Supplemental Methods

Participants

Following the baseline scan session, depressed participants were randomized to receive a six-month course of either Venlafaxine Extended Release (hereafter referred to simply as venlafaxine) or Fluoxetine treatment. In week 1, patients received 37.5mg or 20mg of Venlafaxine or Fluoxetine, respectively. In week 2, patients received 75mg or 20mg of Venlafaxine or Fluoxetine, respectively; these dosing levels were the minimum dosing levels for the study. Further titration was based on clinical response (side effects and antidepressant effect). Maximum dosing was Venlafaxine of 300mg or Fluoxetine of 80mg.

Task

Negative pictures were selected according to the International Affective Picture System (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). Arousal ratings did not differ significantly across positive and negative images ($t<1$), thus allowing us to manipulate valence while controlling for stimulus intensity. Stimuli were presented using E-Prime software (Psychology Software Tools, Pittsburgh, PA) via a fiber-optic goggle system (Avotec, Stuart, FL) with a screen resolution of 800 x 600 pixels.

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 (1, 2). 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 ferocious dog, a participant might imagine that the dog's leash broke and the dog is going to bite them). 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., victims of a car accident survived and healed well). 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.

Image acquisition.

Images were collected on a General Electric 3 Tesla scanner (GE Medical Systems, Waukesha, WI) 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 × 64 matrix; 240 mm field of view (FOV); repetition time (TR)/echo time (TE)/Flip, 2000 ms/30 ms/60°; 190 whole-brain volumes per run]. A high-resolution T1-weighted anatomical image was also acquired (T1-weighted inversion recovery fast gradient echo; 256 × 256 in-plane resolution; 240 mm FOV; 124 × 1.1 mm axial slices).

Behavioral measures.

Reaction time to image onset, as well as pupil dilation measures were acquired. Reaction time from two participants was lost due to hardware error. Assessing pupil dilation provides an unobtrusive measure of autonomic arousal (3) 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 (4-6). 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 (2, 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, Teltow, Germany), 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. (2002) (unpublished MatLab code) with MatLab software (MathWorks, Natick, MA), 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 Analysis.

Our single subject general linear model 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 for each trial type. The estimated hemodynamic response functions were converted to percentage signal change values and averaged across time points corresponding to the peak hemodynamic response during the regulation period (8–14s after stimulus onset).

For analyses specifically examining nucleus accumbens function, we used an a priori region of interest from the Harvard-Oxford subcortical atlas implemented by FSL with a probability of 25% that all voxels were within the nucleus accumbens (8, 9). Subsequently, we used Analysis of Functional NeuroImages's (AFNI) program AlphaSim to calculate the required small volume corrected cluster-size threshold for $p<.05$. Single-voxel and connectivity analyses were similarly thresholded at $p < 0.05$, corrected for multiple comparisons using cluster-size

thresholding based (k > 18 voxels for small volume correction with the apriori nucleus accumbens region of interest in the univariate analyses, and k > 54 voxels for whole brain masked) on Monte Carlo simulation (the AlphaSim program in Analysis of Functional NeuroImages). Normalized voxels were 2mm isotropic and smoothed with a 5mm Gaussian kernel.

For the analysis relating to whether changes in sustained nucleus accumbens activity (2^{nd} half vs. 1^{st} half) is uniquely associated with gains in positive affect as compared with more traditional analytic strategies, we performed the following analysis. In addition to using the difference metric described above in which the scan session is broken into halves (2^{nd} half vs. 1^{st} half), we performed a more traditional fMRI analysis in which fMRI signal is aggregated across the experimental session and treated uniformly. For each participant, we extracted the mean beta value across the significant nucleus accumbens cluster from the difference metric (2^{nd} half vs. 1^{st} half) as well as from the traditional, aggregated metric. Using multiple regression, we then examined whether the difference metric continued to be associated with gains in positive affect while including the aggregated metric as an additional independent variable. This also allowed us to examine whether the aggregated metric, on its own, correlated with gains in positive affect. See main text for results from this analysis.

