



Published in final edited form as:

JAMA Psychiatry. 2013 November 1; 70(11): . doi:10.1001/jamapsychiatry.2013.2430.

Increases in prefrontal cortex activity when regulating negative emotion predicts symptom severity trajectory over six months in depression

Aaron S. Heller, M.S.

Laboratory for Affective Neuroscience Waisman Laboratory for Brain Imaging and Behavior
Department of Psychology University of Wisconsin – Madison

Tom Johnstone, Ph.D.

Centre for Integrative Neuroscience & Neurodynamics Department of Psychology University of Reading

Michael J. Peterson, M.D.

Department of Psychiatry University of Wisconsin – Madison

Gregory G. Kolden, Ph.D.

Departments of Psychology and Psychiatry University of Wisconsin – Madison

Ned H. Kalin, M.D.

Departments of Psychiatry and Psychology Lane Neuroimaging Laboratory HealthEmotions
Research Institute University of Wisconsin – Madison

Richard J. Davidson, Ph.D.

Laboratory for Affective Neuroscience Waisman Laboratory for Brain Imaging and Behavior,
Center for Investigating Healthy Minds Departments of Psychology and Psychiatry University of
Wisconsin – Madison

Abstract

Context—Emotion regulation is critically disrupted in depression and use of paradigms tapping these processes may uncover essential changes in neurobiology during treatment. In addition, as neuroimaging outcome studies of depression commonly utilize solely baseline and endpoint data – which is more prone to week-to-week noise in symptomatology – we sought to use all data points over the course of a six-month trial.

Objective—To examine changes in neurobiology resulting from successful treatment.

Design—Double-blind trial examining changes in the neural circuits involved in emotion regulation resulting from one of two antidepressant treatments over a six-month trial. Participants were scanned pretreatment, at 2 months and 6 months posttreatment.

Setting—University functional magnetic resonance imaging facility.

Participants—21 patients with Major Depressive Disorder and without other Axis I or Axis II diagnoses.

Interventions—Venlafaxine XR (doses up to 300mg) or Fluoxetine (doses up to 80mg).

Main Outcome Measure—Neural activity, as measured using functional magnetic resonance imaging during performance of an emotion regulation paradigm as well as regular assessments of symptom severity by the Hamilton Rating Scale for Depression. To utilize all data points, slope trajectories were calculated for rate of change in depression severity as well as rate of change of neural engagement.

Results—Those depressed individuals showing the steepest decrease in depression severity over the six months were those individuals showing the most rapid increases in BA10 and right DLPFC activity when regulating negative affect over the same time frame. This relationship was more robust than when using solely the baseline and endpoint data.

Conclusions—Changes in PFC engagement when regulating negative affect correlate with changes in depression severity over six months. These results are buttressed by calculating these statistics which are more reliable and robust to week-to-week variation than difference scores.

Emotion dysregulation is a core component in the pathophysiology of Major Depressive Disorder (MDD)^{1, 2}. In particular, the ability to adaptively regulate negative affect is thought to be an important mechanism by which depressed individuals recover from MDD and is part of the theoretical rationale of several empirically supported psychotherapies³. Meta-analyses of neuroimaging studies using emotion regulation paradigms has shown that both the prefrontal cortex (PFC) and amygdala appear to be involved in the regulation of emotion⁴, whereby it is hypothesized that the PFC enacts “top-down” control of the amygdala and impacts its firing patterns⁵. Studies have often found specific roles for the dorsolateral PFC (DLPFC) and medial PFC (mPFC) in emotion regulation⁶. While the DLPFC does not have direct projections to the amygdala, the mPFC does and the DLPFC may exert top-down control of amygdala function via the mPFC⁷. Recently, it has been suggested that more dorsal regions of the mPFC are involved in the appraisal of emotion while more ventral portions of the mPFC are involved in the regulation of emotion⁷. Yet, despite near universal agreement that improvement of emotion regulation is essential to effective treatment, we are not aware of neuroimaging studies to date which have examined changes in the neurobiological substrates underlying emotion regulation processes as a result of treatment.

Studies examining changes in the neurobiology of depression over the course of treatment have produced somewhat inconsistent results. For example, meta-analyses examining changes in fMRI and PET following anti-depressant treatment have found that activity in a variety of PFC, thalamic, and insular areas increase during treatment, whereas activity in the amygdala, hippocampus, ventral ACC and other PFC areas appear to decrease during treatment^{8, 9}. It appears that results depend to a significant degree on what type of paradigm is used (e.g., either a resting state or one of several task activation paradigms). It is also common for studies to follow MDD patients for eight weeks or less – whereas brain activation changes as well as symptom severity may change far beyond the first eight weeks of treatment.

