Published in final edited form as:
Biol Psychiatry. 2009 November 1; 66(9): 886–897. doi:10.1016/j.biopsych.2009.06.021.

The Effects of Psychotherapy on Neural Responses to Rewards in Major Depression

Gabriel S. Dichter[A,B,C,D,*], **Jennifer N. Felder**[B], **Christopher Petty**[E], **Joshua Bizzell**[A,B,C], **Monique Ernst**[F], and **Moria J. Smoski**[D]

[A]Department of Psychiatry, University of North Carolina at Chapel Hill School of Medicine, CB# 7160, Chapel Hill, NC 27599-7160

[B]Neurodevelopmental Disorders Research Center, University of North Carolina at Chapel Hill School of Medicine, CB# 3366, 101 Manning Drive, Chapel Hill, NC 27599-7160

[C]Duke-UNC Brain Imaging and Analysis Center, Duke University Medical Center, Durham, NC, 27710

[D]Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Box 3026, Durham NC 27710

[E]Mental Illness Research Education and Clinical Center, Durham VA Medical Center, Durham, NC 27710

[F]The Mood and Anxiety Disorders Program, NIMH/NIH, Department of Health and Human Services, Bethesda, MD

Abstract

Background—Unipolar major depressive disorder (MDD) is characterized by anomalous neurobiological responses to pleasant stimuli, a pattern that may be linked to symptoms of anhedonia. However, the potential for psychotherapy to normalize neurobiological responses to pleasant stimuli has not been evaluated.

Methods—Twelve adults with and 15 adults without MDD participated in two identical functional magnetic resonance imaging (fMRI) scans that utilized a Wheel of Fortune task. Between scans, MDD outpatients received Behavioral Activation Therapy for Depression, a psychotherapy modality designed to increase engagement with rewarding stimuli and reduce avoidance behaviors.

Results—75% of adults with MDD were treatment responders, achieving post-treatment HAM-D score of six or below. Relative to changes in brain function in the matched nondepressed group, psychotherapy resulted in functional changes in structures that mediate responses to rewards, including the paracingulate gyrus during reward selection, the right caudate nucleus (i.e., the dorsal striatum), during reward anticipation, and the paracingulate and orbital frontal gyri during reward feedback. There was no effect of diagnostic status or psychotherapy on in-scanner task-related behavioral responses.

Conclusions—Behavioral Activation Therapy for Depression, a psychotherapy modality designed to increase engagement with rewarding stimuli and reduce avoidance behaviors, results

[*]Address correspondence by dichter@med.unc.edu, or by mail to: Dr. Gabriel S. Dichter, Department of Psychiatry, University of North Carolina School of Medicine, CB# 3366, 101 Manning Drive, Chapel Hill, NC 27599-3366.

Financial Disclosures
None to declare.

in improved functioning of unique reward structures during different temporal phases of responses to pleasurable stimuli, including the dorsal striatum during reward anticipation.

Keywords

Depression; fMRI; Reward; Cingulate Gyrus; Striatum; Orbital Frontal Cortex

Introduction

Neuroimaging research into the neurobiology of unipolar major depressive disorder (MDD) has established a model of the pathophysiology of MDD that implicates impaired cortico-limbic functioning in the onset and maintenance of depressive symptoms (1–4). The majority of this research has focused on either (a) resting states data (5–7), or (b) the processing of unpleasant stimuli (8–11). However, far less research has focused on processing pleasant events, and thus the biological basis of anhedonia in MDD is less well understood. Furthermore, the potential for change in regional neuroanatomical functioning in response to pleasant events after antidepressant treatment has not bee evaluated.

Functional neuroimaging studies of responses to pleasant stimuli in MDD implicate the striatum (12–14) as well as a host of other reward structures, including the medial prefrontal cortex (15, 16), the pregenual and subgenual anterior cingulate, and the medial frontal gyrus (17, 18). However, these studies have assessed responses to the *presentation* of pleasant stimuli, whereas nonclinical neuroimaging studies have documented that certain reward structures, and the striatum in particular, responds preferentially to *anticipation* of pleasant stimuli (19–21).

To date, four studies of reward processing in MDD have investigated responses to different temporal phases of reward processing. Forbes and colleagues (22) reported that children with MDD demonstrated decreased orbitofrontal cortex, anterior cingulate, amygdala, and caudate activation during both reward anticipation and feedback, but found little evidence of differential effects contingent on the temporal phase of the response. Additionally, MDD participants had a range of comorbid disorders. Forbes and colleagues (23) reported reduced striatal activation in depressed adolescents during reward anticipation and reward outcome that predicted positive affect in natural environments. Knutson and colleagues (24) employed a monetary incentive delay task and found no striatal activation differences between adult groups during reward anticipation, but increased anterior cingulate activation during anticipation of monetary gains in MDD.

Finally, our own research group reported (25) anomalous neural responses during reward selection, anticipation, and feedback in adults with MDD using a Wheel-of-Fortune task (19). The MDD group was characterized by reduced striatal activation during reward selection, anticipation, and feedback, by hyperresponsivity in orbitofrontal cortex during reward selection, and by decreased activation of the middle frontal gyrus and the anterior cingulate during reward selection and anticipation. This study demonstrated unique regions of functional deficits in MDD during different temporal phases of reward processing, and, most critically, that striatal dysfunction in MDD was evident during the anticipatory phase.

There is a growing neuroimaging literature evaluating response to antidepressant interventions in MDD. Antidepressant medications increase glucose metabolism in the dorsolateral, ventrolateral, and medial aspects of the prefrontal cortex and the anterior cingulate cortex (26) as well as the striatum (27–30), the insular cortex (31), extrastriate cortex (32), and the caudate nucleus and thalamus (33). Although less research has examined functional neural responses after psychotherapy, available data suggest that

psychotherapy predicts metabolic changes in the cingulate and frontal cortices (8, 34–37), basal ganglia (38), and hippocampus (39). Furthermore, a consistent pattern has emerged that antidepressant response is predicted by pretreatment functioning of the anterior cingulate, shown in studies of response to sleep deprivation (40–43), psychopharmacologic intervention (1, 26, 44–46), and cognitive behavioral therapy (34, 35). However, no study has examined brain activation changes after antidepressant treatment (medication or psychotherapy) using tasks sensitive to the chronometry of reward responses. This omission is striking given that reward anticipation may represent the most valid method to assay treatments that putatively improve anhedonia (47).

