Published in final edited form as:
Biol Psychiatry. 2011 November 15; 70(10): 962–968. doi:10.1016/j.biopsych.2011.06.031.

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

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Abstract

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Financial Disclosures: Sharee N. Light, Aaron S. Heller, Tom Johnstone, Michael J. Peterson, Gregory G. Kolden and Richard J. Davidson reported no biomedical financial interests or potential conflicts of interest. Dr. Ned H. Kalin is a consultant related to the development of psychotropic agents (or serves on the Scientific Advisory Board) for the following companies: Astra Zeneca, Bristol-Myers-Squibb, CeNeRx Biopharma, Corcept, Cyberonics, Forest Laboratories, General Electric Corp., Jazz Pharmaceuticals, Eli Lilly, Neuronetics, Sanofi Syntholabs, and Wyeth Pharmaceuticals. Wyeth Pharmaceuticals funded this study. Dr. Ned H. Kalin has stock options in Corcept and CeNeRx and is principal owner of Promoter Neurosciences.

Background—Anhedonia, a reduced ability to experience pleasure, is a chief symptom of Major Depressive Disorder (MDD) and is related to reduced fronto-striatal connectivity when attempting to up-regulate positive emotion. The present study examined another facet of positive emotion regulation associated with anhedonia—namely, the down-regulation of positive affect—and its relation to prefrontal cortex (PFC) activity.

Method—Neuroimaging data were collected from 27 individuals meeting criteria for MDD as they attempted to suppress positive emotion during a positive emotion regulation task. Their PFC activation pattern was compared to the PFC activation pattern exhibited by 19 healthy controls 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). PFC activity at Time 1 was used to predict change in anhedonia over time. Analyses were conducted utilizing hierarchical linear modeling (HLM) software.

Results—Depressed individuals who could not inhibit positive emotion—evinced by reduced right ventrolateral prefrontal cortex (RVLPFC) 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 ($p<.05$). Controls 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.

Keywords

anhedonia; prefrontal cortex; positive emotion regulation; positive empathy; Major Depressive Disorder; cognitive control

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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 MDD are impaired in their ability to sustain the up-regulation of positive affect by cognitive means, and this is associated with reduced dorsomedial prefrontal cortex-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 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 non-conscious 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 controls (5). Taken together, these findings suggest that depressed individuals may have to work *harder* to integrate cognitive and emotional information about positive stimuli as a means to experience some level of happiness, whereas controls can experience a similar level of happiness with much less effort (6–7).

In contrast, it may be *easy* for depressed individuals who are also anhedonic to down-regulate 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 non-response to antidepressant treatment. 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

27 medication-free right-handed adults (age range=19–53 years; mean age=31.48 years, *SD*=11.58; 12 males) who met DSM-IV diagnostic criteria for current Major Depressive Disorder (single or recurrent episode) participated in this study. These participants were compared to a control group made up of 19 healthy controls (age range=20–60 years; mean age=31.84, *SD*=14.65; 9 males). 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 prior to 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 fMRI scan. Participants met standard MRI compatibility criteria. All participants were screened for and excluded if they (a) met DSM-IV criteria for alcohol or drug abuse/dependence, (b) had a personal or family history of bipolar disorder, or (c) 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 (MASQ) (9–10) and the HRSD (11). The *Anhedonic Depression* (MASQ-AD) subscale 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 is 22. Higher scores indicate greater *inability* to experience pleasure. The MASQ-AD scale was given a total of 3 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 4 times, at T1, T2 and T3, and also at the screening visit.

Antidepressant medication

Individuals with MDD underwent double-blind randomization to 1 of 2 treatment groups: venlafaxine-ER or fluoxetine. 10 individuals with MDD were in the venlafaxine-ER group,

17 individuals with MDD were in the fluoxetine group at T1; 24 depressed individuals were still active in the study at T2. 19 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 (IAPS). The 144 pictures included in this study were selected based on IAPS 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*=0.62), and a mean arousal rating of 5.44 (*SD*=0.80).