Another reason for a lack of concordance between treatment studies of depression may be methodological: In treatment studies of depression many intermediate measures of symptom severity are discarded and only baseline and endpoint measures are examined. This approach is helpful for understanding final symptom severity, but does so at the cost of examining the course of medication response. One problem with this approach is the potential large week-to-week variability in symptoms, which could lead to reduced accuracy if only baseline and endpoint data are used. Such issues can be compounded when taking categorical approaches (e.g., remitter vs. non-remitter) as the cut-point distinctions are arbitrary¹⁰. As the NIMH Treatment of Depression Collaborative Research Program noted¹¹, endpoint and categorical approaches to assessing treatment outcome often make restrictive statistical assumptions and

discard potentially informative data. Instead, this workgroup suggested employment of Random Regression Models whereby a trajectory (ie., slope) is calculated for each patient or treatment arm. This allows for utilizing all data points, is robust in the face of missing data, allows for irregularly spaced measurement occasions, and can increase reliability of outcome measures. These approaches have been successfully used in outcome studies¹²⁻¹⁵.

As emotion dysregulation is generally regarded to be an essential feature of depression, utilizing an experimental paradigm designed specifically to tap these psychological processes has important ecological validity; there are no studies of which we are aware which have examined relations between changes in symptom severity resulting from treatment and changes in brain regions subserving emotion regulation. In addition, following patients for longer than the customary 8 weeks post-treatment may be important in uncovering novel neurobiological circuits correlating with rate of treatment response. Lastly, the development of novel methodological approaches to examining relations between changes in symptom severity and brain engagement may be important for better understanding treatment response.

To that end, a six-month treatment outcome study was conducted in which untreated patients with Major Depressive Disorder (MDD) were assessed prior to and during treatment with one of two antidepressants (Venlafaxine ER or Fluoxetine). Patients were scanned on three occasions: pretreatment, 2-months, and 6 months into treatment. Depression severity was assessed regularly. Given that the regulation of negative affect is thought to be a central component of MDD^{1, 2}, we utilized a paradigm designed to tap these processes. Given that the PFC as well as the amygdala have been implicated in the successful regulation of emotion⁴, we predicted that trajectories of change in these areas would correlate with trajectories of HAMD change.

Methods

Participants

At the baseline, 29 medication-free, right-handed adults satisfying DSM-IV¹⁶ criteria for unipolar major depressive disorder. Subjects were recruited through community advertisements. Patients were medication free for at least 2 weeks prior to study entry. At enrollment, subjects were screened for standard MRI compatibility criteria, CNS medications, comorbid substance abuse/dependence, other comorbid DSM-IV Axis I (including Anxiety) or Axis II diagnoses, and a personal or familial history of bipolar disorder. Patients in this sample were screened for and excluded if they suffered from a comorbid Axis I disorder. Patients were required to have had depressive symptoms for at least 1 month prior to enrollment and scores >17 on the 21-item HAMD at enrollment and baseline fMRI assessment. Subjects participating in this study are the same as those who participated in¹⁷⁻²⁰. This study was approved by the Institutional Review Board and subjects provided informed written consent.

Following the initial, pretreatment scan session, patients were randomized to receive a six-month course of either Venlafaxine ER or Fluoxetine treatment. These patients were only receiving antidepressant medication treatment - they were not receiving other forms of therapy. In week 1, patients received 37.5mg or 20mg of Venlafaxine ER or Fluoxetine, respectively. In week 2, patients received 75mg or 20mg of Venlafaxine ER 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 ER of 300mg or Fluoxetine of 80mg. HAMD scores were acquired approximately weekly for the first 5 weeks (until an effective dose was achieved), roughly every other week for the next month, and approximately once a month through the

completion of the six month study. Approximately 11 HAMD interviews were performed over 6 months if the patient completed the study. During the first 2 months of treatment, the average dosage for those depressed patients randomized to receive Fluoxetine was 37mg/day (SD=8.7mg/day); the average dosage for those patients receiving Venlafaxine ER was 118mg/day (SD=36.6mg/day). Over the entire study, the average dosage for those depressed patients randomized to receive Fluoxetine was 43.62mg/day (SD=11.76mg/day); the average dosage for patients receiving Venlafaxine ER was 158.63mg/day (SD=62.06mg/day). For regression analyses controlling for medication quantity, we used the average dosage patients took over the entire study as a single dosage of Venlafaxine and a single dosage of Fluoxetine are thought to be of rough clinical equivalence. The rationale for using two different types of medication was twofold. First, it was to examine the general neurobiological substrates underlying medication treatment response. To do this, two medications were required to be able to examine such generalized patterns. A secondary goal was to be able to compare the neurobiological profiles resulting from both a SSRI and a SNRI, although our sample sizes were ultimately not large enough to be able to directly compare the treatments with sufficient statistical power.

At two and six months, depressed subjects returned for two additional fMRI assessments. Eight patients discontinued participation, leaving 21 patients. There was a marginally significant difference in initial HAMD score between those depressed patients completing the trial and those not completing the trial ($t(27) = 1.93, p=0.06$), such that those completing the trial had lower initial HAMD scores. After unblinding, it was revealed that twelve patients had taken a trial of venlafaxine ER and nine patients had begun a trial of fluoxetine. Analyses incorporated medication “responders” and “nonresponders.”

