the lingering effects of negative stimuli on BOLD response to positive stimuli.

**Behavioral Measures.** See *SI Text*.

**Image Analysis.** See *SI Text* for additional details. Individual subject data were slice-time corrected, motion corrected, and analyzed in AFNI (48). Our GLM included covariates intended to model each of the six trial types (positive/negative stimulus; enhance, attend, and suppress reappraisal instruction), and for both the early and late phases of the scanning session (early: runs 1–3; late: runs 4–6) as well as six motion estimate covariates (49).

These smoothed contrast maps were then entered into a multiple linear regression analysis, in which contrasts were weighted to yield those brain areas that displayed a depressed group-specific decrease in activation across time. Specifically, our weights were as follows: first half-control (+1); second half-control (+1); first half-depressed (+1); second half-depressed (–3). The outcome

of this analysis is essentially a weighted Group  $\times$  Time interaction for the positive “enhance” vs. positive “suppress” as well as the “enhance” vs. “attend” condition contrast. To examine time as a continuous variable, we performed a second analysis in which we modulated the amplitude of each run in a linear fashion. Connectivity analyses were performed using the beta series correlation method described in (50). More details on this method can be found in the *SI Text*.

Univariate statistical maps were thresholded at  $P < 0.05$ , corrected for multiple comparisons using cluster-size thresholding based ( $k > 50$  voxels) on Monte Carlo simulation (the AlphaSim program in AFNI) using a whole-brain mask. The connectivity statistical maps were thresholded at  $P < 0.05$ , small volume corrected for multiple comparisons using a PFC mask which included clusters found to be significant in a recent metaanalysis of fMRI studies of emotion regulation (51) and resulted in clusters exceeding a minimum of  $k = 15$  voxels. For further details see the *SI Text*.

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# Supporting Information

Heller et al. 10.1073/pnas.09106511106

## SI Text

**Participants.** Because depression is a heterogeneous disorder (e.g., 1), we over-recruited the MDD group in an attempt to ensure sufficient power to address the underlying neural abnormalities subserving the binary category of MDD.

**Task.** Negative pictures were selected according to the IAPS norms to be both unpleasant (1, most unpleasant, to 9, most pleasant;  $M = 2.95$ ; SD, 0.87) and arousing (1, least arousing, to 9, most arousing;  $M = 5.44$ ; SD, 0.80), whereas positive images were pleasant ( $M = 7.13$ ; SD, 0.62) and arousing ( $M = 5.28$ ; SD, 0.58). Stimuli were presented using E-Prime software (Psychology Software Tools) via a fiber-optic goggle system (Avotec) with a screen resolution of  $800 \times 600$  pixels.

**Behavioral Measures.** Reaction time to image onset, as well as pupil dilation measures were acquired. Assessing pupil dilation provides an unobtrusive measure of autonomic arousal (2) with pupil constriction driven primarily by the parasympathetic branch of the autonomic nervous system (ANS), and pupil dilation primarily reflecting activity of the sympathetic branch. Pupil dilation is thus an indicator of increased cognitive and attentional load during effortful top-down regulation (3–5). To assess autonomic arousal associated with effortful reappraisal, we measured the extent to which the pupil dilated during the active reappraisal period of each stimulus trial. Based on our previous research showing pupil dilation to be a sensitive index of the cognitive effort during reappraisal in healthy individuals (6, 7), we examined whether pupil dilation changed across the scan session for either of the groups.

**Pupil Data Acquisition and Analysis.** Horizontal pupil diameter data were acquired continuously at 60 Hz using an iView X system (v. 1.3.31) with a remote eye-tracking device (SensoMotoric Instruments), which was interfaced with the fiber optic goggle system. Pupil data from four controls and six depressed individuals were not usable because of technical problems. Pupil dilation data were processed using algorithms written by Siegle et al. (4) with MatLab software (MathWorks), modified in our laboratory. Blinks were identified and eliminated using local regression slopes and amplitude thresholds. Data were smoothed with a five-sample rolling average and linearly detrended over each scan run. For successive 500-ms bins in each trial, the proportion of time that the eye was open and mean pupil diameter were calculated. Pupil values were then range-corrected to standardize according to the pretrial maximally dilated pupil diameter and the maximally constricted pupil diameter in the 2 s after picture onset [(current pupil diameter – minimum pupil diameter)/(maximum pupil diameter – minimum pupil diameter)]. Data were averaged across a 5 s interval starting 1 s after instruction and continuing until picture offset (the reappraisal period). Data were then analyzed using mixed-model GLM (subject as a random factor nested within the fixed factor group, and reappraisal as a within subject fixed factor).