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 800×600 pixels. A 1 s fixation cross coupled with a tone oriented subjects to the upcoming trial. Each image was presented for 10 s, followed by a 6 s 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. were given (1). There were 24 repetitions of the positive “enhance,” “suppress,” and “maintain” conditions evenly distributed over six scans, each lasting 380 s. 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 sundae, the participant could imagine that the ice cream cone was fake. Participants had to reframe 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), which was interfaced with the fiber optic goggle system. Pupil dilation data were processed using MatLab software (MathWorks). 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 6 s 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 introspective requirements. Participants were scored on accuracy and reaction time.

Image acquisition

Brain images were collected on a General Electric 3 Tesla scanner (Waukesha, WI) equipped with a standard clinical whole-head transmit-receive quadrature head coil (33 × 4mm sagittal T2-weighted gradient-echo EPI slices; 1 mm interslice gap; 64×64 matrix; 240mm FOV; TR/TE/Flip = 2000 ms/ 30 ms/ 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 FOV; 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 (GLM) with a separate regressor for each trial type, six motion estimate covariates (Cox, 1996), 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 (AUC) of the estimated HRF for the period 8s to 14s post-stimulus onset, chosen to correspond to the period of peak response. This AUC contrast was normalized to Talairach Space using FLIRT (17), and entered into a voxel-wise random effects GLM analysis. All resulting statistical maps were thresholded at $p<0.05$, 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) (HLM) was used to chart anhedonia trajectory. Hierarchical linear modeling is a type of multilevel analysis, and has been used with electrophysiological data before (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 = P0 + P1 (depressed individual's prefrontal "positive suppress" − "positive maintain" percent signal change score @ T1) + error.
2. Anhedonia (MASQ-AD) score at time y = P0 + P2 (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 66–103. The mean MASQ-AD score for depressed individuals was 63.35 (s.e. = 4.15) and 56.29 (s.e. = 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 ranging from 27–56. The mean HRSD score for depressed individuals was 21.19 (s.e. = 54), 8.56 (s.e. = .87), and 5.12 (s.e. = 1.92) at T1, T2 and T3, respectively.

We first confirmed that individuals with MDD differed from controls 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 × 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 was completed for the depressed group. We found that depressed participants showed greater activation in right VLPFC ($p<.05$, corrected for multiple comparisons, peak activation x=25, y=−29, z=−16; 1034 voxels; Figure 1B) and dorsomedial prefrontal cortex (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" contrast 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. RVLPFC 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 controls *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.

Additional HLM 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 RVLPFC activity did, the marginal effect of DMPFC activity from T2 to T3 ($p=.09$) suggests that activation in this region may interact with RVLPFC 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 RVLPFC activity during the positive suppress condition relative to the positive maintain condition at T1. Therefore, RVLPFC 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 RVLPFC 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-Anhedonic Depression 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 RVLPFC cluster displayed in Figure 1B. We found that RVLPFC activity during the attempted suppression of negative

affect did not significantly predict anhedonia slope (all *p*'s >.05), and 0% of the variance in MASQ-AD score change was accounted for by differences in RVLPFC activity during the *"negative suppress"* condition relative to the *"negative maintain"* condition at T1. This suggests that RVLPFC activity during the active attempt to *dampen positive emotion* is *uniquely* related to changes in anhedonia over time.

Analysis with controls

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

Button press

Controls (*M*=94% accuracy rate, *SD*=.08) and depressed individuals (*M*=90% accuracy rate, *SD*=.11) were equally able to accurately identify the positive pictures as positive via button press (*p*=.31); and controls (*M*=1.26 s, *SD*=.29) and depressed individuals (*M*=1.34 s, *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 controls and depressed individuals were both able to decode the hedonic information presented to them.

