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

Sharee N. Light, Aaron S. Heller, Tom Johnstone, Gregory G. Kolden, Michael J. Peterson, Ned H. Kalin, and Richard J. Davidson

Background: Anhedonia, a reduced ability to experience pleasure, is a chief symptom of major depressive disorder and is related to reduced frontostriatal connectivity when attempting to upregulate positive emotion. The present study examined another facet of positive emotion regulation associated with anhedonia—namely, the downregulation of positive affect—and its relation to prefrontal cortex (PFC) activity.

Methods: Neuroimaging data were collected from 27 individuals meeting criteria for major depressive disorder as they attempted to suppress positive emotion during a positive emotion regulation task. Their PFC activation pattern was compared with the PFC activation pattern exhibited by 19 healthy control subjects during the same task. Anhedonia scores were collected at three time points: at baseline (time 1), 8 weeks after time 1 (i.e., time 2), and 6 months after time 1 (i.e., time 3). Prefrontal cortex activity at time 1 was used to predict change in anhedonia over time. Analyses were conducted utilizing hierarchical linear modeling software.

Results: Depressed individuals who could not inhibit positive emotion—evidenced by reduced right ventrolateral prefrontal cortex activity during attempts to dampen their experience of positive emotion in response to positive visual stimuli—exhibited a steeper anhedonia reduction slope between baseline and 8 weeks of treatment with antidepressant medication ($p < .05$). Control subjects showed a similar trend between baseline and time 3.

Conclusions: To reduce anhedonia, it may be necessary to teach individuals how to counteract the functioning of an overactive pleasure-dampening prefrontal inhibitory system.

Key Words: Anhedonia, cognitive control, major depressive disorder, positive emotion regulation, positive empathy, prefrontal cortex

Depressed individuals who have anhedonia, a reduced ability to experience pleasure, have difficulty sustaining positive emotion over time (1). Specifically, previous research indicates that individuals with major depressive disorder (MDD) are impaired in their ability to sustain the upregulation of positive affect by cognitive means, and this is associated with reduced dorsomedial prefrontal cortex (DMPFC)-striatal connectivity (1). Individuals with depression may also excessively dampen or inhibit positive emotion. This tendency may be due to the functioning of relatively automatic and stable inhibitory cognitive appraisal strategies in anhedonic individuals. These positive affect dampening appraisal strategies can be quantified by measuring prefrontal cortex activity during a positive emotion-inducing task. This, as yet, understudied aspect of anhedonia may be revealed by differential prefrontal cortex (PFC) activity during an emotion regulation task (2). Variation in neural activity during the attempted down-regulation of positive affect may predict antidepressant treatment response.

The ability to inhibit inappropriate responses is central to cognitive control, and overlapping brain mechanisms, namely the inferior frontal gyrus/ventrolateral prefrontal cortex (VLPFC), mediate inhibition across different tasks (3). However, there may be instances when cognitive control interferes with normal emotional experience and expression. For example, the occurrence of anhedonia may be due, in part, to conscious or nonconscious tendencies to dampen positive emotion. Anecdotally, many depressed individuals minimize positive input. Though VLPFC activity is mostly linked to cognitive operations, there is some evidence to suggest this region also contributes to emotional processes. For example, depressed individuals exhibited greater VLPFC activity while passively viewing positive facial stimuli intended to prompt them to think about a very positive autobiographical memory previously reported on a life events questionnaire, relative to neutral stimuli (4). Similarly, depressed individuals exhibited greater VLPFC activity during the presentation of positively valenced picture-caption pairs (relative to negatively valenced picture-caption pairs) relative to control subjects (5). Taken together, these findings suggest that when passively taking in/processing hedonic information, depressed individuals may have to work harder to integrate cognitive and emotional information about positive stimuli as a means to

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experience some level of happiness, whereas control subjects can experience a similar level of happiness with much less effort (6,7); and this process relates to overactivity in VLPFC.