In addition to using a difference metric (2^{nd} half vs. 1^{st} half), in which time is arbitrarily categorized into two chunks, we treated time continuously (as a function of run) by using a linear regressor (amplitude modulation in Analysis of Functional NeuroImages). This analysis yields a beta estimate for each subject which corresponds to the rate of change of nucleus accumbens activity over time. Using this beta estimate, we tested whether nucleus accumbens activity, when treated continuously correlated with gains in positive affect.

Connectivity Analysis

Connectivity analyses were performed using the beta series correlation method described in Rissman et al., (10). 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 six seconds 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, obtained by averaging empirically derived hemodynamic response functions (10). The onsets of temporally adjacent covariates were spaced at least 4 s apart (11) 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 (12-14). The least squares solution of the general linear model yielded a set of 236 beta values of interest (2 trial components x 2 picture valences x 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. See main text for results.

Supplemental Results

Correlations between self-report measures

We examined the correlations between the various self-report measures. In the depressed sample, negative affect at baseline was correlated with negative affect at 8 weeks (r=0.66, p=.001); positive affect at baseline was not correlated with positive affect at 8 weeks (r=0.30, p=0.18). Positive affect and negative affect were not correlated at baseline (r=-0.29, p=0.20), nor were they correlated at 8 weeks (r=-0.34, p=0.14). Change in positive affect and negative affect scores from baseline to 8 weeks were significantly inversely correlated (r = -0.61, p = .004). Otherwise, assessments of HAMD, positive affect, and negative affect at both baseline and 8 weeks in the depressed sample were not significantly correlated (see table 1). In the control sample, negative affect at baseline was correlated with negative affect at 8 weeks (r=0.76, p=.002); positive affect at baseline was correlated with positive affect at 8 weeks (r=0.75, p=.002). Positive affect and negative affect were not correlated at baseline (r=-0.28, p=0.33), nor were they correlated at 8 weeks (r=-0.40, p=0.16). In addition, in the control sample, change in positive affect and negative affect from 0 to 8 weeks were not significantly correlated (r=-0.45, p=0.10). Given that the control group demonstrated a significant correlation between positive affect sampled at baseline and positive affect sampled at 8 weeks (r=0.75), while the depressed group did not (r=0.30), we examined whether the magnitude of these correlations were significantly different between the groups. This test of the difference in correlations was at trend level (z=1.75, p=.08).

Concerns regarding dual-task

One concern could be that participants are performing two tasks – one involving a button response and one involving the regulation of emotion. However, the mean RT to the valence of

the image at pretreatment was 1380 ms and 1238 ms at 8-weeks into treatment for depressed patients and 1252ms and 1433ms for controls at the same two time points. Because the regulation instruction did not occur until 4000 ms into image presentation, and it was time points related to the emotion regulation instruction that were specifically analyzed. Therefore, it is highly unlikely that engaging in a button response affected the brain activity when regulating emotion.

Supplemental fMRI analyses

We examined whether the relationship between changes in sustained nucleus accumbens activity across time when attempting to enhance positive emotion and gains in self-reported positive affect was specific to the enhancement of positive affect, or to the enhancement of affect more generally. Accordingly, we simultaneously included both changes in sustained nucleus accumbens activity when attempting to enhance positive emotion (in response to positive IAPS slides) and when attempting to enhance negative emotion (in response to negative IAPS slides) to examine associations with gains in positive affect. Increases in sustained nucleus accumbens activity when enhancing positive affect was uniquely associated with gains in positive affect ($B = 19.96$, $t(18) = 2.34$, $p = .03$), while changes in sustained nucleus accumbens activity when enhancing negative affect was not uniquely associated with gains in positive affect ($B = 5.14$, $t(18) = 0.76$, $p = .45$). This suggests that the relationship between increases in sustained nucleus accumbens activity and gains in self-reported positive emotion is specific to the enhancement of positive affect and not related to the process of enhancement of affect more generally.

When controlling for changes in sustained nucleus accumbens activity when decreasing a positive affective response to a positively valenced image (ie., the “positive suppress” condition) from 0 – 8 weeks, a trend level relationship remained between sustained nucleus accumbens

activity when increasing positive emotion and gains in positive affect (B=15.94, t(18)=1.45,p=0.08 [one-tailed]). In this regression model, there was no relationship between changes in sustained nucleus accumbens activity in the "suppress" condition and gains in positive affect (B=4.993, t(18)=0.817, p=0.42).