The present investigation evaluated the effects of Brief Behavioral Activation Treatment for Depression (48) on brain activation using a Wheel of Fortune task that dissociates reward choice selection, anticipation, and feedback. Because of linkages between animal models of MDD, decreased reward seeking behaviors, and functioning of the striatum (49–51), we had particular interest in psychotherapy-induced changes in striatal functioning during reward anticipation. We hypothesized that psychotherapy would cause decreased depressive symptoms accompanied by increased striatal functioning. We further hypothesized that psychotherapy would impact the activity of regions shown to have aberrant functioning pre-psychotherapy in a variety of studies, including the subgenual anterior cingulate cortex during reward decision-making, the striatum during reward anticipation, and the middle frontal gyrus and the orbitofrontal gyrus during reward feedback (24, 25).

Method

Participants

Inclusion/exclusion criteria and Time 1 fMRI results have been reported previously (25). After a complete description of the study to participants, written informed consent was obtained. Participants were paid $45 for each imaging session. Sixteen depressed (9 females) and 15 nondepressed (9 females) participants enrolled in the study. One depressed female withdrew after her initial interview. Not included in the MRI analyses are the data from one depressed female who had frank abnormalities in brain anatomy. Two depressed participants did not return for psychotherapy sessions after the first imaging session. Thus, the final sample was 12 depressed (6 females, average age 39.0 ± 10.4 years) and 15 nondepressed (9 females, average age 30.8 ± 9.6 years) participants. Groups did not differ in age [MDD mean(SD)= 34.8(14.3) years, range = 23–53; nondepressed mean(SD)= 30.8 (9.7) years, range = 21–43], estimated verbal IQ (52) (MDD=112.8, nondepressed =117.7), smoking status (all nondepressed participants were non-smokers, all but two depressed participants were non-smokers), the number of days between scans [MDD mean(SD)=102.2 (15.4) days; nondepressed mean(SD)=102.5 (10.1) days], p's > .05, or gender distribution, χ^2 (1) = .99 p >0.32, but differed in socioeconomic status (53) [MDD mean(SD)= 36.8 (12.0); nondepressed mean(SD)= 45.8 (2.4).

Brief Behavioral Activation Treatment for Depression (BATD)

MDD outpatients received an average of 11.4 (SD=2.0; range: 8–14) weekly sessions of Brief Behavioral Activation Treatment for Depression (BATD). Additional sessions (up to a total of 15 sessions; average of 1.4 per participant) were subsequently offered to help participants consolidate therapeutic gains and transition to follow-up care, as necessary. Early responders were given the option to end therapy after eight sessions and non-responders received the maximum number of sessions before being referred for additional treatment.

BATD is a structured and validated psychotherapy method designed to increase engagement with functional, potentially rewarding behaviors and reduce avoidance behaviors (48). Patients are encouraged to expose themselves to reinforcing situations and to inhibit the behavioral withdrawal often characteristic of MDD (54). Behavioral activation interventions were recently shown to be as effective as Cognitive Behavioral Therapy or paroxetine in reducing depressive symptoms in a large-scale clinical trial (55).

fMRI Task

The Wheel of Fortune (WOF) task is a computerized two-choice decision-making task involving probabilistic monetary outcomes (see Figure 1). Participants were instructed that they would take home up to $45 of the money they won ($40 minimum) and that they should try to win as much money as possible. On each trial, participants first chose between two options, each with an assigned probability of winning a certain amount of money. If correct, the participant won the designated amount; if not, the participant won nothing.

Three conditions were used (56): selecting between (i) a 10% chance of winning $7 and a 90% chance of winning $ 1; (ii) a 30% chance of winning $2 and a 70% chance of winning $1; and (iii) two 50% chances of winning $2. The task was originally designed so that all possible options would be selected by most participants. Each of the three monetary conditions was displayed as a two-slice wheel of fortune, with each slice representing a distinct option. The area of the slice matched the likelihood of winning (e.g., 10%) an explicit amount of money (e.g., $7). A control condition included all the sensory-motor attributes of the monetary conditions, but lacked decision-making, anticipation of a gain, and response to gain. This control condition consisted of a wheel of fortune, but this wheel was of a single color (i.e., no slices).

During the “selection” phase, participants viewed one type of wheel and were asked to select either the blue or the magenta slice by pressing the button corresponding to where the color was located (i.e., right or left). During the “anticipation” phase, participants continued to view the wheel while a six-point rating scale appeared on the screen to prompt them to rate their level of confidence of winning (1=unsure, 6=sure). During the "feedback” phase, participants were shown the dollar amount won ($0 if not won), the cumulative dollar amount, and a six-point pictorial rating scale along which they rated how they felt (1=neutral, 6=very happy, if a win trial; 1=very sad, 6=neutral if a loss trial). During the control condition, participants made button responses in a random fashion during all phases of the task. All responses were recorded on two four-key button-boxes, using three buttons per hand. This version of the task is identical to that described in Ernst et al (2004), except the anticipation and feedback phases included six, instead of five, behavioral response options.

Participants completed four runs of 46 trials that lasted approximately 12 min each. Each trial lasted between 10.5 – 14.5 s and was composed of three phases: selection (3 s), anticipation (jittered between 3.5–7.5 s), and feedback (4 s). Inter-trial intervals were 1–8 s (i.e., the ITI was jittered). Selection-phase responses were given with the right hand. Stimuli were presented using Eprime presentation software (Psychology Software Tools Inc., Pittsburgh, PA) and displayed through magnet-compatible goggles (Resonance Technology, Inc., Northridge CA).

Imaging Methods

Scanning was performed on a General Electric 4T LX NVi MRI scanner system equipped with 41 mT/m gradients (General Electric, Waukesha, Wisconsin, USA). A quadrature birdcage radio frequency head coil was used for transmit and receive. A high resolution T1-

weighted image with 68 slices was acquired using a 3D fast SPGR pulse sequence (TR = 500 ms; TE = 20 ms; FOV = 24 cm; image matrix = 256 × 256; voxel size = 1.67 mm^3) and used for coregistration with the functional data. This structural image was aligned in a near axial plane defined by the anterior and posterior commissures. Whole brain functional images were acquired using an Echo Planar Imaging pulse sequence sensitive to blood oxygenation level dependent contrast (TR, 1500 ms; TE, 31 ms; FOV, 24 cm; image matrix, 64 × 64; α= 62°; voxel size = 53.4375 mm^3; 34 axial slices). Functional images were aligned similarly to the T1-weighted structural image. A semi-automated high-order shimming program ensured global field homogeneity.