In contrast, it may be easy for depressed individuals who are also anhedonic to downregulate positive affect. The neural circuits engaged during such a process should be determined so that methods can be developed to counteract the functioning of such a pleasure-dampening brain system, should it exist. Unlike trying to experience positive affect under normal circumstances, dampening positive affect may not require significant voluntary cognitive effort in depressed individuals (8). This may be a rather automatic process in individuals who are depressed. Therefore, we reasoned that greater activity in VLPFC when trying to get rid of positive emotion, hypothesized to be a marker of successful positive affect inhibition, may be a predictor of nonresponse to antidepressant treatment (i.e., greater VLPFC activity during passive exposure to positive stimuli or during effortful attempts to suppress positive emotion may both serve as indicators of poor ability to experience positive emotion). We suggest that some individuals prone to anhedonia (i.e., either individuals with MDD and anhedonia or individuals who experience anhedonia as a personality trait) unwittingly dampen their potential ability to experience positive emotion when exposed to everyday positive cues, and this may relate to an overactive cognitive control system in the brain.

Methods and Materials

Participants

Twenty-seven medication-free right-handed adults (age range = 19 – 53 years; mean age = 31.48 years, SD = 11.58; 12 male participants) who met DSM-IV diagnostic criteria for current major depressive disorder (single or recurrent episode) participated in this study. These participants were compared with a control group made up of 19 healthy control subjects (age range = 20 – 60 years; mean age = 31.84 years, SD = 14.65; 9 male participants). Individuals in the control group were selected to equate the groups for age and sex. Individuals with MDD had depressive symptoms for at least 1 month before their screening visit and a score of 18 or higher on the Hamilton Rating Scale for Depression (HRSD) at screening and at the time of the first functional magnetic resonance imaging (fMRI) scan. Participants met standard magnetic resonance imaging compatibility criteria. All participants were screened for and excluded if they 1) met DSM-IV criteria for alcohol or drug abuse/dependence, 2) had a personal or family history of bipolar disorder, or 3) were using any medication that affects central nervous system function. The research was approved by the University of Wisconsin-Madison Health Sciences Institutional Review Board. All participants provided written informed consent. Subjects participating in this study are the same as those who participated in a previous fMRI study (1).

Self-Report

All participants filled out the Mood and Anxiety Symptom Questionnaire (9,10) and the HRSD (11). The Mood and Anxiety Symptom Questionnaire Anhedonic Depression subscale (MASQ-AD) assesses an individual’s ability to experience positive emotions within the past week. There are 22 items that can each garner 1 to 5 points. The maximum obtainable score is 110; the minimum obtainable score is 22. Higher scores indicate greater inability to experience pleasure. The MASQ-AD scale was given a total of three times: at the time of the first fMRI scan (time 1 = T1) and at 8 weeks (time 2 = T2) and 6 months (time 3 = T3) after the first scan. The HDRS was given four times: at T1, T2, and T3 and also at the screening visit.

Antidepressant Medication

Individuals with MDD underwent double-blind randomization to one of two treatment groups: venlafaxine-ER or fluoxetine. Ten individuals with MDD were in the venlafaxine-ER group and 17 individuals with MDD were in the fluoxetine group at T1; 24 depressed individuals were still active in the study at T2. Nineteen individuals with MDD completed all three assessments: 9 in the venlafaxine-ER group and 10 in the fluoxetine group. Only fMRI data collected before pharmacotherapy began (i.e., at T1) were used in analyses.

Emotion Regulation Task

Participants were scanned at T1, T2, and T3, while viewing a sequence of 72 positive and 72 negative pictures taken from the International Affective Picture System. The 144 pictures included in this study were selected based on International Affective Picture System pleasantness and arousal norms (12). Pleasantness and arousal ratings for each picture ranged from 1 (most unpleasant/least arousing) to 9 (most pleasant/most arousing). The positive pictures included in this study had a mean pleasantness rating of 7.13 (SD = .62) and a mean arousal rating of 5.44 (SD = .80).

Stimuli were presented using E-Prime software (Psychology Software Tools, Pittsburgh, Pennsylvania) via a fiber-optic goggle system (Avotec, Stuart, Florida) with a screen resolution of 800 × 600 pixels. A 1-second fixation cross coupled with a tone oriented subjects to the upcoming trial. Each image was presented for 10 seconds, followed by a 6-second blank screen. Four seconds into picture presentation, an audio prompt instructed the participant to enhance or suppress their emotional response to the picture or maintain attention to the picture without altering their emotional reaction whatsoever (13,14). The same instructions described in Heller et al. (1) were given. There were 24 repetitions of the positive enhance, suppress, and maintain conditions evenly distributed over six scans, each lasting 380 seconds. For the suppress condition, participants were told to “Imagine that the image is unreal, from a movie or dream.” For example, in response to the picture of an ice cream cone, the participant could imagine that the ice cream cone was fake. Participants had to refract the positive image into something less pleasant.