In order to examine whether the relationship between changes in sustained nucleus accumbens activity and gains in self-reported positive affect follow a linear function, we treated time continuously by using a linear regressor (ie., amplitude modulation, see supplemental methods) and examined the relationship between changes in sustained nucleus accumbens activity and gains in positive affect. Interestingly, when time was treated continuously using a linear regressor, individual differences in sustained nucleus accumbens activity was not correlated with gains in positive affect (r = 0.19, t(19) = 0.86, p=0.40). This suggests that the best function to relate change in brain activity over time with gains in positive affect may not be linear, and may be more sigmoidal in shape.

Given the findings between changes in anhedonia as assessed by the MASQ and changes in sustained nucleus accumbens activity when upregulating positive affect, we ran a voxel-wise regression looking to see whether changes in sustained nucleus accumbens-connectivity resulting from treatment was associated with changes in MASQ assessed anhedonia. Interestingly, no area survived multiple comparison correction when correlating with changes in MASQ, suggesting a relatively specific effect of changes in sustained nucleus accumbens-prefrontal cortex connectivity and state positive affect.

Mean effects among depressed patients

Among patients, the mean level of sustained nucleus accumbens activity did not change across two months of treatment (t(20) = 0.28, p = .78). Likewise, there was no change in the

mean level of sustained nucleus accumbens-MFG connectivity ($t(20) = -0.14$, $p = 0.99$), nor was there a significant change in mean level of sustained nucleus accumbens-ventromedial prefrontal cortex connectivity ($t(20) = -1.70$, $p = 0.11$). In our view, these null effects underscore the potential utility of exploiting individual differences to unmask and understand the brain bases of heterogeneity in treatment response.

The relation between affective responding on different time scales and psychopathology is not yet known (e.g., within vs. across trials). In this study, we aimed to specifically examine one slice of this relationship (temporal dynamics across trials), but it is unknown the degree to which it is related to other time scales. However, to address the relationship between these two time-scales, we extracted the fitted time course from the nucleus accumbens cluster in the positive enhance condition (aggregated across the scan session) for both pre-treatment and 8-weeks into treatment for each subject. With the time course, we calculated a slope for the time points which corresponded to the maximal BOLD response to the regulation instruction (8 sec – 14 sec). This slope corresponds to the rate of change in of nucleus accumbens activity when regulating positive emotion. This is one method for examining variability in sustained activity within trials. For each depressed patient we subtracted the pretreatment within-trial slope measures from the 8-weeks within-trial slope measure and correlated that with changes in positive affect. Change in within-trial slope of nucleus accumbens activity in the positive enhance condition (from pretreatment to 8-weeks) was not correlated with change in positive affect ($r=0.16$, $p=0.47$). There was not a significant correlation between changes in the within trial slope (calculated here) and changes in the across trial (presented originally in the manuscript) effect ($r=-0.05$, $p=0.82$) either. We performed the same analysis for the positive "attend" condition because we thought the effect of cognitive regulation might mask a

relationship between changes in within-trial dynamics and positive affect. There was again, no significant relationship (r=0.23, p=0.32). There was not a significant correlation between changes in the within trial slope (calculated here) and changes in the across trial (presented originally in the manuscript) effect (r=0.12, p=0.61). This suggests that the across trial and within trial effects are at least somewhat orthogonal in this sample with this paradigm.

Supplemental Discussion

In our previous report, in addition to examining sustained nucleus accumbens activity using a difference metric (2^{nd} half vs. 1^{st} half, as we did in this report), we also examined the relationship using a linear regressor (ie., amplitude modulation) to assess change of nucleus accumbens activity over time. Using this linear regressor in the initial finding, we similarly found that depressed patients evidenced a lack of sustained nucleus accumbens activity, whereas healthy control participants showed sustained nucleus accumbens activity. In this initial finding, however, we did not examine whether individual differences in the beta-value for the linear regressor correlated with self-reported positive affect; we solely demonstrated that the difference metric (Pretreatment: 2^{nd} half vs. 1^{st} half) was related to self-reported positive affect. This is consistent with what we found, that at 8-weeks post treatment using the 2^{nd} half vs. 1^{st} half difference metric, changes in sustained nucleus accumbens activity correlated with gains in self-reported positive affect across that same time. These results suggest that the function best fitting the relationship between changes in positive affect and sustained nucleus accumbens activity may not be linear and be more step-wise, although future work should examine this issue further.