**Image Acquisition.** Images were collected on a General Electric 3 Tesla scanner (GE Medical Systems) equipped with a standard clinical whole-head transmit-receive quadrature head coil. Functional images were acquired using a T2\*-weighted gradient-echo, echo planar imaging (EPI) pulse sequence [33 sagittal slices, 4-mm thickness, 1-mm interslice gap;  $64 \times 64$  matrix; 240 mm field of view (FOV); repetition time (TR)/echo time (TE)/Flip, 2,000 ms/30 ms/60°; 190 whole-brain volumes per run]. A high-resolution T1-weighted anatomical image was also acquired (T1-weighted inver-

sion recovery fast gradient echo;  $256 \times 256$  in-plane resolution; 240 mm FOV;  $124 \times 1.1$ -mm axial slices).

**Image Analysis.** Our single subject GLM included covariates intended to model each of the six trial types (positive/negative stimulus; enhance, attend, and suppress reappraisal instruction), and for both the early and late phases of the scanning session (early: runs 1–3; late: runs 4–6) as well as six motion estimate covariates. We also included a second-order polynomial used to model the baseline and slow signal drift. Regressors consisted of a set of five sine basis functions to produce separate estimated hemodynamic response functions (HRFs) for each trial type. The estimated HRFs were converted to percentage signal change values, and within-subjects contrasts were calculated between the enhance and suppress conditions for positive pictures (i.e., positive enhance – positive suppress; 1<sup>st</sup> Half, 2<sup>nd</sup> Half), averaged across time points corresponding to the peak hemodynamic response during the regulation period (8–14 s after stimulus onset). Contrasts were normalized to Talairach space and smoothed using a 5 mm full-width at half-maximum Gaussian filter.

Following single subject GLM analysis, we normalized and smoothed the maps and subsequently contrasted the “enhance” and “suppress”, as well as the “enhance” vs. “attend” brain maps for each subject prior to performing random effects group analyses. We elected not to use the amplitude modulator for all analyses because the time course plots as well as the connectivity analyses required splitting the scan session into discrete sections. We also performed the same analysis for negative stimuli in order to compare the group differences in neural activity to positive vs. negative slides.

**Connectivity Analysis.** Connectivity analyses were performed using the beta series correlation method described in (8). Briefly, this approach requires that separate parameter estimates (beta values) be computed for each trial. Trials were modeled as having two components: one component occurring at the onset of the image presentation—before regulation instruction; the second component being placed 6 s after image onset, modeling the neural response to the regulation of emotion. BOLD responses during stimulus onset and regulation periods were modeled as brief epochs of neural activity convolved with an in-house canonical hemodynamic response function (HRF), obtained by averaging empirically derived HRFs (8). The onsets of temporally adjacent covariates were spaced at least 4 s apart (9) to minimize the contamination of the regulation period covariate by residual stimulus onset period activity. This approach has been used to successfully model separate components of a trial in numerous published studies (10–12). The least squares solution of the GLM yielded a set of 236 beta values of interest (2 trial components  $\times$  2 picture valences  $\times$  3 regulation instructions [24 enhance, suppress trials; 12 attend trials]). Nuisance covariates included the second-order polynomial used to model the baseline and slow signal drift, as well as six motion estimate covariates. Beta values were sorted by trial type so that a series of betas exist for each component of each condition. The extent to which brain regions interact during a particular task stage is quantified by the extent to which their respective beta series from that condition are correlated.

**Correction for Multiple Comparisons.** With the AlphaSim clustering technique, the overall family-wise error rate (FWE) is controlled by simulating null data sets with the same spatial autocorrelation as

found in the residual images and creating a frequency distribution of different cluster sizes. Clusters with a size that exceeds the minimum cluster size corresponding to the a priori chosen FWE are retained for additional analysis. This cluster-based method of

thresholding, analogous to cluster-based thresholding using Gaussian Random Field Theory (13), is an alternative to voxel-based correction and is often more sensitive to activation when one can reasonably expect multiple contiguous activated voxels (14, 15).

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**Table S1. LNAcc connectivity; weighted Group × Time effect for “enhance” condition**

Location	Cluster maximum			No. of voxels	Cluster volume, mm <sup>3</sup>	F value	P value
	x	y	z				
L middle frontal gyrus (8)	-37	13	59	24	192	11.95	8.4×10 <sup>-4</sup>

*k* > 15 voxels. L, left; R, right; numerals in parentheses indicate the Brodmann area; the *x*, *y*, *z* coordinates use the Talaraich system. *F* and *P* values correspond to the peak.