FMRI Design

All three scan sessions were identical in timing, procedure and design. Subjects were scanned while viewing a sequence of 72 positive and 72 negative images from the International Affective Picture System IAPS;²¹ 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). 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. The same images were used at all scan sessions; however, the order of image presentation was randomized across the scans. Trials began with a 1s fixation cross and auditory tone. Then, an image was presented for 10s, followed by a 6s blank screen. To ensure compliance, at the onset of each image, subjects used a button response pad to judge whether the image was positive or negative. Four seconds following image onset, an auditory prompt instructed subjects to increase (“enhance”) or decrease (“suppress”) their emotional response to the image or to continue to “attend” to the picture (Figure 1). Participants were trained during a previous session while positioned inside a mock scanner on the use of cognitive reappraisal strategies to re-evaluate the images as more or less emotional. 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). 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). Alternatively, on attend trials, participants were instructed to maintain their attention to the picture without changing their affective experience. Across 6 380-sec scans,

there were 24 trials of the regulation conditions and 12 trials of the attend condition for each valence (order pseudorandomized).

Image acquisition

Images were collected on a General Electric 3 Tesla scanner 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).

Analysis of change in depression symptoms

To use the totality of the HAMD symptom data, we performed a multiple regression analysis for each depressed patient in which the vector of depression severity scores on the 21-item HAMD over the study was regressed on the square root of the number of days since the initial, pretreatment HAMD. For each patient, this yielded a B-estimate which corresponded to the rate of change of HAMD score over the square root of time plus a constant of 1 for the time variable. We used a square root transformation of time because previous reports^{11, 13} have suggested that reductions in symptom severity are nonlinear over time following treatment with antidepressants. This can be seen descriptively in Figure 2. Further supporting the rationale for using a square root transform of time, the mean R^2 for the HAMD trajectory regressions across subjects was significantly higher when using the square root transformation (mean $R^2=0.65$, $SD=0.23$) of time+1 as opposed to the non-transformed time variable (mean $R^2=0.55$, $SD=0.22$; paired t-test: $t(20)=6.46$, $p<.001$).

Image analysis

At each of the three time points, fMRI data were slice-time and motion corrected using AFNI²². EPI data were normalized to the 2mm MNI152 template using FSL's linear and nonlinear normalization algorithms FLIRT/FNIRT and smoothed (5mm FWHM). These data were then analyzed as single-subject GLMs to model each of the six trial types (positive/negative stimulus; enhance, attend, and suppress reappraisal instruction), 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 seven sine basis functions to produce separate estimated hemodynamic response functions (HRFs) for each trial type over the entire trial. The estimated HRFs 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). In order to examine brain function when regulating negative affect, contrast maps were created for each subject at all three time points by subtracting the “attend” condition from the “suppress” condition in response to negative stimuli.

We performed a similar analysis as we did with HAMD scores to utilize data from all three scan sessions in assessing treatment induced change in brain activity when regulating emotion. As with the individual HAMD trajectories, time, in this case, corresponded to the number of days since the first scan occurred. Thus, for each subject, on a voxel-by-voxel basis, we regressed the vector of the three negative “suppress” vs. “attend” contrast values on the vector of three time values (again square root transformed). For each subject, this yielded a B-estimate at each voxel corresponding to the rate of change of fMRI when regulating emotion resulting from treatment.

For the analyses using the more traditional approach of examining change using difference scores (end vs. starting points), we subtracted initial HAMD score from final HAMD score. For fMRI analyses, in a voxelwise manner, we subtracted initial negative “suppress” vs. “attend” from final negative “suppress” vs. “attend”.

Group Analysis

Each patient now had two B-estimates following initiation of antidepressant treatment. One B-estimate corresponded to rate of change of HAMD scores, the other B-estimate corresponded to rate of change of fMRI activity when regulating emotion. In order to examine which brain areas displayed a rate of change correlating with rate of change of HAMD symptoms, we performed a between subjects correlation, correlating the B-estimate from change in brain activity over time, with the B-estimate indicating rate of change in HAMD scores. Brain areas demonstrating a significant association in this analysis can be interpreted as reflecting the rate of change of depression severity. Resulting group analysis brain maps were thresholded at $p < .005$ with cluster size of $k > 51$ voxels. This corresponds to $p < .05$ corrected for multiple comparisons based on Monte Carlo simulation (the AlphaSim program in AFNI) using a whole-brain mask. Group analyses relating to the difference scores were performed identically. For analyses of Grey Matter Probability (GMP), we used FSL's FAST algorithm²³.

For comparability with studies examining treatment to eight weeks, we performed a similar analysis with only the first two fMRI time points and HAMD measurements to 8 weeks. We calculated a difference score of the negative suppress vs. attend condition for the two fMRI sessions and correlated that with HAMD trajectory over the first 8 weeks.

We also performed a connectivity analysis to examine whether slope of amygdala-PFC connectivity related to HAMD trajectory. We utilized an anatomical amygdala seed from the Juelich atlas²⁴ and used the beta-seed connectivity approach²⁵. We specifically looked at those PFC regions which were significant in the univariate analysis. We subsequently calculated slope of change in connectivity across the three time points and correlated with HAMD slope as described above.