This report contributes to our previous findings with this sample by examining change in the neural correlates underlying depressed using an ecologically valid, emotion regulation paradigm. Our previous findings (15-17) solely examined the brain at baseline, whereas this

report examined changes resulting from treatment. However, it is clear from the previous findings that engagement of ventrolateral prefrontal cortex appears to be important when down-regulating both negative emotion (17) and is associated with changes in trait anhedonia when down-regulating positive affect (15). Given distinct cognitive processes required when down-regulating, as opposed to up-regulating emotion, it is not surprising that we find a distinct set of prefrontal cortical regions involved in the up-regulation of positive emotion as opposed to the down-regulation of both negative and positive emotion.

We have primarily examined one time scale – that of the ability to continually engage reward-related circuitry across trials. However, the temporal dynamics of affective responses within trials as has been examined as well (18-20) and likely carries equal import for understanding the dynamics of affect and psychopathology. The ability to repeatedly engage reward circuitry across trials when presented with positive events may be important for health and well-being because positive and negative events occur intermixed in life over time. As a result, it may be particularly important for an individual to be able to continue to engage reward circuitry when a positive event occurs even in the midst of negative ones. On the other hand, the ability to sustain affective responses to an individual positive event more closely mimics the notion of "savoring", which has recently been exploited to develop novel psychotherapeutic treatments for depression (21, 22). It is likely that both effects are of significance for understanding and treating psychopathology. Perhaps most importantly, the variance shared in these two separate time scales has not been examined in detail and work to this effect is required to disentangle the unique contribution of these effects on individual differences and psychopathology.

Researchers working at the nonhuman level work have found that the nucleus accumbens responds differentially to the anticipation vs. consumption of reward (23), suggesting that differentiating these phases of reward processing in depression is theoretically important (24). A recent publication by Pizzagalli and colleagues (25) 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 Nucleus Accumbens during the consummatory phase of the trial. While a rich non-human literature underscores the complexity of the nucleus accumbens in reward processing (23), the findings of Pizzagalli and colleagues suggest that the inability to sustain nucleus accumbens 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 nucleus accumbens activity tracks the hedonic value of outcomes (26, 27). As there was no anticipation period of our task, we specifically examined the brain's response to onset of an appetitive stimulus. Therefore, it is likely that our findings relate more strongly to the consummatory component of reward processing, as opposed to the anticipatory component. It is also relevant that the use of an emotion regulation paradigm where individuals are attempting to increase their positive affect using **cognitive** strategies may be better suited to uncover interactions between the prefrontal cortex and ventral striatum than studies examining reward responsiveness or executive function alone. However, it will be important for future studies to separate the components of reward in fronto-striatal networks in tasks requiring more or less executive function invovlement.

These findings may also provide a conceptual framework for understanding the mechanisms through which various psychological interventions that explicitly attempt to

improve depressed patients' ability to sustain positive affect operate. For example, Behavioral Activation treatment (28), an empirically supported psychological intervention with similar rates of efficacy as Cognitive Therapy and antidepressant medications (29) emphasizes sustained engagement with rewarding and pleasurable activities as one of the key ingredients in treating depressed. More recently, Fava (22), and McMakin (21) have shown that treatments specifically designed to increase a depressed patient's ability to sustain positive affect (ie., "savoring") appear to be successful in the treatment of major depression.

While some have argued that Cognitive Therapy is not particularly effective at increasing positive affect in depressed (30), Behavioral Activiation, Well-being therapy, and other psychotherapies may be more effective in increasing positive affect in depression (22, 28, 31). Therefore, it would be helpful for future studies to examine whether the changes in sustained nucleus accumbens activity when enhancing positive emotion correlates with gains in positive affect when treated with various psychotherapeutic techniques. Relatedly, it will be important to determine if these newer interventions explicitly designed to enhance aspects of positive affect produce a more robust and/or more rapid change in fronto-striatal circuitry than more traditional psychotherapeutic or pharmacological interventions.