The primary neuroimaging analysis was to evaluate voxels that revealed significant 2 (Group: MDD, nondepressed) X 2 (Time: Time 1, Time 2) interactions on contrasts of interest. Activation values were uncorrected and combined with a cluster extent threshold of eight uninterpolated voxels (supplemental materials provide a fuller description of these analyses). For the selection and anticipation phases, monetary and control trials were compared; for the feedback phase, win and loss feedback trials were compared separately to control feedback trials. Because voxels corresponding to significant interactions may reflect increased, decreased, or unchanged signal intensity in the MDD group relative to change in the nondepressed group, whole-brain analyses were followed by two-tailed within-groups t-tests (α=.05) of changes in signal intensity in voxels identified by the interaction test described above. In this manner, statistical tests of fMRI changes due to psychotherapy were restricted to voxels with significant interaction effects. This approach allows for a reduction in the number of post-hoc statistical tests performed. Activation localizations were based on Harvard-Oxford cortical and subcortical structural probabilistic atlases as implemented in FSLView v3.0.

Results

Between-groups tests of Time 1 data have been reported previously (25). Here, we focus on the critical Group X Time interaction effects.

Symptom Profiles and Psychotherapy Outcomes

Table 1 illustrates symptom profiles of participants at both timepoints. Group X Time tests yielded significant interaction effects in depressive symptoms measured by both the HAM-D (57) and the BDI (58), *p*'s<.0001, reflecting significant declines in both measures in the MDD group, *p*'s<.0001. Two measures of symptoms of anhedonia, the Jackson Appetitive Motivation Scale (59) and the Behavioral Activation / Behavioral Inhibition Scale (60), did not show significant interactions.

Within the MDD group, HAM-D scores changed from 23.8 (SD=2.3) at Time 1 to 8.7 (SD=9.4) at Time 2 (*p*<.003). 75% (9/12) of participants were responders, defined as Time 2 HAM-D scores of six or below, and 83% (10/12) of participants were partial responders, defined as Time 2 HAM-D scores of 10 or below.

Wheel of Fortune Outcome

Figure 2 depicts in-scanner WoF behavioral outcomes. All Group X Trial Type X Time interactions were not significant, *p's* > .10 (supplemental materials provide a fuller description of these analyses).

Wheel of Fortune Imaging Data

Selection Phase—The top of Figure 3 depicts voxels with significant 2 (Group: Depressed, Nondepressed) X 2 (Time: Time 1, Time 2) interaction effects on the money vs.

control contrast during reward selection. Table 2 denotes all clusters showing significant interactions, as well at the results of paired *t-tests* on signal intensity differences between timepoints in the MDD group in clusters with significant interaction effects. Areas that showed increased activation in the MDD group after psychotherapy included the paracingulate gyrus (marginally significant at p=.06), the left putamen, the right supramarginal gyrus, and the left posterior temporal fusiform cortex. Areas that showed decreased activation in the MDD group, relative to baseline MDD scans, included the left amygdala, the left superior frontal gyrus, the left superior lateral occipital cortex, the left occipital pole, the left postcentral gyrus, the left precentral gyrus, the right supramarginal gyrus, and the right inferior temporal gyrus.

Anticipation Phase—The bottom of Figure 3 depicts voxels with significant 2 (Group: Depressed, Nondepressed) X 2 (Time: Time 1, Time 2) interaction effects on money vs. control contrasts during reward anticipation. Table 3 denotes clusters showing significant Group X Time interactions, as well at the results of paired *t-tests* on signal intensity differences between timepoints in the MDD group in clusters with significant interaction effects. Areas that showed increased activation in the MDD group after psychotherapy included the left caudate, the anterior cingulate gyrus, the left middle and superior frontal gyri, the left lingual gyrus, the left lateral and superior-lateral occipital cortex, the left posterior parahippocampal gyrus, the right insular cortex, right precuneus, right subcallosal cortex, right posterior temporal fusiform cortex, and bilateral precentral gyrus and temporal poles. Areas that showed decreased activation in the MDD group after psychotherapy included only the anterior inferior temporal gyrus.

Feedback Phase—Data from win and non-win trials were analyzed separately. Figure 4 depicts voxels with significant 2 (Group: Depressed, Nondepressed) X 2 (Time: Time 1, Time 2) interactions for win vs. control (top) and non-win vs. control (bottom) contrasts. Table 4 denotes clusters showing significant Group X Time interactions for these contrasts, as well at the results of paired *t-tests* on signal intensity differences between timepoints in the MDD group in clusters with significant interaction effects.

Areas that showed increased activation in the MDD group after psychotherapy during win feedback included the left planum temporale, right superior lateral occipital cortex, and right posterior temporal fusiform cortex. Areas that showed decreased activation after psychotherapy included the left posterior cingulate, left caudate, left postcentral gyrus, and left paracingulate gyrus. During non-win feedback, psychotherapy resulted in increased activation in left lingual gyrus, left angular gyrus, left anterior superior temporal gyrus, left orbital frontal cortex, left posterior superior temporal gyrus, and right planum temporale, right posterior superior temporal gyrus, and right temporal pole. During non-win feedback, psychotherapy resulted in decreased activation in left putamen, left superior lateral occipital cortex, left precentral gyrus, and left anterior supramarginal gyrus in the MDD group.

Discussion

The goal of the present study was to elucidate BATD-related changes in brain function during reward processing in MDD. Given animal evidence indicating that a potential final common pathway of antidepressant treatments may be up-regulation of mesolimbic systems (61), and because of linkages between mesolimbic functioning and reward anticipation (49, 62), primary hypotheses concerned BATD-related changes in the striatum during reward anticipation.