Pupil Dilation

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, Boston, Massachusetts), which was interfaced with the fiber-optic goggle system. Pupil dilation data were processed using MatLab software (MathWorks, Natick, Massachusetts). For successive 500-millisecond 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 seconds after picture onset [current pupil diameter – minimum pupil diameter]/(maximum pupil diameter – minimum pupil diameter)]. Data were averaged across a 6-second interval starting at the onset of the regulation instruction and continuing until picture offset (i.e., the reappraisal period).

Self-Report During the Experimental Task

Participants had to judge, via button press, whether each image presented to them was positive or negative. This method was used as a means to ascertain the extent to which each participant was able to accurately take in hedonic information with minimal intro-
spective requirements. Participants were scored on accuracy and reaction time.

Image Acquisition

Brain images were collected on a General Electric 3 Tesla scanner (Waukesha, Wisconsin) equipped with a standard clinical whole-head transmit-receive quadrature head coil (33 × 4 mm sagittal T2-weighted gradient-echo echo-planar imaging slices; 1 mm interslice gap; 64 × 64 matrix; 240 mm field of view; repetition time/echo time/flip angle = 2000 milliseconds/30 milliseconds/60°; 219 whole-brain volumes per run). A high-resolution T1-weighted anatomical image was also acquired (T1-weighted inversion recovery fast gradient echo; 256 in-plane resolution; 240 mm field of view; 124 × 1.1 mm axial slices).

Image Analysis

Individual participant data were slice-time corrected, motion corrected, and analyzed in AFNI (15) using a general linear model with a separate regressor for each trial type, six motion estimate covariates (16), and a second-order polynomial used to model the baseline and slow signal drift. Regressors consisted of a set of five sine functions (16) to produce separate estimated hemodynamic response functions (HRFs) for each trial type. The estimated HRFs were converted to percent signal change values. A within-subject contrast—positive suppress minus positive maintain—was calculated for the depressed group. This contrast was calculated as the area under the curve of the estimated HRF for the period 8 seconds to 14 seconds poststimulus onset, chosen to correspond to the period of peak response. This area under the curve contrast was normalized to Talairach space using FLIRT (FMRIB Centre, Oxford, United Kingdom) (17) and entered into a voxel-wise random effects general linear model analysis. All resulting statistical maps were thresholded at \( p < .05 \), corrected for multiple comparisons using cluster size thresholding (\( k > 50 \)) based on Monte Carlo simulation (the AlphaSim program in AFNI) using a whole-brain mask.

Statistical Approach

Hierarchical linear modeling (18) was used to chart anhedonia trajectory. Hierarchical linear modeling is a type of multilevel analysis and has been used with electrophysiological data previously (19,20). Our level 1 model estimated the association between anhedonia score and time elapsed (i.e., T1, T2, and T3). Our level 2 model introduced prefrontal cortex activity in the depressed group during the positive suppress condition minus the positive maintain condition to explain individual differences in anhedonia trajectory. A linear model was built. Each within-epoch linear function was treated as a random factor, allowing the linear slope to vary between participants. The intercept was treated as a fixed factor to maximize our ability to discern treatment-dependent changes in trajectory between participants. The anhedonia trajectory during each epoch was characterized as follows: 1) anhedonia (MASQ-AD) score at time \( x = P_0 + P_1 \) (depressed individual’s prefrontal positive suppress – positive maintain percent signal change score @ T1) + error; and 2) anhedonia (MASQ-AD) score at time \( y = P_0 + P_2 \) (depressed individual’s prefrontal positive suppress – positive maintain percent signal change score @ T1) + error.

Results

The depressed group had a mean MASQ-AD score of 85.12 (SD = 9.23) at T1, with scores ranging from 66 to 103. The mean MASQ-AD score for depressed individuals was 63.35 (SE = 4.15) and 56.29 (SE = 2.99) at T2 and T3, respectively. In contrast, the control group had a mean MASQ-AD score of 39.75 (SD = 8.23) at T1, with scores...