Pupil dilation

It is possible that increased RVLPFC activity during the positive suppress condition relative to the positive maintain condition indicates that depressed individuals (and healthy controls) were generally engaged in a more effortful process when attempting to suppress positive affect. If so, depressed individuals (and controls) 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 ANOVA—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 vs. Non-completers

Table 2 shows the results of an ANOVA run to compare the characteristics of venlafaxine-ER completers (and non-completers) to fluoxetine completers (and non-completers). There were no significant differences between groups (all *p*'s ≥ .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* RVLPFC activity during the positive suppress condition relative to the positive maintain condition during a positive emotion regulation task (Table 1, Figure 2). This finding suggests that *lower* RVLPFC activity during the positive suppress condition is more "normal," and less RVLPFC dysfunction at T1 is associated with reduction in anhedonia by T2. Those who exhibit more RVLPFC 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 RVLPFC because the task requires a certain level of cognitive control. For example, in healthy controls, the ability to

suppress positive emotion likely requires an ability to halt the pre-potent tendency to fully experience or even relish in positive emotion in response to everyday positive stimuli, and RVLPFC 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 controls 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 *down* regulate negative emotion (2), the present findings suggest that *too much* VLPFC activity is problematic for individuals who are depressed, and a) relates to an inability to down-regulate negative emotion appropriately, resulting in the experience of excessive negative affect (2), b) relates to a keen ability to inhibit positive affect, resulting in a reduced ability to experience pleasure (supporting evidence herein), and c) may make the experience of any degree of positive emotion an effortful task (1, 4–5).

RVLPFC 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: a) 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); b) 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 1 or 2 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 "under-used" or even "foreign" to the client; c) 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 non-specific 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 provides some evidence to the contrary, our data could be limited by a ceiling effect. Further studies will need to be conducted to more rigorously rule this factor out.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank Michael Anderle and Ron Fisher for technical support. This work was supported by National Institutes of Health Grants: P50 MH069315 and R01 MH043454-19 (to Richard J. Davidson). Additional support was provided by Wyeth-Ayerst Pharmaceuticals (to Ned H. Kalin), and grants from the Fetzer Institute.

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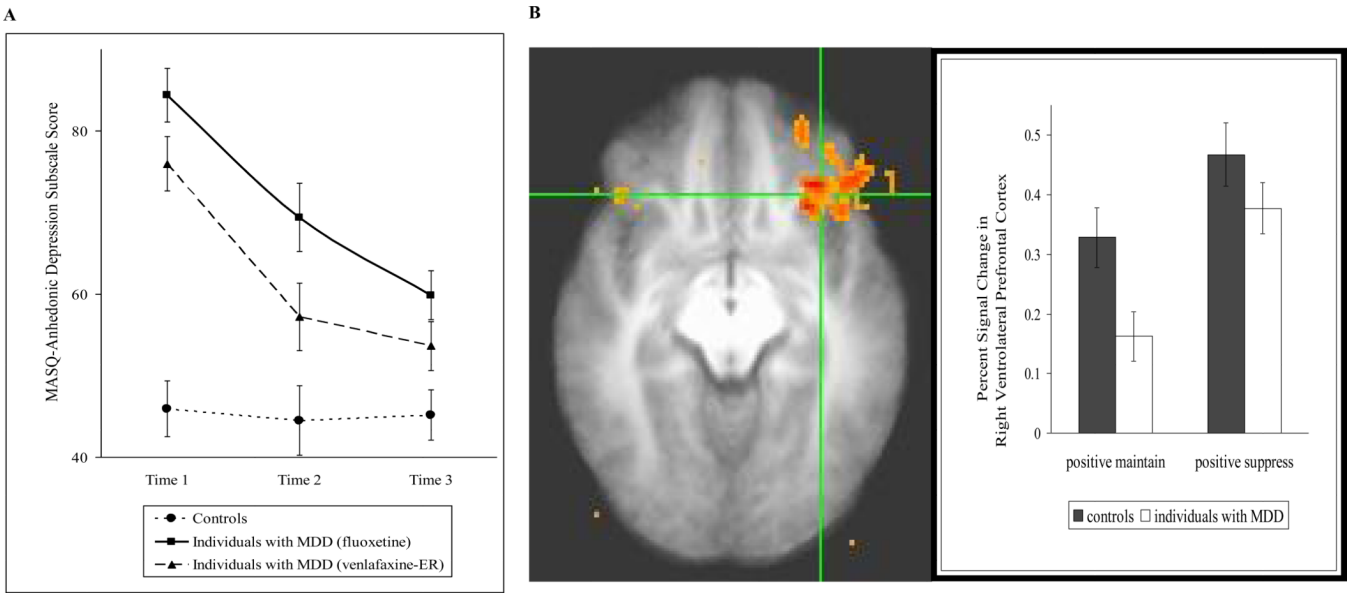