Reward Selection

Analyses of selection data revealed a number of prefrontal regions with differential group responses over time, including the paracingulate gyrus, bilateral orbital cortex bilateral frontal pole, bilateral inferior frontal gyri, as well as limbic and occipital regions. Analyses of the effects of BATD in the MDD group revealed significant increases in functioning of the right paracingulate gyrus, the right posterior superior temporal gyrus, and portions of the left supramarginal gyrus. Increased activation in the right paracingulate gyrus, though only marginally significant, is particularly noteworthy, given that this region has been shown to predict treatment response in an array of functional and metabolic imaging paradigms (e.g., 2, 63, 64), though we note that this effect was a trend and should thus be interpreted with caution. Areas showing decreased activation after BATD included the right amygdala, a finding that was unexpected and bears replication. In a recent study using a modification of the WOF task, Smith and colleagues (65) reported that selection of relatively larger rewards activated the amygdala more strongly. Thus, in the present context, BATD treatment may have decreased perceived reward magnitudes. Alternatively, at baseline there may have been a mildly aversive quality to choosing a response for MDD participants due to the indecisiveness that defines the disorder (66), and BATD treatment may have diminished this aversive response. Other areas with decreased activation included the right superior frontal gyrus, right occipital cortex, right precentral gyrus, right precentral gyrus, left supramarginal gyrus, and left inferior temporal gyrus.

Reward Anticipation

Analyses of reward anticipation revealed differential group activation changes in the left caudate nucleus, as well as a number of prefrontal regions, including the left cingulate gyrus, left frontal gyrus, and right insula. In line with predictions, analyses of change within the MDD group alone revealed that BATD produced significant increased activation in all these regions, including the left caudate nucleus (i.e., the dorsal striatum). These findings represent the first report of BATD-related increases in striatal activity during reward anticipation in MDD. A number of other areas demonstrated increased activity after BATD, including clusters in the left lingual gyrus, left occipital cortex, left parahippocampal gyrus, and right temporal cortex. No clusters showed decreased activation after BATD relative to changes in nondepressed group activations.

BATD-related increased striatal activity during reward anticipation is consistent with preclinical and clinical models of MDD and anhedonia that implicate mesolimbic dysregulation in the pathophysiology of MDD (67–71) and is consistent with the conceptualization that the mechanisms of action of a range of antidepressant interventions is improved mesolimbic functioning (61, 72–77).

Reward feedback

A number of frontal and limbic regions showed decreased activation after BATD, including the right caudate nucleus and a large cluster in the left paracingulate gyrus. The decrease in right caudate activation after BATD treatment in the MDD group was surprising and bears replication. Caudate activation has been linked to learning cue-outcome contingencies (78, 79), particularly when potential gains require a motor response (80, 81). In the current study, though wins were probabilistically determined, they were not directly contingent on behavioral performance (e.g., reaction time or accuracy). Given that MDD is characterized by decreased estimation of contingencies between behaviors and outcomes (i.e., decreased positivity bias) (82), symptom remission may have normalized cue-outcome contingency estimations and thus caudate activation – this feature of the WoF may account for the apparent contradiction between the finding of decreased right caudate activation after BATD

and other reports of reduced caudate activation in MDD (83, 84), particularly given that groups did not differ at time 1 scans (23).

In contrast, analyses of non-win feedback revealed BATD-related increased activation in the right lateral OFG. We interpret this finding to reflect the role of the OFC in modulating the affective evaluation of rewards, expectation, motivation, decision-making and goal-directed behavior (85–87), and, more specifically, to process violations of affective feedback expectancies (88). In other words, it may be the case that, at pre-treatment, individuals with MDD expected not to win positive outcomes; however, BATD may have induced a change in this expectancy, such that not winning actually violated their expectancies to relatively a greater degree, prompting greater OFC activation relative to their pre-treatment scans.

Limitations and Conclusions

The finding of increased striatal activation during reward anticipation after BATD was localized to the dorsal striatum (i.e., caudate), rather then ventral striatum (i.e., nucleus accumbens). The nucleus accumbens is thought to mediate internal representations of predicted reward (79), whereas the caudate mediates linking rewards to behavior, reward-related decision-making, and encoding motivational feedback (89–92). The localization of activation to the caudate during reward anticipation may have been due to the WoF task: in contrast to other tasks used to assess reward anticipation (21, 93), the WoF requires behavioral responses during all phases. This cognitive component may have prompted dorsal, rather than ventral, striatal responses (94).

The paracingulate cortex was reactive to BATD during two phases of reward responding (i.e. selection and win feedback). The localization of the paracingulate cortex across these three analyses (center of activations: +2, +52, −2, −4, 44, −8, and −2, 28, −10) overlaps the subgenual cingulate cortex (Brodmann's area 25). Subgenual cingulate metabolism has been shown to predict response to a range of antidepressant interventions (both pharmacologic and psychotherapy) (2, 3, 26, 95), and subgenual cingulate reactivity to emotional stimuli has been implicated as a predictor of response to cognitive behavioral treatment (CBT) in MDD using fMRI (37). This is in contrast to activation of medial aspects of the prefrontal cortex, which has been shown to predict response to sleep deprivation (43), and to activity of the rostral ACC (approximately Brodmann areas 24 and 32), which has been shown to predict response to psychotropic medication in non-psychotic depression using electromagnetic tomography (46, 96). More broadly, the present study adds to the growing body of literature linking subregions of the anterior cingulate not only to the pathophysiology of MDD, but to symptom remission in a variety of contexts.

We note that the present investigation did not include placebo or wait-list control groups, and thus it is unknown whether functional brain changes in the MDD group were due to the BATD intervention or to other variables, such as spontaneous improvement of symptoms over time. Additionally, many brain regions reactive to psychotherapy were clearly outside of reward structures. In this initial study, post-hoc tests of the effects of BATD in the MDD group were not corrected for multiple comparisons, and thus findings regarding the effects of BATD warrant replication. We also note that the three types of reward trials (i.e., equal, moderate, and high risk) were combined, and activation magnitudes of certain brain regions, such as the medial prefrontal cortex and the striatum, are known to vary parametrically with reward magnitudes (97, 98). Finally, the relatively broader age range of the MDD group is an additional limitation of this study.