**Table S2. Group × Time effect for “attend” vs. baseline**

Location	Cluster maximum			No. of voxels	Cluster volume, mm <sup>3</sup>	<i>F</i> value	<i>P</i> value
	<i>x</i>	<i>y</i>	<i>z</i>				
Medial frontal gyrus (8/32)	3	27	40	446	3,568	19.59	$2.7 \times 10^{-5}$
Posterior cingulate (30)	-3	-49	20	272	2,176	15.61	$1.5 \times 10^{-4}$
L putamen	-19	7	8	223	1,784	22.22	$8.8 \times 10^{-6}$
R middle frontal Gyrus (44/48)	45	15	26	192	1,536	19.68	$2.6 \times 10^{-5}$
R thalamus	7	-17	6	143	1,144	19.03	$3.4 \times 10^{-5}$
R lingual gyrus	21	-53	0	121	968	14.21	$2.9 \times 10^{-4}$
R paracentral gyrus	3	-23	46	113	904	18.96	$3.5 \times 10^{-5}$
R anterior insula	31	25	10	76	608	18.24	$4.8 \times 10^{-5}$
L precentral gyrus (6)	-45	-1	48	70	560	17.84	$5.7 \times 10^{-5}$
Medial frontal gyrus (10/32)	-3	49	18	63	504	21.41	$1.2 \times 10^{-5}$
R superior frontal gyrus (6)	5	11	62	63	504	17.00	$8.3 \times 10^{-5}$
R precentral gyrus (4)	45	-11	44	60	480	13.80	$3.5 \times 10^{-4}$
L hippocampus	-23	-15	-12	59	472	23.53	$5.1 \times 10^{-6}$
L inferior frontal gyrus (47)	-33	31	2	58	464	19.10	$3.3 \times 10^{-5}$
R middle temporal gyrus (21)	63	-21	-6	54	432	16.82	$9.0 \times 10^{-5}$

*k* > 50 voxels. L, left; R, right; numerals in parentheses indicate the Brodmann area; the *x*, *y*, *z* coordinates use the Talaraich system. *F* and *P* values correspond to the peak.

**Table S3. Group × Time effect for “enhance” vs. “attend” condition**

Location	Cluster maximum			No. of voxels	Cluster volume, mm <sup>3</sup>	<i>F</i> value	<i>P</i> value
	<i>x</i>	<i>y</i>	<i>z</i>				
Lingual gyrus (18)	15	−85	−8	45	360	13.51	$4.0 \times 10^{-4}$
Inferior lingual gyrus (17)	−1	−81	−12	20	160	12.29	$7.1 \times 10^{-4}$
L postcentral gyrus (48)	−53	−15	14	18	144	11.97	$8.3 \times 10^{-4}$

*k* > 15 voxels. L, left; R, right; numerals in parentheses indicate the Brodmann area; the *x*, *y*, *z* coordinates use the Talaraich system. *F* and *P* values correspond to the peak.

**Table S4. Group Test for “enhance” vs. “suppress” condition. (Aggregated across time)**

Location	Cluster maximum			No. of voxels	Cluster volume, mm <sup>3</sup>	t value	P value
	x	y	z				
L superior temporal gyurs (22, 42)	−57	−25	12	126	1,008	4.01	$2.4 \times 10^{-4}$
L cingulate gyrus (23)	−13	−27	36	110	880	4.08	$2.0 \times 10^{-4}$
R precuneus (7)	7	−61	52	69	552	3.76	$5.2 \times 10^{-4}$
L insula (13)	−31	5	14	67	536	4.09	$1.9 \times 10^{-4}$
R precuneus (7)	11	−73	44	63	504	4.33	$9.1 \times 10^{-5}$

All clusters correspond to Controls > Depressed. No voxels were significant for Depressed > Controls.  $k > 50$  voxels. L, left; R, right; numerals in parentheses indicate the Brodmann area; the x, y, z coordinates use the Talaraich system. t and P values correspond to the peak.

**Table S5. Group Test for “enhance” vs. “attend” condition. (Aggregated across time)**

Location	Cluster maximum			No. of voxels	Cluster volume, mm <sup>3</sup>	t value	P value
	x	y	z				
L post central gyrus	-54	-22	20	65	520	3.87	$3.8 \times 10^{-4}$

All clusters correspond to Controls > Depressed. No voxels were significant for Depressed > Controls.  $k > 50$  voxels. L, left; R, right; the x, y, z coordinates use the Talarach system. *t* and *P* values correspond to the peak.