Results

Symptom Change

Patients completing the six-month trial were interviewed with the HAMD an average of 12 times ($sd=0.54$). Their final HAMD assessment visit – coinciding with the third and final MRI session – was an average of 189 days ($sd=10.48$) after the initial HAMD assessment and MRI session. At the initial time point, the mean HAMD score was 20.33 ($sd=2.22$), and at the final time point the mean HAMD score was 6.00 ($sd=4.30$). At final assessment, 14 of the 21 patients had “remitted” (HAMD score ≤ 7) and 2 of the non-remitting 7 patients were medication “responders” ($\geq 50\%$ decrease). HAMD at final assessment was significantly lower than at initial assessment ($t(20)=14.46$, $p < 0.001$). The average B-estimate indicating rate of change of HAMD score over time (square root transformed) across subjects was -1.22 ($sd=0.43$). For the non-square root transformed data the mean B-estimate was -0.07 ($sd=0.03$). As can be seen in Figure 2, individual patients demonstrated substantial variability at the final HAMD assessment (as compared with their most recent previous assessments), highlighting the potential power in utilizing a trajectory-based approach for assessing symptom change. At the initial time point the mean HAMD score was 1.07 ($sd=1.44$).

Correlation between HAMD trajectory and fMRI trajectory when regulating negative affect

The between-subjects correlation, examining the relation between treatment-related BOLD signal changes during the regulation of negative affect and HAMD trajectory revealed several areas. Perhaps most interestingly, two areas of prefrontal cortex, BA10 (peak: -4, 62, 12; Figure 3a) and Right DLPFC (BA 9; peak: 18, 50, 44; Figure 3b) demonstrated a significant negative association with HAMD rate of change, such that those individuals showing the steepest increase, over the six-month trial, in negative “suppress” vs. “attend” BOLD signal in these prefrontal regions were those individuals showing the most rapid decrease in HAMD score. Controlling for age and gender in the two PFC regions did not attenuate the relationship. Other areas which showed a similar association can be seen in Table 1.

We found no such relationship between HAMD trajectory and negative “suppress” vs. “attend” trajectory in the Amygdala, contrary to our prediction. Furthermore, recent models of antidepressant treatment change²⁶ have suggested that change in Amygdala activity in response to negative stimuli (in the absence of emotion regulation) may predate changes in PFC activity. As a result, we calculated a similar trajectory for the negative “attend” condition only and correlated that with HAMD trajectory. Using the negative “attend” trajectory, we did not see a relationship with HAMD trajectory within the Amygdala, even at the more liberal threshold of $p < .01$.

Analyses addressing specificity

To examine the specificity of these findings, we performed several control analyses. When controlling for medication type (e.g., Fluoxetine vs. Venlafaxine), the relationship between HAMD trajectory and BA10 trajectory remained significant ($B = -11.46$, $t(18) = -3.09$, $p = .006$); the effect of medication was not significant ($B = -0.10$, $t(18) = -0.62$, $p = 0.54$). Similarly, when controlling for medication type, the relationship between HAMD trajectory and DLPFC trajectory remained significant ($B = -11.72$, $t(18) = -2.91$, $p = .009$); the effect of medication was not significant ($B = -0.02$, $t(18) = -0.13$, $p = 0.90$). This suggests that drug type does not account for this relationship.

Because this effect could be driven by individual differences in initial depression severity, we next ran analyses controlling for baseline HAMD score. When controlling for baseline HAMD score, the relationship between HAMD trajectory and BA10 trajectory slightly increased in significance ($B = -11.86$, $t(18) = -3.98$, $p < .001$); interestingly, the effect of baseline HAMD was also significant ($B = -0.09$, $t(18) = -3.18$, $p = 0.005$) such that individuals with higher baseline HAMD scores had steeper HAMD trajectories. When controlling for baseline HAMD, the relationship between HAMD trajectory and DLPFC trajectory remained significant ($B = -9.71$, $t(18) = -2.53$, $p = .02$); in this case, the effect of baseline HAMD was not significant ($B = -0.06$, $t(18) = -1.63$, $p = 0.12$). This suggests that these findings are due to relationships in the trajectory specifically and not initial depression severity per se.

Lastly, we examined the condition when subjects were increasing positive affect, namely the positive “enhance” vs. positive “attend” conditions. We calculated fMRI trajectories for each subject, and correlated it with HAMD trajectory. There were no significant associations between HAMD trajectory and trajectory of upregulating positive affect when correcting for multiple comparisons done voxelwise. This may be due, in part to the fact that the HAMD has only three items inquiring about reductions in positive affect in MDD.

Correlation between HAMD baseline to endpoint difference and fMRI difference when regulating negative affect

To evaluate whether calculating HAMD and fMRI trajectories yields additional and potentially more robust information as compared with the more traditional difference score approach, we assessed whether the significant effects between BA10, DLPFC and HAMD trajectories held when using baseline and six-month difference scores. The correlation between BA10 difference score and HAMD difference score was trending toward significance ($r = -0.39$, $p=.08$), and the correlation between RDLPFC difference score and HAMD difference score was not significant ($r = -0.37$, $p=.10$). Note that the association is in the same direction as the trajectory based approach, simply that in these areas the correlation is attenuated – when testing whether the difference in correlations was significant between the trajectory and difference score approaches, neither were significantly different from one another ($p=0.41$ for BA10, and $p=0.39$ for DLPFC). However, given the relatively strict requirements for multiple comparison correction in imaging paradigms, we would not have found these effects using the traditional difference score approach.