One concern could be the degree to which brain responses to negative stimuli impacted on subsequent responses to positive stimuli. Despite the fact that this analysis would be grossly underpowered with this design, we do not think this issue strongly affects interpretation of our findings. If positive trials were preceded by other positive trials approximately as often as by negative trials, we believe that lingering effects of the negative stimuli on positive trials would likely average out. We performed a χ^2 test to examine this and found that there were no significant differences in the valence of trials preceding a positive trial (42% of the positive trials

were preceded by a positive trial and 57% of the positive trials were preceded by a negative trial; χ^2=1.37; p=.241).

It is unclear why positive affect changed in the control sample. We believe that the change in positive affect in the control sample may have been due to random variation and unlikely due to more fundamental change in affective symptoms or functioning (HAMD scores for controls were at baseline and did not change). Several lines of evidence support this. First, there was a significant Group x Affect interaction suggesting that depressed patients showed changes in both positive affect and negative affect in response to treatment, whereas controls only showed changes in positive affect. There was also a significant main effect of Group on change, suggesting that depressed patients affect changed more than controls overall. There was also a very significant main effect of Group on positive affect ($F(1,33)=26.92$, $p<.001$) such that controls had significantly higher positive affect than depressed patients. In addition, while the depressed patients showed a significant drop of anhedonic symptoms (as assessed by the MASQ), healthy controls did not.

The failure to find an overall treatment effect on sustained nucleus accumbens activity and fronto-striatal connectivity, in conjunction with the finding of individual differences in the magnitude of change in these neural measures correlating with treatment response on measures of positive affect, underscores the value of an individual differences approach. The lack of a main effect of treatment may reflect variability in treatment response and it is precisely such situations that call for analyses of individual differences. It also may be the case that a treatment modality that more explicitly targets positive affect such as Behavioral Activation therapy or well-being therapy (22, 28), may produce a larger gain in positive affect as well as on the

measures of sustained nucleus accumbens activation and fronto-striatal connectivity that are featured in this report.

We should note several limitations of the study. First, as the sample was made up of individuals with "pure" depression (i.e., with no comorbidity), it is unclear whether these findings would extend to depressed populations containing a comorbid anxiety, substance abuse, or Axis II diagnosis. While having a relatively "pure" depressed sample can be helpful in terms of minimizing unwanted variability due to concurrent psychiatric diagnoses, comorbidity is the norm, as opposed to the exception in depression (32). Another limitation of the study is the sole use of antidepressants. A noted shortcoming of antidepressants in the treatment of depression is their relative lack of effectiveness in increasing positive affect (22). Thus, it would be helpful for future studies to examine whether the changes in sustained nucleus accumbens activity when enhancing positive emotion correlates with gains in positive affect when treated with various psychotherapeutic techniques.

Given the frequency of scanning and assessment of affect (twice over an 8 week period), the reviewer is correct that we are unable to address temporal directionality. It could be that affect is changing prior to changes in the brain, vice-versa, or they could be changing in tandem. To assess such questions, participants would need to be assessed (with both a fMRI scan and affect assessment) much more frequently. Unfortunately, this dataset did not contain such temporal resolution – burden upon depressed patients would be significant as well. Nonetheless, this is a very important point and future work should assess depressed patients much more frequently in order to address issues related to temporal directionality.