**Figure 1.** (A) Repeated measures analysis of variance. A main effect of group (\( p < .001 \)) and a main effect of time (\( p < .001 \)) emerged. Furthermore, the group \( \times \) time interaction was significant (\( p < .001 \)). Control subjects had lower anhedonia scores relative to individuals with major depressive disorder (MDD) at all three time points (all \( ps < .05 \)). Individuals with MDD exhibited a significant reduction in anhedonia from time 1 to time 2 (\( ps < .01 \)) but not from time 2 to time 3 (\( ps > .10 \)). (B) Right ventrolateral prefrontal cortex (RVLPFC) cluster derived from the MDD group positive suppress – positive maintain contrast (Montreal Neurological Institute coordinates: \( x = 25, y = -29, z = -16 \); 1034 voxels). There was a significant regulation effect \( (F_{1,45} = 28.01; p < .001) \), a group effect \( (F_{1,45} = 4.0; p = .05) \), and a nonsignificant group \( \times \) regulation effect \( (F_{1,45} = 1.27; p = .27) \). Greater RVLPFC activity during the positive suppress condition versus the positive maintain condition may reflect cognitive control processes and the inhibition of the prepotent response to freely experience positive emotion. The disruption of this process is associated with reductions in anhedonia. MASQ, Mood and Anxiety Symptom Questionnaire.

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We first confirmed that individuals with MDD differed from control subjects in anhedonia level and investigated whether there was any significant drug effect (Figure 1A). We found that drug type did not predict change in anhedonia over time \((p > .05)\). Next, given the significant group \(\times\) time interaction \(F(1,27) = 14.17; p < .001\); Figure 1A), we investigated how prefrontal cortex activity during the instruction to dampen positive emotion (relative to the maintain condition) may relate to change in anhedonia in depressed individuals. Therefore, a direct contrast of whole brain activity in the positive suppress condition relative to the positive maintain condition completed for the depressed group. We found that depressed participants showed greater activation in right VLPFC (RVLPFC) \((p < .05\), corrected for multiple comparisons, peak activation \(x = 25, y = -29, z = -16\); 1034 voxels; Figure 1B) and DMPFC \((p < .05\), corrected for multiple comparisons, peak activation \(x = 9, y = -31, z = 26\); 782 voxels) during the positive suppress condition relative to the positive maintain condition. Control subjects also showed greater activation in the positive suppress condition relative to the positive maintain condition in the same RVLPFC cluster identified in the depressed group (Figure 1B).

Next, we used hierarchical linear modeling to investigate whether the above-mentioned prefrontal activations during the positive suppress condition relative to the positive maintain condition predicted anhedonia trajectory over time. We built a linear model, entering DMPFC and RVLPFC activity derived from the positive suppress minus positive maintain condition as predictors of anhedonia (MASQ-AD) trajectory (Table 1). Both prefrontal clusters were entered into the model to determine each region’s unique contribution to anhedonia change. Right VLPFC activity exerted a unique effect on anhedonia slope between T1 and T2 such that lesser RVLPFC activity at T1 during the positive suppress condition relative to the positive maintain condition predicted greater reduction in anhedonia over the first 8 weeks of antidepressant treatment \((\beta = 1.51, p < .05); Table 1, Figure 2\). This finding is in contrast to the overall finding that control subjects and depressed participants exhibited increased activity in RVLPFC during the positive suppress condition relative to the positive maintain condition (Figure 1B).

Utilizing a formula described by Snijders and Bosker (21), it was determined that 61% of the variance in MASQ-AD score change (in depressed individuals) was accounted for by differences in RVLPFC activity at T1 during the positive suppress condition relative to the positive maintain condition.

### Table 1. Hierarchical Linear Model of Prefrontal Activity Predicting Anhedonia Over Time

<table>
<thead>
<tr>
<th>Model Components</th>
<th>Coefficient Estimate</th>
<th>Predictors</th>
<th>Predictor Coefficient Estimate</th>
<th>Standard Error</th>
<th>Approximate df</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\beta_{0}), Intercept</td>
<td>73.06</td>
<td>Depressed individuals RVLPFC activity during the positive suppress minus positive maintain condition</td>
<td>-1.69</td>
<td>1.41</td>
<td>38</td>
<td>.240</td>
</tr>
<tr>
<td>(\beta_{1}(T1 \to T2))</td>
<td>-6.90</td>
<td>Depressed individuals RVLPFC activity during the positive suppress minus positive maintain condition</td>
<td>1.51</td>
<td>1.78</td>
<td>13</td>
<td>.002</td>
</tr>
<tr>
<td>(\beta_{2}(T2 \to T3))</td>
<td>-.53</td>
<td>Depressed individuals RVLPFC activity during the positive suppress minus positive maintain condition</td>
<td>-.39</td>
<td>.87</td>
<td>13</td>
<td>.664</td>
</tr>
</tbody>
</table>