Figure 1.

(A) Repeated Measures ANOVA. A main effect of group (p<.001) and a main effect of time (p<.001) emerged. Furthermore, the group × time interaction was significant (p<.001). Controls had lower anhedonia scores relative to individuals with MDD at all 3 time points (all ps<.05). Individuals with MDD exhibited a significant reduction in anhedonia from T1 to T2 (ps<.01), but not from T2 to T3 (ps>.10). (B) RVLPFC cluster derived from the MDD group "positive suppress" – "positive maintain" contrast (MNI 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 non-significant group × regulation effect (F(1,45)=1.27; p=.27). Greater RVLPFC activity during the "positive suppress" condition vs. the "positive maintain" condition may reflect cognitive control processes and the inhibition of the pre-potent response to freely experience positive emotion. The disruption of this process is associated with reductions in anhedonia.

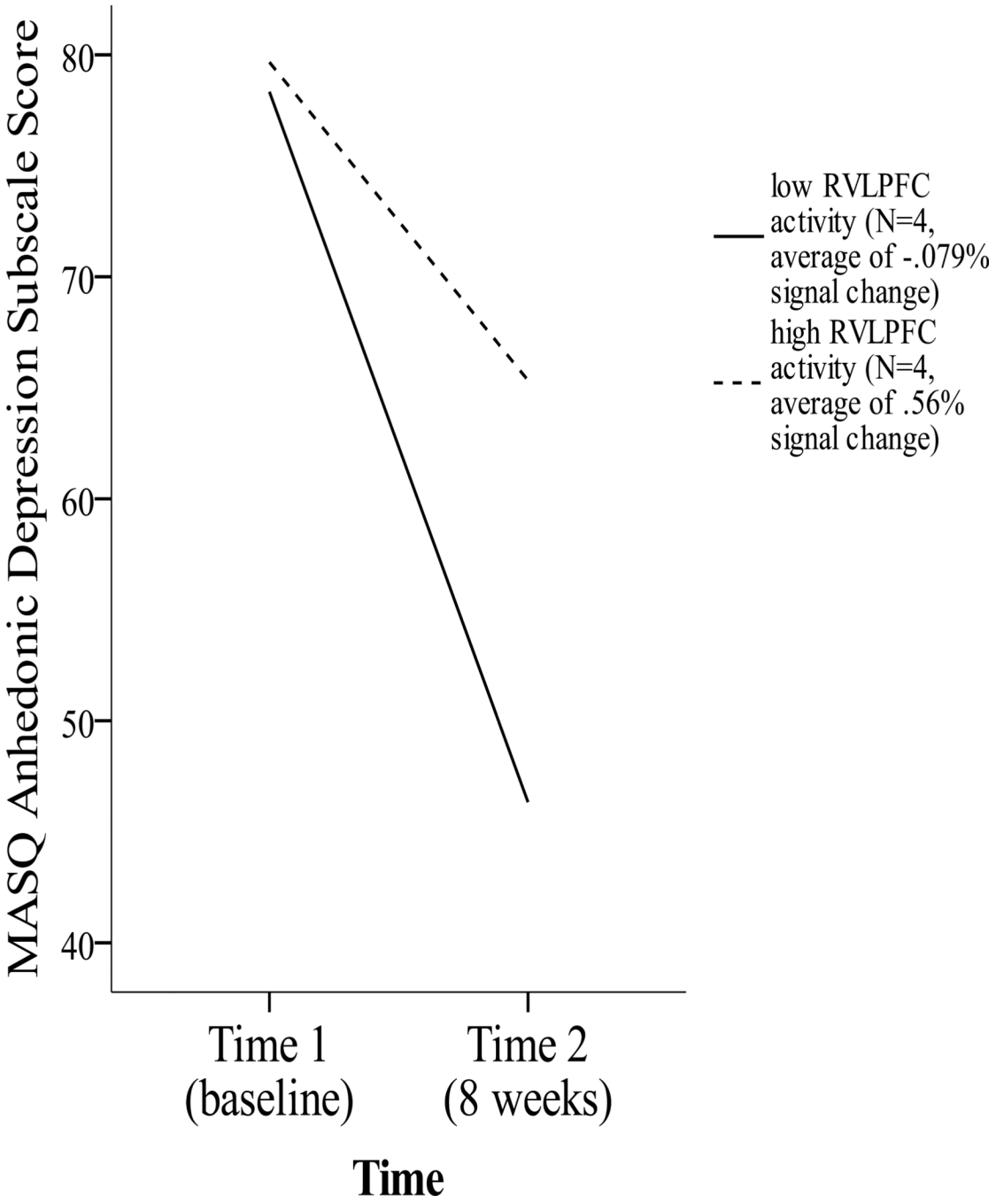

Figure 2.
Examples of actual anhedonia trajectories for depressed individuals who exhibited high (those depressed individuals with the top 4 percent signal change scores) and low (those depressed individuals with the bottom 4 percent signal change scores) RVLPFC activity during the “positive suppress” condition relative to the “positive maintain” condition. This graph depicts the finding of the HLM model and is provided for illustrative purposes only.