References

1. Jackson DC, Malmstadt JR, Larson CL, Davidson RJ: Suppression and enhancement of emotional responses to unpleasant pictures. Psychophysiology 2000; 37:515-522
2. Urry HL, van Reekum CM, Johnstone T, Kalin NH, Thurow ME, Schaefer HS, Jackson CA, Frye CJ, Greischar LL, Alexander AL, Davidson RJ: Amygdala and ventromedial prefrontal cortex are inversely coupled during regulation of negative affect and predict the diurnal pattern of cortisol secretion among older adults. J Neurosci 2006; 26:4415-4425
3. Loewenfeld IE: The pupil: anatomy, physiology, and clinical applications. Ames, IA: Iowa State UP; 1993.
4. Kahneman D, Beatty J: Pupil diameter and load on memory. Science 1966; 154:1583-1585
5. Siegle GJ, Steinhauer SR, Stenger VA, Konecky R, Carter CS: Use of concurrent pupil dilation assessment to inform interpretation and analysis of fMRI data. Neuroimage 2003; 20:114-124
6. Ohira H, Nomura M, Ichikawa N, Isowa T, Iidaka T, Sato A, Fukuyama S, Nakajima T, Yamada J: Association of neural and physiological responses during voluntary emotion suppression. Neuroimage 2006; 29:721-733
7. van Reekum CM, Johnstone T, Urry HL, Thurow ME, Schaefer HS, Alexander AL, Davidson RJ: Gaze fixations predict brain activation during the voluntary regulation of picture-induced negative affect. Neuroimage 2007; 36:1041-1055
8. Kennedy DN, Lange N, Makris N, Bates J, Meyer J, Caviness VS, Jr.: Gyri of the human neocortex: an MRI-based analysis of volume and variance. Cereb Cortex 1998; 8:372-384
9. Makris N, Meyer JW, Bates JF, Yeterian EH, Kennedy DN, Caviness VS: MRI-Based topographic parcellation of human cerebral white matter and nuclei II. Rationale and applications with systematics of cerebral connectivity. Neuroimage 1999; 9:18-45
10. Rissman J, Gazzaley A, D'Esposito M: Measuring functional connectivity during distinct stages of a cognitive task. Neuroimage 2004; 23:752-763
11. Zarahn E, Aguirre G, D'Esposito M: A trial-based experimental design for fMRI. Neuroimage 1997; 6:122-138
12. Curtis CE, Rao VY, D'Esposito M: Maintenance of spatial and motor codes during oculomotor delayed response tasks. J Neurosci 2004; 24:3944-3952
13. Postle BR, Zarahn E, D'Esposito M: Using event-related fMRI to assess delay-period activity during performance of spatial and nonspatial working memory tasks. Brain Res Brain Res Protoc 2000; 5:57-66
14. Ranganath C, Cohen MX, Dam C, D'Esposito M: Inferior temporal, prefrontal, and hippocampal contributions to visual working memory maintenance and associative memory retrieval. J Neurosci 2004; 24:3917-3925
15. Light SN, Heller AS, Johnstone T, Kolden GG, Peterson MJ, Kalin NH, Davidson RJ: Reduced right ventrolateral prefrontal cortex activity while inhibiting positive affect is associated with improvement in hedonic capacity after 8 weeks of antidepressant treatment in major depressive disorder. Biol Psychiatry 2011; 70:962-968
16. Heller AS, Johnstone T, Shackman AJ, Light SN, Peterson MJ, Kolden GG, Kalin NH, Davidson RJ: Reduced capacity to sustain positive emotion in major depression reflects diminished maintenance of fronto-striatal brain activation. Proc Natl Acad Sci U S A 2009; 106:22445-22450