Though this preliminary investigation evaluated a relatively small number of patients, findings suggests that BATD results in recovery of function in brain regions related to processing rewards. By utilizing a paradigm that allowed for an assessment of the different

phases of responses to rewards, we were able to evaluate the effects of BATD on reward selection, reward anticipation, and reward feedback. Imaging data revealed that BATD normalized functioning in hypothesized areas, including the paracingulate cortex during reward selection, the striatum during reward anticipation, and the orbital frontal cortex during reward feedback. We conclude that functional changes within the reward network may be a valuable biomarker of the effects of antidepressant treatments in MDD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors would like to thank Todd Harshbarger and Syam Gadde for assistance with image analysis, Prue Cuper, Shian Ling Keng, and Justin Woodlief for assistance with data collection, and MRI technologists Susan Music, Natalie Goutkin, and Talaignair Venkatraman for assistance with data acquisition. This research was supported by MH078145 to G. Dichter. Assistance for this study was provided by the Neuroimaging Core of the UNC Neurodevelopmental Disorders Research Center. M. Smoski was supported by NIMH T32-MH070448, a NARSAD Young Investigator award, and a career development award from Duke University Medical Center, NICHD K12 HD043446. G. Dichter was supported by Postdoctoral Research in Neurodevelopmental Disorders, NICHD T32-HD40127, NARSAD Young Investigator awards, a career development award from UNC-Chapel Hill, NIH/NCRR K12 RR023248, and NIMH K23 MH081285.

References

1. Mayberg HS. Limbic-cortical dysregulation: a proposed model of depression. J Neuropsychiatry Clin Neurosci. 1997; 9(3):471–481. [PubMed: 9276848]
2. Ressler KJ, Mayberg HS. Targeting abnormal neural circuits in mood and anxiety disorders: from the laboratory to the clinic. Nat Neurosci. 2007; 10(9):1116–1124. [PubMed: 17726478]
3. Mayberg HS. Modulating dysfunctional limbic-cortical circuits in depression: towards development of brain-based algorithms for diagnosis and optimised treatment. Br Med Bull. 2003; 65:193–207. [PubMed: 12697626]
4. Seminowicz DA, Mayberg HS, McIntosh AR, Goldapple K, Kennedy S, Segal Z, Rafi-Tari S. Limbic-frontal circuitry in major depression: a path modeling metanalysis. Neuroimage. 2004; 22(1):409–418. [PubMed: 15110034]
5. Greicius MD, Flores BH, Menon V, Glover GH, Solvason HB, Kenna H, Reiss AL, Schatzberg AF. Resting-state functional connectivity in major depression: abnormally increased contributions from subgenual cingulate cortex and thalamus. Biol Psychiatry. 2007; 62(5):429–437. [PubMed: 17210143]
6. Drevets WC. Prefrontal cortical-amygdalar metabolism in major depression. Ann N Y Acad Sci. 1999; 877:614–637. [PubMed: 10415674]
7. Pizzagalli DA, Oakes TR, Fox AS, Chung MK, Larson CL, Abercrombie HC, Schaefer SM, Benca RM, Davidson RJ. Functional but not structural subgenual prefrontal cortex abnormalities in melancholia. Mol Psychiatry. 2004; 9(4):325. 393–405. [PubMed: 14699431]
8. Fu CH, Williams SC, Cleare AJ, Scott J, Mitterschiffthaler MT, Walsh ND, Donaldson C, Suckling J, Andrew C, Steiner H, Murray RM. Neural responses to sad facial expressions in major depression following cognitive behavioral therapy. Biol Psychiatry. 2008; 64(6):505–512. [PubMed: 18550030]
9. Hamilton JP, Gotlib IH. Neural substrates of increased memory sensitivity for negative stimuli in major depression. Biol Psychiatry. 2008; 63(12):1155–1162. [PubMed: 18281017]
10. Lee BT, Seok JH, Lee BC, Cho SW, Yoon BJ, Lee KU, Chae JH, Choi IG, Ham BJ. Neural correlates of affective processing in response to sad and angry facial stimuli in patients with major depressive disorder. Prog Neuropsychopharmacol Biol Psychiatry. 2008; 32(3):778–785. [PubMed: 18207298]
11. Dannlowski U, Ohrmann P, Bauer J, Kugel H, Arolt V, Heindel W, Kersting A, Baune BT, Suslow T. Amygdala reactivity to masked negative faces is associated with automatic judgmental bias in

major depression: a 3 T fMRI study. J Psychiatry Neurosci. 2007; 32(6):423–429. [PubMed: 18043766]