Correlation between HAMD trajectory and Grey Matter Probability trajectory

As several studies have suggested that changes in brain structure may accompany changes in depressive symptom severity, we calculated Grey Matter Probability (GMP) maps for each depressed patient at all three time points and ran a similar voxel-wise regression as for the functional data. There was no significant correlation between GMP trajectory in BA10 and HAMD trajectory ($r=-0.05$, $p=0.82$). When controlling for GMP trajectory, the association between BOLD signal BA10 trajectory when regulating negative affect and HAMD trajectory remained significant ($B=-12.11$, $t(18)=-3.19$, $p=.005$) and the association between BA10 GMP trajectory and HAMD trajectory was not significant ($B=-12.10$, $t(18)=0.43$, $p=.67$). There was also no significant correlation between GMP trajectory in the RDLPFC and HAMD trajectory ($r=-0.23$, $p=0.32$). Similarly, when controlling for GMP trajectory, the association between BOLD signal RDLPFC trajectory when regulating negative affect and HAMD trajectory remained significant ($B=-11.84$, $t(18)=-2.83$, $p=.01$) and the association between RDLPFC GMP trajectory and HAMD trajectory was not significant ($B=-0.54$, $t(18)=-0.02$, $p=.98$). This suggests that the findings are not due to changes in structure and are specific to functional changes.

We computed a slope measure for each participant's HAMD scores across the initial 2 months – up to the point at which the second scan occurred. We also computed a difference score for change in brain activity when regulating negative affect and we performed a between subjects voxelwise correlation of these two individual difference metrics. Interestingly, no areas survived multiple comparison correction for this analysis at two months.

For the connectivity analysis we examined whether rate of change in amygdala-BA10, or amygdala-RDLPFC connectivity predicted HAMD trajectory. We found no significant relationship between rate of change of connectivity in either the DLPFC-Amygdala ($p=0.54$) or BA10-Amygdala ($p=0.65$) and HAMD trajectory.

Comment

Emotion regulation is a core feature of the pathophysiology in depression, however studies examining brain changes during the regulation of emotion over the course of treatment has not been undertaken. As such, over six months of antidepressant treatment, we calculated depression severity as well as fMRI trajectories for each participant as they performed an emotion regulation task. Performing a between-subjects regression with these two measures

revealed that the rate of change of activity in BA10 and RDLPFC when regulating negative affect tracked with rate of change of depression severity such that those depressed patients evidencing more rapid increases in BA10 and RDLPFC activity were those individuals showing the most rapid decrease in depression symptom severity. We did not find such a relationship in the Amygdala, or when upregulating positive affect as opposed to down-regulating negative affect. In addition, calculation of symptom and brain trajectories following treatment in psychiatric studies has several virtues, including increasing the reliability of change statistics. Use of both more reliable statistical measures in addition to use of theoretically motivated experimental paradigms, may lead to a greater concordance across studies and aid in designing better treatments.

This finding fits with some previous work examining the neurobiological correlates underlying symptom change in depression. Studies have found increases in DLPFC activity resulting from 8 weeks of antidepressant treatment²⁷, or increases in medial PFC activity resulting from treatment^{28, 29}. This finding is also partially consistent with a model for treatment change suggesting that increases in PFC and decreases in amygdala engagement would follow successful depression treatment²⁶. The lack of a finding in the amygdala when either regulating negative affect or solely during reactivity is notable, however. It may be that use of a paradigm designed to more specifically probe amygdala reactivity e.g.,^{30, 31}, as opposed to the emotion regulation paradigm used here would have more power to reveal relationships between trajectory of amygdala reactivity and trajectory of depression severity.

Given the importance of the regulation of emotion in mood disorders such as depression^{1, 2}, utilizing paradigms with face validity may be particularly important in uncovering unique neurobiological substrates underlying the disorder and its successful treatment. In particular, changes in distinct brain networks appear to be related to changes in symptom severity depending on the type of task used, and whether there is a task at all (e.g., at rest). This is not to say that emotion regulation paradigms are the only or best approach – other paradigms designed to examine disturbances in emotional reactivity, memory, or cognitive disruption are all important to understanding the neurobiology underlying depression and its treatment. This highlights not only the heterogeneity of the neurobiology underlying depression, but also the importance of the field to consider which imaging paradigms may be the most valuable in aiding our understanding of the disorder.

There are at least two reasons for why we may have seen a lack of a relationship between changes in amygdala activity and changes in depression severity. First, it may be due to the paradigm that was used and less to due to a reduced role for the amygdala in depression treatment. In particular, a paradigm designed to more robustly activate the amygdala may yield greater variance across time points and be sensitive to changes resulting from treatment than the emotion regulation paradigm used here. Second, evidence suggests that while the psychological effects of antidepressant may take weeks, its effect on amygdala activity may occur much more rapidly (ie., within hours³²). As a result, there may have been a disconnect between changes in amygdala activity and HAMD change making it difficult to find such a relationship.