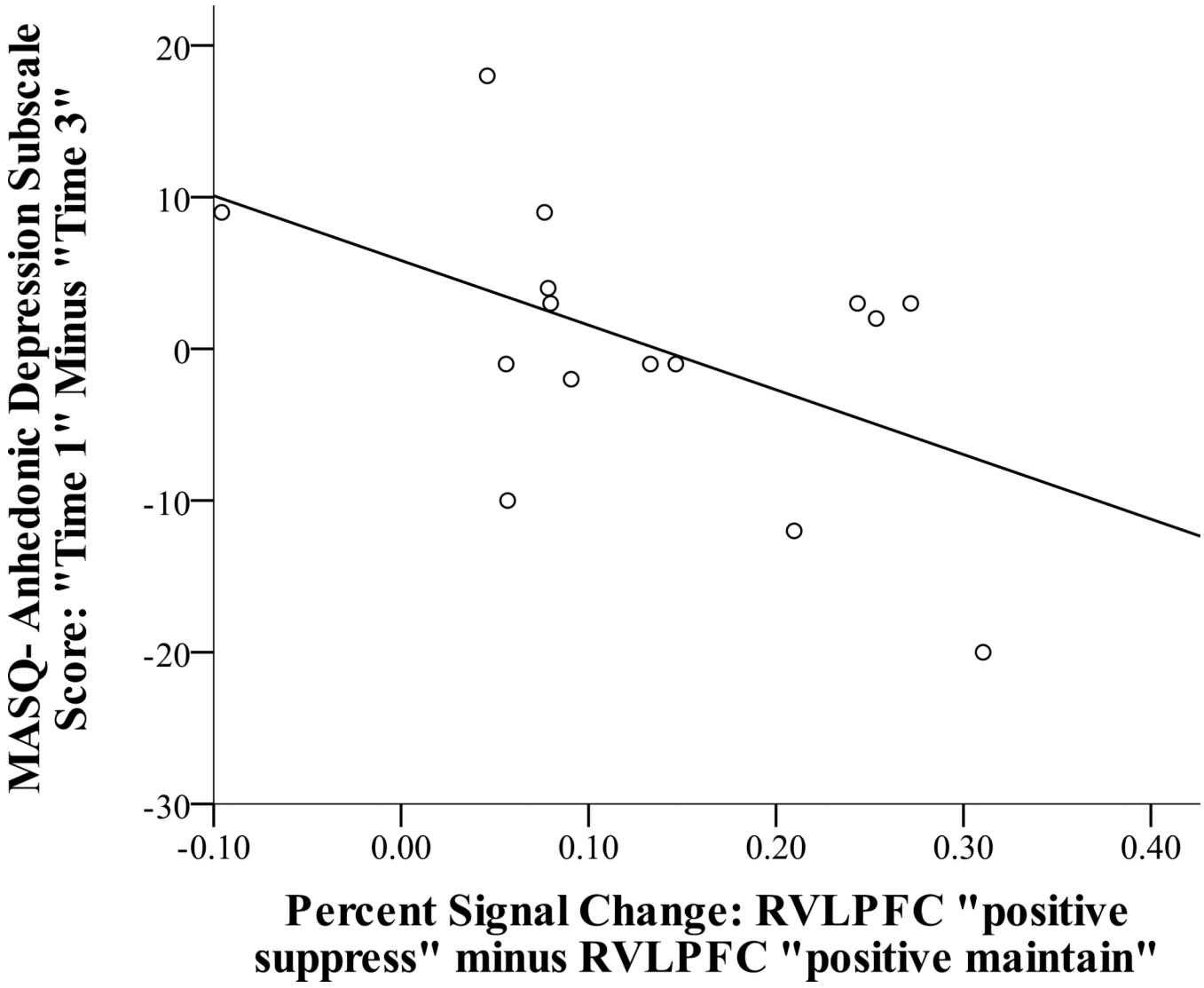

Figure 3.
In controls, the less RVLPFC activity shown at T1 during the “positive suppress” condition relative to the “positive maintain” condition, the greater the reduction in anhedonia from T1 to T3 (p=.05; r^2=26%).

Table 1

Hierarchical linear model (HLM) of prefrontal activity predicting anhedonia over time. 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 (β = 1.51, $p<.05$).

Model components	β coefficient estimate	Predictors	Predictor β coefficient estimate	Standard error	Approx. df	*p*-value
β_{00} intercept	73.06	*Depressed individuals RVLPFC activity during the "positive suppress" minus "positive maintain" condition*	−1.69	1.41	38	.240
		Depressed individuals DMPFC activity during the "positive suppress" minus "positive maintain" condition	−1.48	2.00	13	.753
β_{10} (T1 to T2)	−6.90	*Depressed individuals RVLPFC activity during the "positive suppress" minus "positive maintain" condition*	1.51	1.78	13	**.002**
		Depressed individuals DMPFC activity during the "positive suppress" minus "positive maintain" condition	−.39	.87	13	.664