12. Mitterschiffthaler MT, Kumari V, Malhi GS, Brown RG, Giampietro VP, Brammer MJ, Suckling J, Poon L, Simmons A, Andrew C, Sharma T. Neural response to pleasant stimuli in anhedonia: an fMRI study. Neuroreport. 2003; 14(2):177–182. [PubMed: 12598724]
13. Kumar P, Waiter G, Ahearn T, Milders M, Reid I, Steele JD. Abnormal temporal difference reward-learning signals in major depression. Brain. 2008; 131(Pt 8):2084–2093. [PubMed: 18579575]
14. Steele JD, Kumar P, Ebmeier KP. Blunted response to feedback information in depressive illness. Brain. 2007; 130(Pt 9):2367–2374. [PubMed: 17586866]
15. Kumari V, Mitterschiffthaler MT, Teasdale JD, Malhi GS, Brown RG, Giampietro V, Brammer MJ, Poon L, Simmons A, Williams SC, Checkley SA, Sharma T. Neural abnormalities during cognitive generation of affect in treatment-resistant depression. Biol Psychiatry. 2003; 54(8):777–791. [PubMed: 14550677]
16. Ochsner KN, Ray RD, Cooper JC, Robertson ER, Chopra S, Gabrieli JD, Gross JJ. For better or for worse: neural systems supporting the cognitive down- and up-regulation of negative emotion. Neuroimage. 2004; 23(2):483–499. [PubMed: 15488398]
17. Liotti M, Mayberg HS, McGinnis S, Brannan SL, Jerabek P. Unmasking disease-specific cerebral blood flow abnormalities: mood challenge in patients with remitted unipolar depression. Am J Psychiatry. 2002; 159(11):1830–1840. [PubMed: 12411216]
18. Keedwell PA, Andrew C, Williams SCR, Brammer MJ, Zelaya F, Phillips ML. The Neural Correlates of Depression Biol Psychiatry (Abstract). 2003; 53:171S.
19. Ernst M, Nelson EE, McClure EB, Monk CS, Munson S, Eshel N, Zarahn E, Leibenluft E, Zametkin A, Towbin K, Blair J, Charney D, Pine DS. Choice selection and reward anticipation: an fMRI study. Neuropsychologia. 2004; 42(12):1585–1597. [PubMed: 15327927]
20. Knutson B, Fong GW, Adams CM, Varner JL, Hommer D. Dissociation of reward anticipation and outcome with event-related fMRI. Neuroreport. 2001; 12(17):3683–3687. [PubMed: 11726774]
21. Knutson B, Adams CM, Fong GW, Hommer D. Anticipation of increasing monetary reward selectively recruits nucleus accumbens. J Neurosci. 2001; 21(16):RC159. [PubMed: 11459880]
22. Forbes EE, Christopher May J, Siegle GJ, Ladouceur CD, Ryan ND, Carter CS, Birmaher B, Axelson DA, Dahl RE. Reward-related decision-making in pediatric major depressive disorder: an fMRI study. J Child Psychol Psychiatry. 2006; 47(10):1031–1040. [PubMed: 17073982]
23. Forbes EE, Hariri AR, Martin SL, Silk JS, Moyles DL, Fisher PM, Brown SM, Ryan ND, Birmaher B, Axelson DA, Dahl RE. Altered Striatal Activation Predicting Real-World Positive Affect in Adolescent Major Depressive Disorder. Am J Psychiatry. 2008
24. Knutson B, Bhanji JP, Cooney RE, Atlas LY, Gotlib IH. Neural Responses to Monetary Incentives in Major Depression. Biol Psychiatry. 2008; 63(7):686–692. [PubMed: 17916330]
25. Smoski MJ, Felder J, Bizzell J, Green S, Ernst M, Lynch TR, Dichter GS. FMRI of Alterations in Reward Selection, Anticipation, and Feedback in Major Depressive Disorder. Journal of Affective Disorders. in press.
26. Mayberg HS, Brannan SK, Tekell JL, Silva JA, Mahurin RK, McGinnis S, Jerabek PA. Regional metabolic effects of fluoxetine in major depression: serial changes and relationship to clinical response. Biol Psychiatry. 2000; 48(8):830–843. [PubMed: 11063978]
27. Drevets WC, Bogers W, Raichle ME. Functional anatomical correlates of antidepressant drug treatment assessed using PET measures of regional glucose metabolism. Eur Neuropsychopharmacol. 2002; 12(6):527–544. [PubMed: 12468016]
28. Milak MS, Parsey RV, Keilp J, Oquendo MA, Malone KM, Mann JJ. Neuroanatomic correlates of psychopathologic components of major depressive disorder. Arch Gen Psychiatry. 2005; 62(4): 397–408. [PubMed: 15809407]
29. Saxena S, Brody AL, Ho ML, Zohrabi N, Maidment KM, Baxter LR Jr. Differential brain metabolic predictors of response to paroxetine in obsessive-compulsive disorder versus major depression. Am J Psychiatry. 2003; 160(3):522–532. [PubMed: 12611834]
30. Fu CH, Williams SC, Cleare AJ, Brammer MJ, Walsh ND, Kim J, Andrew CM, Pich EM, Williams PM, Reed LJ, Mitterschiffthaler MT, Suckling J, Bullmore ET. 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. 2004; 61(9):877–889. [PubMed: 15351766]

31. Davidson RJ, Irwin W, Anderle MJ, Kalin NH. The neural substrates of affective processing in depressed patients treated with venlafaxine. Am J Psychiatry. 2003; 160(1):64–75. [PubMed: 12505803]
32. Fu CH, Williams SC, Brammer MJ, Suckling J, Kim J, Cleare AJ, Walsh ND, Mitterschiffthaler MT, Andrew CM, Pich EM, Bullmore ET. Neural responses to happy facial expressions in major depression following antidepressant treatment. Am J Psychiatry. 2007; 164(4):599–607. [PubMed: 17403973]
33. Walsh ND, Williams SC, Brammer MJ, Bullmore ET, Kim J, Suckling J, Mitterschiffthaler MT, Cleare AJ, Pich EM, Mehta MA, Fu CH. A longitudinal functional magnetic resonance imaging study of verbal working memory in depression after antidepressant therapy. Biol Psychiatry. 2007; 62(11):1236–1243. [PubMed: 17601497]
34. Kennedy SH, Evans KR, Kruger S, Mayberg HS, Meyer JH, McCann S, Arifuzzman AI, Houle S, Vaccarino FJ. Changes in regional brain glucose metabolism measured with positron emission tomography after paroxetine treatment of major depression. Am J Psychiatry. 2001; 158(6):899–905. [PubMed: 11384897]
35. Smith GS, Reynolds CF 3rd, Pollock B, Derbyshire S, Nofzinger E, Dew MA, Houck PR, Milko D, Meltzer CC, Kupfer DJ. Cerebral glucose metabolic response to combined total sleep deprivation and antidepressant treatment in geriatric depression. Am J Psychiatry. 1999; 156(5): 683–689. [PubMed: 10327899]
36. Brody AL, Saxena S, Stoessel P, Gillies LA, Fairbanks LA, Alborzian S, Phelps ME, Huang SC, Wu HM, Ho ML, Ho MK, Au SC, Maidment K, Baxter LR Jr. Regional brain metabolic changes in patients with major depression treated with either paroxetine or interpersonal therapy: preliminary findings. Arch Gen Psychiatry. 2001; 58(7):631–640. [PubMed: 11448368]
37. Siegle GJ, Carter CS, Thase ME. Use of FMRI to predict recovery from unipolar depression with cognitive behavior therapy. Am J Psychiatry. 2006; 163(4):735–738. [PubMed: 16585452]
38. Martin SD, Martin E, Rai SS, Richardson MA, Royall R. Brain blood flow changes in depressed patients treated with interpersonal psychotherapy or venlafaxine hydrochloride: preliminary findings. Arch Gen Psychiatry. 2001; 58(7):641–648. [PubMed: 11448369]
39. Goldapple K, Segal Z, Garson C, Lau M, Bieling P, Kennedy S, Mayberg H. Modulation of cortical-limbic pathways in major depression: treatment-specific effects of cognitive behavior therapy. Arch Gen Psychiatry. 2004; 61(1):34–41. [PubMed: 14706942]
40. Wu JC, Gillin JC, Buchsbaum MS, Hershey T, Johnson JC, Bunney WE Jr. Effect of sleep deprivation on brain metabolism of depressed patients. Am J Psychiatry. 1992; 149(4):538–543. [PubMed: 1554042]
41. Ebert D, Feistel H, Barocka A. Effects of sleep deprivation on the limbic system and the frontal lobes in affective disorders: a study with Tc-99m-HMPAO SPECT. Psychiatry Res. 1991; 40(4): 247–251. [PubMed: 1811242]
42. Ebert D, Feistel H, Kaschka W, Barocka A, Pirner A. Single photon emission computerized tomography assessment of cerebral dopamine D2 receptor blockade in depression before and after sleep deprivation--preliminary results. Biol Psychiatry. 1994; 35(11):880–885. [PubMed: 8054411]
43. Wu J, Buchsbaum MS, Gillin JC, Tang C, Cadwell S, Wiegand M, Najafi A, Klein E, Hazen K, Bunney WE Jr. Fallon JH, Keator D. Prediction of antidepressant effects of sleep deprivation by metabolic rates in the ventral anterior cingulate and medial prefrontal cortex. Am J Psychiatry. 1999; 156(8):1149–1158. [PubMed: 10450253]
44. Brody AL, Saxena S, Mandelkern MA, Fairbanks LA, Ho ML, Baxter LR. Brain metabolic changes associated with symptom factor improvement in major depressive disorder. Biol Psychiatry. 2001; 50(3):171–178. [PubMed: 11513815]
45. Brody AL, Saxena S, Silverman DH, Alborzian S, Fairbanks LA, Phelps ME, Huang SC, Wu HM, Maidment K, Baxter LR Jr. Brain metabolic changes in major depressive disorder from pre- to post-treatment with paroxetine. Psychiatry Res. 1999; 91(3):127–139. [PubMed: 10641577]