Our finding that changes in BA10 and RDLPFC trajectory track changes in symptom severity raises the question of how does rate of change in engagement of these specific subregions of PFC correspond to rate of improvement in HAMD. Both of these areas have been found by a meta-analysis to be involved in the regulation of emotion⁴, but work has yet to identify the roles of specific subregions of PFC during the regulation of affect. Recently, it has been suggested that the medial PFC network can be subdivided into a dorsal area subserving the appraisal of emotion and a more ventral area subserving the regulation of affect⁷. The PFC areas found in this study fall within the dorsal nexus. While it may be

surprising that the PFC regions were in more dorsal portions of the PFC and within this “appraisal” subdivision, it may in fact be that how a depressed patient interprets stimuli in their life is an important feature of how patients improve resulting from treatment.

In fact, slope trajectories in several regions other than the PFC were associated with HAMD trajectory. These included the occipital gyrus and middle temporal gyri. As we suggested above that the location of the PFC regions raise the possibility that brain areas responsible for appraisal processes are changing as depression severity is changing it may not be surprising that other, perceptual areas are showing similar relationships. It may be that rates of change in such perceptual areas, in concert with the frontal areas, subserve changes in how depressed patients are in fact experiencing such affective stimuli.

The most significant limitation in comparing a dataset with only 3 time points to one with 12 time points is the mismatch in resolution. Ideally, we would have had 12 fMRI scans as well as 12 HAMD assessments - although it would have been prohibitively costly to complete such a study, not to mention respondent burden. As such, one limitation is that we were required to examine only linear relationships over the six-month trial. While we ran linear regressions to compute fMRI slopes (and correlate with HAMD slopes), a depressed patients brain may change in non-linear ways when regulating negative affect and use of non-linear functions may better model both the psychological and biological change resulting from treatment. Inherent in this limitation is that with greater scanning resolution, we would have also been able to look at whether rates of brain changes differ early on in treatment vs. later in treatment. In our view, these are very important questions for future research.

Patients in this sample were screened for and excluded if they suffered from comorbid Axis I disorder. Clinically, this is less common – depressed patients often present with comorbid Axis I disorders including Generalized Anxiety. In our view, this is both a strength and limitation. It is a strength in that we are modeling the neural correlates of reductions in depressive symptoms specifically resulting from treatment. Using a more representative sample with patients suffering from a variety of comorbid Axis I disorders might enhance the generalizability of the findings that BA10 and DLPFC trajectories track with reductions in HAMD, but also may introduce noise as patients experience reductions in additional clusters of symptoms. Future work examining relations between changes neurobiological trajectories resulting from treatment with changes in symptom severity should be more inclusive as to comorbidity to address these questions.

In sum, changes in PFC engagement when regulating negative affect track with changes in depression symptoms severity over six months. These results were buttressed by calculating change statistics which are theoretically more reliable than the simple use of difference scores. We believe that use of paradigms which are thought to tap core features of the disorder being studied in addition to employing statistics which make use of all the data acquired can increase reliability and foster cross-study comparison as findings are less reliant that an individual data point (symptom or fMRI measure) is robust and accurate.

Most importantly, the findings from this study underscore the utility of probing emotion regulation in depression and indicate that decreases in depression severity with treatment are associated with increases in prefrontal activation during the voluntary regulation of negative affect. These findings are consistent with the conjecture that increased prefrontal activation during the regulation of negative affect confers some benefit and may facilitate more rapid recovery following negative challenge and thus, over time, result in decreased depression severity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