RVLPFC activity during the positive suppress minus positive maintain condition positively predicted the anhedonia slope from T1 to T2. The lower the activity in RVLPFC during the positive suppress condition relative to the positive maintain condition, the greater the reduction in anhedonia from T1 to T2 \((\beta = 1.51, p < .05)\).

DMPFC, dorsomedial prefrontal cortex; RVLPFC, right ventrolateral prefrontal cortex; T1, time 1; T2, time 2; T3, time 3.

Figure 2. Examples of actual anhedonia trajectories for depressed individuals who exhibited high (those depressed individuals with the top 4% signal change scores) and low (those depressed individuals with the bottom 4% signal change scores) right ventrolateral prefrontal cortex (RVLPFC) activity during the positive suppress condition relative to the positive maintain condition. This graph depicts the finding of the hierarchical linear model and is provided for illustrative purposes only. MASQ, Mood and Anxiety Symptom Questionnaire.
Additional Hierarchical Linear Modeling Analyses

The T1 to T3 model proved to be a better model, as the T1 to T2 model accounted for less variance (i.e., 32%). Though DMPFC activity did not significantly predict change in anhedonia as RVLPCF activity did, the marginal effect of DMPFC activity from T2 to T3 \( (p = .09) \) suggests that activation in this region may interact with RVLPCF activation to influence anhedonia change over time, supporting previous findings relating DMPFC activity to aspects of anhedonia \( (1) \).

Furthermore, again using the formula suggested by Snijders and Bosker \( (21) \), we found that 0% of the variance in HRSD score from T1 to T2 was accounted for by differences in RVLPCF activity during the positive suppress condition relative to the positive maintain condition at T1. Therefore, RVLPCF activity while attempting to suppress positive emotion relates specifically to changes in anhedonia rather than change in general symptoms of depression.

Lastly, we wanted to determine whether individual differences in activation pattern—derived from the exact same RVLPCF cluster (at time 1) described in Figure 1B—during the attempted suppression of negative emotion during our emotion regulation task also predicted change in MASQ-AD score over time, just as the attempted suppression of positive emotion did. We then compared the effect sizes of the two models. Toward this end, the percent signal change scores from the negative suppress minus negative maintain condition were derived from the exact same RVLPCF cluster displayed in Figure 1B. We found that RVLPCF activity during the attempted suppression of negative affect did not significantly predict anhedonia slope \( (\text{all } p > .05) \), and 0% of the variance in MASQ-AD score change was accounted for by differences in RVLPCF activity during the negative suppress condition relative to the negative maintain condition at T1. This suggests that RVLPCF activity during the active attempt to dampen positive emotion is uniquely related to changes in anhedonia over time.

Analysis with Control Subjects

To determine whether control subjects exhibited a similar relationship between anhedonia change and RVLPCF activity during the positive suppress condition relative to the positive maintain condition, we ran a regression analysis. We found a trend for greater RVLPCF activity to predict an increase in anhedonia in control subjects from T1 to T3 \( (r^2 = .26\%, p = .05; \text{Figure 3}) \). This pattern is in the same direction as that found in depressed individuals. Right VLPFC activity did not predict an increase in anhedonia in control subjects from T1 to T2 \( (r^2 = .2\%, p = .60) \).

Button Press

Control subjects (mean = 94% accuracy rate, SD = .08) and depressed individuals (mean = 90% accuracy rate, SD = .11) were equally able to accurately identify the positive pictures as positive via button press \( (p = .31) \), and control subjects (mean = 1.26 seconds, SD = .29) and depressed individuals (mean = 1.34 seconds, SD = .38) did not differ on the amount of time it took to accurately decide that a picture was positive \( (p = .24) \). These two findings suggest control subjects and depressed individuals were both able to decode the hedonic information presented to them.