46. Pizzagalli D, Pascual-Marqui RD, Nitschke JB, Oakes TR, Larson CL, Abercrombie HC, Schaefer SM, Koger JV, Benca RM, Davidson RJ. Anterior cingulate activity as a predictor of degree of treatment response in major depression: evidence from brain electrical tomography analysis. Am J Psychiatry. 2001; 158(3):405–415. [PubMed: 11229981]
47. Willner P. Dopamine and depression: a review of recent evidence. III. The effects of antidepressant treatments. Brain Res. 1983; 287(3):237–246. [PubMed: 6318882]
48. Hopko DR, Lejuez CW, Ruggiero KJ, Eifert GH. Contemporary behavioral activation treatments for depression: Procedures, principles, and progress. Clinical Psychology Review. 2003; 23:699–717. [PubMed: 12971906]
49. Aberman JE, Ward SJ, Salamone JD. Effects of dopamine antagonists and accumbens dopamine depletions on time-constrained progressive-ratio performance. Pharmacology, Biochemistry & Behavior. 1998; 61(4):341–348.
50. Berridge KC. Food reward: brain substrates of wanting and liking. Neurosci Biobehav Rev. 1996; 20(1):1–25. [PubMed: 8622814]
51. Berridge KC, Robinson TE. What is the role of dopamine in reward: Hedonic impact, reward learning, or incentive salience? Brain Research Reviews. 1998; 28(3):309–369. [PubMed: 9858756]
52. Blair JR, Spreen O. Predicting premorbid IQ: A revision of the national adult reading test. The Clinical Neuropsychologist. 1989; 3:129–136.
53. Hollingshead, AB. Four factor index of social status, Working paper. New Haven, CT: Department of Sociology, Yale University; 1975.
54. Jacobson NS, Dobson KS, Truax PA, Addis ME, Koerner K, Gollan JK, Gortner E, Prince SE. A component analysis of cognitive-behavioral treatment for depression. J Consult Clin Psychol. 1996; 64(2):295–304. [PubMed: 8871414]
55. Dimidjian S, Hollon SD, Dobson KS, Schmaling KB, Kohlenberg RJ, Addis ME, Gallop R, McGlinchey JB, Markley DK, Gollan JK, Atkins DC, Dunner DL, Jacobson NS. Randomized trial of behavioral activation, cognitive therapy, and antidepressant medication in the acute treatment of adults with major depression. J Consult Clin Psychol. 2006; 74(4):658–670. [PubMed: 16881773]
56. Ernst M, Dickstein DP, Munson S, Eshel N, Pradella A, Jazbec S, Pine DS, Leibenluft E. Reward-related processes in pediatric bipolar disorder: a pilot study. J Affect Disord. 2004; 82(Suppl 1):S89–S101. [PubMed: 15571794]
57. Hamilton MA. A rating scale for depression. Journal of Neurology and Neurosurgery in Psychiatry. 1960; 23:56–62.
58. Beck, AT.; Steer, RA.; Brown, GK. Manual for Beck Depression Inventory-II. San Antonio, TX: Psychological Corporation; 1996.
59. Jackson CJ, Smillie LD. Appetitive motivation predicts the majority of personality and an ability measure: a comparison of BAS measures and a re-evaluation of the importance of RST. Personality and Individual Differences. 2004; 36:1627–1636.
60. Carver CS, White T. Behavioral inhibition behavioral activation, and affective responses to impending reward and punishment::The BIS/BAS scales. Journal of Personality and Social Psychology. 1994; 67:319–333.
61. Lammers CH, Diaz J, Schwartz JC, Sokoloff P. Selective increase of dopamine D3 receptor gene expression as a common effect of chronic antidepressant treatments. Mol Psychiatry. 2000; 5(4): 378–388. [PubMed: 10889548]
62. Berridge KC, Robinson TE. What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? Brain Res Brain Res Rev. 1998; 28(3):309–369. [PubMed: 9858756]
63. Konarski JZ, Kennedy SH, McIntyre RS, Rafi-Tari S, Soczynska JK, Mayberg HS. Relationship between regional brain metabolism, illness severity and age in depressed subjects. Psychiatry Res. 2007; 155(3):203–210. [PubMed: 17574393]
64. Kennedy SH, Konarski JZ, Segal ZV, Lau MA, Bieling PJ, McIntyre RS, Mayberg HS. Differences in brain glucose metabolism between responders to CBT and venlafaxine in a 16-week randomized controlled trial. Am J Psychiatry. 2007; 164(5):778–788. [PubMed: 17475737]

65. Smith BW, Mitchell DG, Hardin MG, Jazbec S, Fridberg D, Blair RJ, Ernst M. Neural substrates of reward magnitude, probability, and risk during a wheel of fortune decision-making task. Neuroimage. 2009; 44(2):600–609. [PubMed: 18804540]

66. American Psychiatric Association: Diagnostic and statistical manual of mental disorders, fourth edition: DSM-IV. Washington, DC: 1994.