1. Davidson RJ, Pizzagalli D, Nitschke JB, Putnam K. Depression: perspectives from affective neuroscience. *Annu Rev Psychol.* 2002; 53:545–574. [PubMed: 11752496]
2. Ochsner KN, Gross JJ. Cognitive emotion regulation: Insights from social cognitive and affective neuroscience. *Current Directions in Psychological Science.* Apr; 2008 17(2):153–158.
3. Beck, AT. *Depression: causes and treatment.* University of Pennsylvania Press; Philadelphia: 1970.
4. Kalisch R. The functional neuroanatomy of reappraisal: time matters. *Neurosci Biobehav Rev.* Sep; 2009 33(8):1215–1226. [PubMed: 19539645]
5. Miller EK, Cohen JD. An integrative theory of prefrontal cortex function. *Annu Rev Neurosci.* 2001; 24:167–202. [PubMed: 11283309]
6. Ochsner KN, Gross JJ. The cognitive control of emotion. *Trends Cogn Sci.* May; 2005 9(5):242–249. [PubMed: 15866151]
7. Etkin A, Egner T, Kalisch R. Emotional processing in anterior cingulate and medial prefrontal cortex. *Trends Cogn Sci.* Feb; 2011 15(2):85–93. [PubMed: 21167765]
8. Delaveau P, Jabourian M, Lemogne C, Guionnet S, Bergouignan L, Fossati P. Brain effects of antidepressants in major depression: a meta-analysis of emotional processing studies. *J Affect Disord.* Apr; 2011 130(1–2):66–74. [PubMed: 21030092]
9. Fitzgerald PB, Laird AR, Maller J, Daskalakis ZJ. A meta-analytic study of changes in brain activation in depression. *Hum Brain Mapp.* Jun; 2008 29(6):683–695. [PubMed: 17598168]
10. Dougherty DD, Rauch SL. Brain correlates of antidepressant treatment outcome from neuroimaging studies in depression. *Psychiatr Clin North Am.* Mar; 2007 30(1):91–103. [PubMed: 17362806]
11. Gibbons RD, Hedeker D, Elkin I, et al. Some conceptual and statistical issues in analysis of longitudinal psychiatric data. Application to the NIMH treatment of Depression Collaborative Research Program dataset. *Arch Gen Psychiatry.* Sep; 1993 50(9):739–750. [PubMed: 8357299]
12. Uher R, Muthen B, Souery D, et al. Trajectories of change in depression severity during treatment with antidepressants. *Psychol Med.* Aug; 2009 40(8):1367–1377. [PubMed: 19863842]
13. Elkin I, Gibbons RD, Shea MT, et al. Initial severity and differential treatment outcome in the National Institute of Mental Health Treatment of Depression Collaborative Research Program. *J Consult Clin Psychol.* Oct; 1995 63(5):841–847. [PubMed: 7593878]
14. Reynolds CF 3rd, Frank E, Kupfer DJ, et al. Treatment outcome in recurrent major depression: a post hoc comparison of elderly (“young old”) and midlife patients. *Am J Psychiatry.* Oct; 1996 153(10):1288–1292. [PubMed: 8831436]
15. DeRubeis RJ, Hollon SD, Amsterdam JD, et al. Cognitive therapy vs medications in the treatment of moderate to severe depression. *Arch Gen Psychiatry.* Apr; 2005 62(4):409–416. [PubMed: 15809408]
16. American Psychiatric Association. *Diagnostic criteria from DSM-IV-TR.* American Psychiatric Association; Arlington, VA: 2000.
17. Heller AS, Johnstone T, Light SN, et al. Relationships Between Changes in Sustained Fronto-Striatal Connectivity and Positive Affect in Major Depression Resulting From Antidepressant Treatment. *Am J Psychiatry.* Dec 7. In Press.
18. Heller AS, Johnstone T, Shackman AJ, et al. Reduced capacity to sustain positive emotion in major depression reflects diminished maintenance of fronto-striatal brain activation. *Proc Natl Acad Sci U S A.* Dec 29; 2009 106(52):22445–22450. [PubMed: 20080793]
19. 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.* Aug 15; 2007 27(33):8877–8884. [PubMed: 17699669]
20. Light SN, Heller AS, Johnstone T, et al. 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*. Nov 15; 2011 70(10): 962–968. [PubMed: 21867991]
21. Lang, PJB. Cuthbert, BN. Technical Report A-6. University of Florida; Gainesville, FL: 2005. International affective picture system (IAPS): affective ratings of pictures and instruction manual.
 22. Cox RW. AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Comput Biomed Res*. Jun; 1996 29(3):162–173. [PubMed: 8812068]
 23. Zhang Y, Brady M, Smith S. Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm. *IEEE Trans Med Imaging*. Jan; 2001 20(1):45–57. [PubMed: 11293691]
 24. Eickhoff SB, Paus T, Caspers S, et al. Assignment of functional activations to probabilistic cytoarchitectonic areas revisited. *Neuroimage*. Jul 1; 2007 36(3):511–521. [PubMed: 17499520]
 25. Rissman J, Gazzaley A, D'Esposito M. Measuring functional connectivity during distinct stages of a cognitive task. *Neuroimage*. Oct; 2004 23(2):752–763. [PubMed: 15488425]
 26. DeRubeis RJ, Siegle GJ, Hollon SD. Cognitive therapy versus medication for depression: treatment outcomes and neural mechanisms. *Nat Rev Neurosci*. Oct; 2008 9(10):788–796. [PubMed: 18784657]
 27. Fales CL, Barch DM, Rundle MM, et al. Antidepressant treatment normalizes hypoactivity in dorsolateral prefrontal cortex during emotional interference processing in major depression. *J Affect Disord*. Jan; 2009 112(1–3):206–211. [PubMed: 18559283]
 28. Fu CH, Williams SC, Cleare AJ, et al. Attenuation of the neural response to sad faces in major depression by antidepressant treatment: a prospective, event-related functional magnetic resonance imaging study. *Arch Gen Psychiatry*. Sep; 2004 61(9):877–889. [PubMed: 15351766]
 29. Anand A, Li Y, Wang Y, et al. Antidepressant effect on connectivity of the mood-regulating circuit: an fMRI study. *Neuropsychopharmacology*. Jul; 2005 30(7):1334–1344. [PubMed: 15856081]
 30. 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*. May 1; 2002 51(9):693–707. [PubMed: 11983183]
 31. Hariri AR, Tessitore A, Mattay VS, Fera F, Weinberger DR. The amygdala response to emotional stimuli: a comparison of faces and scenes. *Neuroimage*. Sep; 2002 17(1):317–323. [PubMed: 12482086]
 32. Murphy SE, Norbury R, O'Sullivan U, Cowen PJ, Harmer CJ. Effect of a single dose of citalopram on amygdala response to emotional faces. *Br J Psychiatry*. Jun; 2009 194(6):535–540. [PubMed: 19478294]