Pupil Dilation

It is possible that increased RVLPCF activity during the positive suppress condition relative to the positive maintain condition indicates that depressed individuals (and healthy control subjects) were generally engaged in a more effortful process when attempting to suppress positive affect. If so, depressed individuals (and control subjects) would be expected to show parallel differences in measures sensitive to effort, motivation, and/or workload, such as pupil dilation \( (14) \). Therefore, a repeated measures analysis of variance—group (depressed or control) × pupil dilation (positive maintain versus positive suppress)—was performed. There was no group \( (p > .05) \) or pupil dilation \( (p > .05) \) effect, suggesting that the passive experience of positive emotion versus the attempted suppression of it require similar amounts of mental effort across groups.

Treatment Completers Versus Noncompleters

Table 2 shows the results of an analysis of variance run to compare the characteristics of venlafaxine completers (and noncompleters) to fluoxetine completers (and noncompleters). There were no significant differences between groups \( (\text{all } p \geq .06) \).

Discussion

The greatest percent reduction in anhedonia over the course of 8 weeks of treatment with antidepressant medication occurred among those depressed individuals showing the lowest RVLPCF activity during the positive suppress condition relative to the positive maintain condition during a positive emotion regulation task \( (\text{Table 1, Figure 2}) \). This finding suggests that lower RVLPCF activity during the positive suppress condition is more normal, and less RVLPCF dysfunction at T1 is associated with reduction in anhedonia by T2. Those who exhibit more RVLPCF activity during the positive suppress condition may be recruiting more cortical resources as a means to successfully suppress positive affect.

In general, the attempt to suppress positive affect may recruit RVLPCF because the task requires a certain level of cognitive control. For example, in healthy control subjects, the ability to suppress positive emotion likely requires an ability to halt the prepotent tendency to fully experience or even relish in positive emotion in response to everyday positive stimuli, and RVLPCF and related cognitive control circuitry may be recruited to carry out this task successfully. In contrast, the symptom of anhedonia may result when an overactive cognitive control system acts relatively consistently and automatically, disrupting the person’s ability to freely experience positive affect in response to changing positive stimuli.
Lesser RVLPFC activity while trying to suppress positive emotion is conceptually similar to lesser RVLPFC activity observed in many other studies during a no-go trial of a go/no-go task. In the present context, those depressed individuals who exhibited lesser RVLPFC activity may have made more errors. In other words, they experienced more breakthrough positive affect—or positive affect generated in spite of the instruction not to—which is positive prognostically. For example, in response to a picture of an ice cream cone, those depressed individuals who can maintain a positive perspective on the image despite the verbal instruction to suppress their positive emotion, show a greater reduction in anhedonia over time. This can be thought of as positive affect resiliency. Importantly, our data also showed that control subjects exhibited a similar trend (Figure 3).

When combined with previous results indicating that depressed individuals inappropriately engage lateral PFC-ventromedial PFC-amygdala inhibitory circuitry during attempts to downregulate negative emotion (2), the present findings suggest that too much VLPFC activity is problematic for individuals who are depressed and 1) relates to an inability to downregulate negative emotion appropriately, resulting in the experience of excessive negative affect (2); 2) relates to a keen ability to inhibit positive affect, resulting in a reduced ability to experience pleasure (supporting evidence herein); and 3) may make the experience of any degree of positive emotion an effortful task (1,4,5).

Right VLPFC activity during attempts to dampen positive affect is selectively related to changes in anhedonia, as activation in the same region during attempts to suppress negative affect did not predict reduction in anhedonia and RVLPFC activity during the positive suppress condition did not predict change in general symptoms of MDD as measured by the HRSD.

Ultimately, the present results suggest that we have the ability to inhibit positive affect, whether intentional or unintentional. Effortful resistance to this inhibitory effect may be an important positive predictor of the transition from anhedonia to euthymia. When treating anhedonia, it may not be sufficient to increase the number/frequency/duration of pleasurable activities a depressed individual engages in, as espoused by behavioral activation therapies. Anhedonic individuals may also need training in how not to subvert the generation/experience of positive emotions once they are in contact with positive stimuli. Anhedonic individuals may benefit from learning to recognize, and mentally argue against, pleasure-dampening thoughts/appraisals/behaviors (e.g., engaging in an activity but telling oneself “this activity won’t be enjoyable” or flatly thinking “I don’t deserve a reward” or “my achievement isn’t really that great”) before the initiation of and during the engagement of a potentially rewarding activity (22).