β_{20} (T2 to T3)	−.53	*Depressed individuals RVLPFC activity during the "positive suppress" minus positive maintain" condition*	.05	.04	13	.297
		Depressed individuals DMPFC activity during the "positive suppress" minus "positive maintain" condition	−.11	.06	13	.090

Biol Psychiatry. Author manuscript; available in PMC 2012 November 15.

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Table 2

Characteristics of Treatment Completers vs. Non-completers.

	Fluoxetine Completers	Fluoxetine Non-Completers	Venlafaxine Completers	Venlafaxine Non-Completer	significance
Age	31.95	35.48	30.82	36.20	$p = .88$
RVLPFC activity during the positive suppress condition relative to the positive maintain condition at T1	.24%	.19%	.17%	.40%	$p = .34$
MASQ-Anhedonic Depression score at T1	84.43	84.25	76.40	93.60	$p = .06$
MASQ-Anhedonic Depression score at T2	69.38	75.67	59.10	60.00	$p = .32$
MASQ-Anhedonic Depression score at T3	62.50	---	53.80	---	$p = .21$
HRSD score at T1	20.67	20.25	20.8	22.6	$p = .52$
HRSD score at T2	5.8	12.00	8.80	8.5	$p = .10$
HRSD score at T3	5.67	---	2.50	---	$p = .40$