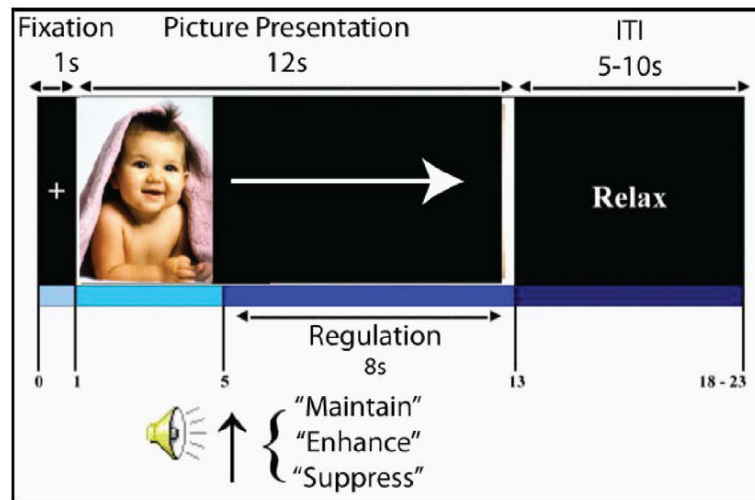


Figure 1. Schematic of the emotion regulation paradigm. This is an example trial in which a positive image was presented. Four seconds into image presentation, participants received an auditory prompt instructing them to “enhance”, “suppress”, or “attend” to their affect.

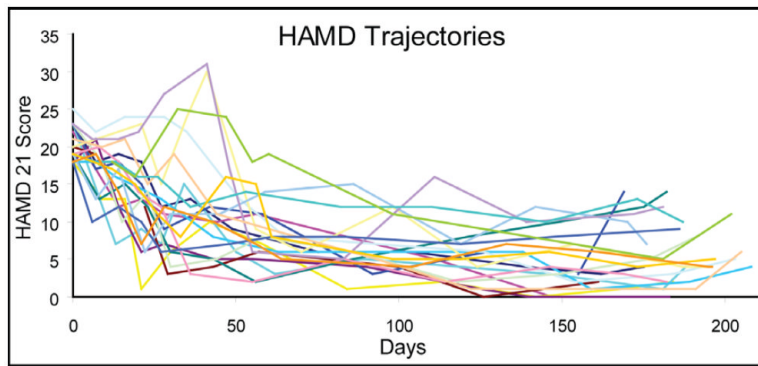


Figure 2. Time course of HAMD scores over time for MDD patients completing the six month trial.

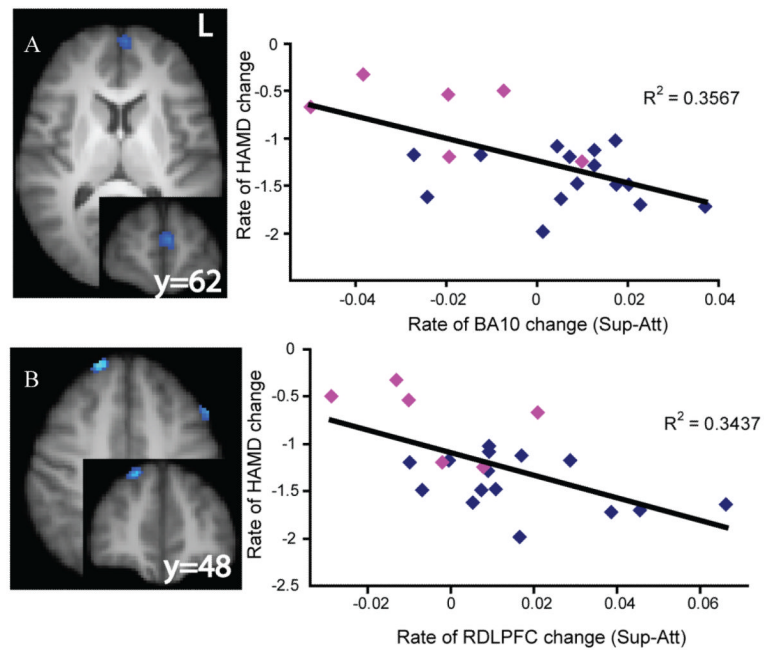


Figure 3. When regulating negative affect, BA10 and RDLPFC trajectory over six months demonstrate significant associations with HAMD trajectory over the same time. Dark blue points are depression “remitters” (HAMD score ≤ 7), pink dots are “non remitters”.

Table 1

Brain regions showing a significant association between HAMD trajectory and fMRI trajectory when regulating negative affect.

Location (BA)	x,y,z(mm)	cluster size (voxels)	max t-value
Superior Occipital Gyrus (17/18)	-4,-90,24	189	-4.24
R Middle Temporal Gyrus (20)	70,-35,-8	109	-4.37
L Middle Temporal Gyrus (21)	-64,-12,-14	102	-4.50
Medial Prefrontal Cortex (10)	-4,62,12	74	-3.83
Cerebellum	14,-86,-40	55	-3.85
R Superior Frontal Gyrus (9)	18,50,44	53	-4.69