17. Johnstone T, van Reekum CM, Urry HL, Kalin NH, Davidson RJ: Failure to regulate: counterproductive recruitment of top-down prefrontal-subcortical circuitry in major depression. J Neurosci 2007; 27:8877-8884
18. Siegle GJ, Steinhauer SR, Thase ME, Stenger VA, Carter CS: Can't shake that feeling: event-related fMRI assessment of sustained amygdala activity in response to emotional information in depressed individuals. Biol Psychiatry 2002; 51:693-707
19. McMakin DL, Santiago CD, Shirk SR: The Time Course of Positive and Negative Emotion in Dysphoria. J Posit Psychol 2009; 4:182-192
20. Dichter GS, Tomarken AJ: The chronometry of affective startle modulation in unipolar depression. J Abnorm Psychol 2008; 117:1-15
21. McMakin DL, Siegle GJ, Shirk SR: Positive Affect Stimulation and Sustainment (PASS) module for depressed mood: A preliminary investigation of treatment-related effects. Cognitive Therapy and Research 2011; 35:217-226
22. Fava GA, Tomba E: Increasing psychological well-being and resilience by psychotherapeutic methods. J Pers 2009; 77:1903-1934
23. Berridge KC, Robinson TE: What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? Brain Res Brain Res Rev 1998; 28:309-369
24. Treadway MT, Zald DH: Reconsidering anhedonia in depression: lessons from translational neuroscience. Neurosci Biobehav Rev 2011; 35:537-555
25. Pizzagalli DA, Holmes AJ, Dillon DG, Goetz EL, Birk JL, Bogdan R, Dougherty DD, Iosifescu DV, Rauch SL, Fava M: Reduced Caudate and Nucleus Accumbens Response to Rewards in Unmedicated Individuals With Major Depressive Disorder. Am J Psychiatry 2009; 166:702-710
26. O'Doherty J, Dayan P, Schultz J, Deichmann R, Friston K, Dolan RJ: Dissociable roles of ventral and dorsal striatum in instrumental conditioning. Science 2004; 304:452-454
27. Tricomi EM, Delgado MR, Fiez JA: Modulation of caudate activity by action contingency. Neuron 2004; 41:281-292
28. Lewinsohn PM: A behavioral approach to depression. In: Friedman RJ, Katz, M. M. , editor. The psychology of depression: Contemporary theory and research. New York: John Wiley & Sons; 1974. p. 30.
29. Dimidjian S, Hollon SD, Dobson KS, Schmaling KB, Kohlenberg RJ, Addis ME, Gallop R, McGlinchey JB, Markley DK, Gollan JK, Atkins DC, Dunner DL, Jacobson NS: Randomized trial of behavioral activation, cognitive therapy, and antidepressant medication in the acute treatment of adults with major depression. J Consult Clin Psychol 2006; 74:658-670
30. Cornwall PL, Scott J: Partial remission in depressive disorders. Acta Psychiatr Scand 1997; 95:265-271
31. Seligman ME, Rashid T, Parks AC: Positive psychotherapy. Am Psychol 2006; 61:774-788
32. Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR, Rush AJ, Walters EE, Wang PS: The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA 2003; 289:3095-3105

TABLE S1. Correlation matrix between HAMD, PANAS Negative Affect, PANAS Positive Affect for control subjects (above the diagonal and in italics) and depressed patients (below the diagonal). Note that control subjects did not complete the MASQ Anhedonia scale. *=p<.05, **=p<.01

	HAMD baseline	HAMD 8 weeks	Negative Affect baseline	Negative Affect 8 weeks	Positive Affect baseline	Positive Affect 8 weeks
HAMD baseline	1.00					
HAMD 8 weeks	0.11	1.00				
Negative Affect baseline	0.03	0.27	1.00	*0.76***	*-0.28*	*-0.29*
Negative Affect 8 weeks	0.02	0.59**	0.66**	1.00	*-0.18*	*-0.40*
Positive Affect baseline	0.08	0.23	-0.29	-0.04	1.00	*0.76***
Positive Affect 8 weeks	-0.23	-0.21	0.01	-0.34	0.30	1.00
MASQ Anhedonia baseline	0.28	0.27	0.65**	0.26	-0.31	0.01
MASQ Anhedonia 8 weeks	0.22	0.72**	0.42	0.67**	0.10	-0.48*

	HAMD Time 2 vs. Time 1	Negative Affect Time 2 vs. Time 1	Positive Affect Time 2 vs. Time 1
HAMD Time2 vs. Time 1	1.00		
Negative Affect Time2 vs. Time 1	0.28	1.00	*-0.45*
Positive Affect Time2 vs. Time 1	-0.22	-0.61**	1.00
MASQ Anhedonia Time 2 vs. Time 1	0.49*	-0.68**	0.56*

TABLE S2: Results from a voxelwise regression examining the relationship between changes in sustained brain activity 2-month$_{(2nd\ Half - 1st\ Half)}$ –Baseline$_{(2nd\ Half - 1st\ Half)}$ with changes in self-reported PA

Location (BA)	*x,y,z(mm)*	*cluster size (voxels)*	*max t-value*
R Inferior Frontal Gyrus (46)	28, 42, 18	323	4.46
Precuneus	-6, -60, 52	249	4.17
R Middle Temporal Gyrus	68, -40, -4	195	5.22
R Middle Temporal Gyrus	66, -12, -12	181	4.64
L Middle Temporal Gyrus	-50, -12, -18	154	4.35
Precuneus	-10, -70, 36	145	4.50
R Inferior Frontal Sulcus (45)	54, 30, 28	133	4.55
L Middle Frontal Gyrus(46)	-38, 42, 30	80	3.99