Recent advances in social cognition/affective neuroscience research, such as the emergence of the concept of positive empathy (20)—the tendency to vicariously share in the positive emotion of another person (i.e., empathic happiness) or the tendency to use positive emotion as a means to cheer up someone who is in a negative or neutral mood state (i.e., empathic cheerfulness)—may provide a useful framework for developing novel treatments for anhedonia. Incorporating findings from recent empathy research, a behavioral therapist working collaboratively with an anhedonic individual could engage in any of the following activities with his/her client to augment traditional cognitive behavioral and/or dialectical behavioral techniques: 1) engage the client in pleasurable activities in-session to reveal dampening tendencies and then actively implement/practice positive empathy and savoring techniques to disrupt such tendencies (e.g., watch a video excerpt together and then collaboratively reflect on/share in/discuss the most enjoyable features of the stimulus/activity from the point of view of the client and therapist—a strategy that should also model/teach/encourage the client to derive personal pleasure even from pedestrian activities); 2) the therapist can remind/teach the client that different positive emotions exist (e.g., joy, contentment, etc.), and the dyad can work to increase the amount of time the client spends in each positive emotional state—i.e., not just one or two to the exclusion of others—via the development of an individualized pleasurable activities list that will help the client to generate ideas about and choose activities that will lead to the experience of a particular target positive emotion (e.g., joy vs. gratitude vs. interest) or set of positive emotions that are underused or even foreign to the client; and 3) the dyad can also work to decrease positive emotion inhibition in the client by increasing his/her ability to vicariously experience positive emotion on a global level via adding simple practices to their daily life, such as soliciting positive information from others on a regular basis (e.g., “tell me something good that happened to you today”) or by doing something good for another person or the planet (e.g., volunteering, recycling, etc.) (23). Mastering any one of these skills may increase well-being and combat the development/maintenance/recurrence of anhedonia.

There are two main limitations that should be noted. First, the absence of a placebo control group does not allow us to differentiate between specific and nonspecific drug responses. It remains unknown to what extent the MDD group might have improved independent of drug treatment. Furthermore, the depressed group and the control group may have differed in terms of hedonic decoding ability. Though our button press accuracy data provide some evidence to the contrary, our data could be limited by a

<table>
<thead>
<tr>
<th></th>
<th>Fluoxetine Completers</th>
<th>Fluoxetine Noncompleters</th>
<th>Venlafaxine Completers</th>
<th>Venlafaxine Noncompleters</th>
<th>Significance</th>
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<td>Age</td>
<td>31.95</td>
<td>35.48</td>
<td>30.82</td>
<td>36.20</td>
<td>p = .88</td>
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<td>RVLPFC Activity During the Positive Suppress Condition Relative to the Positive Maintain Condition at T1</td>
<td>.24%</td>
<td>.19%</td>
<td>.17%</td>
<td>.40%</td>
<td>p = .34</td>
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<tr>
<td>MASQ-Anhedonic Depression Score at T1</td>
<td>84.43</td>
<td>84.25</td>
<td>76.40</td>
<td>93.60</td>
<td>p = .06</td>
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<tr>
<td>MASQ-Anhedonic Depression Score at T2</td>
<td>69.38</td>
<td>75.67</td>
<td>59.10</td>
<td>60.00</td>
<td>p = .32</td>
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<tr>
<td>MASQ-Anhedonic Depression Score at T3</td>
<td>62.50</td>
<td>—</td>
<td>53.80</td>
<td>—</td>
<td>p = .21</td>
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<td>HRSD Score at T1</td>
<td>20.67</td>
<td>20.25</td>
<td>20.80</td>
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<tr>
<td>HRSD Score at T2</td>
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<td>12.00</td>
<td>8.80</td>
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<td>HRSD Score at T3</td>
<td>5.67</td>
<td>—</td>
<td>2.50</td>
<td>—</td>
<td>p = .40</td>
</tr>
</tbody>
</table>

HRSD, Hamilton Rating Scale for Depression; MASQ, Mood and Anxiety Symptom Questionnaire; RVLPFC, right ventrolateral prefrontal cortex; T1, time 1; T2, time 2; T3, time 3.
ceiling effect. Further studies will need to be conducted to more rigorously rule out this factor.

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Supplementary material cited in this article is available online.