67. Swerdlow NR, Koob GF. Dopamine, schizophrenia, mania and depression: Toward a unified hypothesis of cortico-striato-pallido-thalamic function. Behavioral and brain sciences. 1987; 10:197–245.

68. Anisman H, Grimmer L, Irwin J, Remington G, Sklar LS. Escape performance after inescapable shock in selectively bred lines of mice: response maintenance and catecholamine activity. J Comp Physiol Psychol. 1979; 93(2):229–241. [PubMed: 457947]

69. Anisman H, Irwin J, Sklar LS. Deficits of escape performance following catecholamine depletion: implications for behavioral deficits induced by uncontrollable stress. Psychopharmacology (Berl). 1979; 64(2):163–170. [PubMed: 115036]

70. Anisman H, Remington G, Sklar LS. Effect of inescapable shock on subsequent escape performance: catecholaminergic and cholinergic mediation of response initiation and maintenance. Psychopharmacology (Berl). 1979; 61(2):107–124. [PubMed: 108728]

71. Borsini F, Lecci A, Mancinelli A, D'Aranno V, Meli A. Stimulation of dopamine D-2 but not D-1 receptors reduces immobility time of rats in the forced swimming test: implication for antidepressant activity. Eur J Pharmacol. 1988; 148(3):301–307. [PubMed: 2968270]

72. Nestler EJ, Carlezon WA Jr. The mesolimbic dopamine reward circuit in depression. Biol Psychiatry. 2006; 59(12):1151–1159. [PubMed: 16566899]

73. Nestler EJ. Antidepressant treatments in the 21st century. Biol Psychiatry. 1998; 44(7):526–533. [PubMed: 9787876]

74. Halaris AE, Belendiuk KT, Freedman DX. Antidepressant drugs affect dopamine uptake. Biochem Pharmacol. 1975; 24(20):1896–1897. [PubMed: 19]

75. Major LJ, Murphy DL, Lipper S, Gordon E. Effects of clorgyline and pargyline on deaminated metabolites of norepinephrine, dopamine and serotonin in human cerebrospinal fluid. J Neurochem. 1979; 32(1):229–231. [PubMed: 759576]

76. Horst WD, Preskorn SH. Mechanisms of action and clinical characteristics of three atypical antidepressants: venlafaxine, nefazodone, bupropion. J Affect Disord. 1998; 51(3):237–254. [PubMed: 10333980]

77. Ishihara K, Sasa M. Mechanism underlying the therapeutic effects of electroconvulsive therapy (ECT) on depression. Jpn J Pharmacol. 1999; 80(3):185–189. [PubMed: 10461762]

78. Delgado MR, Stenger VA, Fiez JA. Motivation-dependent responses in the human caudate nucleus. Cereb Cortex. 2004; 14(9):1022–1030. [PubMed: 15115748]

79. Knutson B, Cooper JC. Functional magnetic resonance imaging of reward prediction. Curr Opin Neurol. 2005; 18(4):411–417. [PubMed: 16003117]

80. Zink CF, Pagnoni G, Martin-Skurski ME, Chappelow JC, Berns GS. Human striatal responses to monetary reward depend on saliency. Neuron. 2004; 42(3):509–517. [PubMed: 15134646]

81. Tricomi EM, Delgado MR, Fiez JA. Modulation of caudate activity by action contingency. Neuron. 2004; 41(2):281–292. [PubMed: 14741108]

82. Alloy LB, Abramson LY. Judgment of contingency in depressed and nondepressed students: sadder but wiser? J Exp Psychol Gen. 1979; 108(4):441–485. [PubMed: 528910]

83. Forbes EE, Hariri AR, Martin SL, Silk JS, Moyles DL, Fisher PM, Brown SM, Ryan ND, Birmaher B, Axelson DA, Dahl RE. Altered striatal activation predicting real-world positive affect in adolescent major depressive disorder. Am J Psychiatry. 2009; 166(1):64–73. [PubMed: 19047324]

84. Pizzagalli DA, Holmes AJ, Dillon DG, Goetz EL, Birk JL, Bogdan R, Dougherty DD, Iosifescu DV, Rauch SL, Fava M. Reduced caudate and nucleus accumbens response to rewards in unmedicated individuals with major depressive disorder. Am J Psychiatry. 2009; 166(6):702–710. [PubMed: 19411368]

85. Gottfried JA, O'Doherty J, Dolan RJ. Encoding predictive reward value in human amygdala and orbitofrontal cortex. Science. 2003; 301(5636):1104–1107. [PubMed: 12934011]

86. Holland PC, Gallagher M. Amygdala-frontal interactions and reward expectancy. Curr Opin Neurobiol. 2004; 14(2):148–155. [PubMed: 15082318]

87. Walton ME, Devlin JT, Rushworth MF. Interactions between decision making and performance monitoring within prefrontal cortex. Nat Neurosci. 2004; 7(11):1259–1265. [PubMed: 15494729]

88. Schoenbaum G, Saddoris MP, Stalnaker TA. Reconciling the roles of orbitofrontal cortex in reversal learning and the encoding of outcome expectancies. Ann N Y Acad Sci. 2007; 1121:320–335. [PubMed: 17698988]

89. Balleine BW, Delgado MR, Hikosaka O. The role of the dorsal striatum in reward and decision-making. J Neurosci. 2007; 27(31):8161–8165. [PubMed: 17670959]

90. Yamada H, Matsumoto N, Kimura M. Tonically active neurons in the primate caudate nucleus and putamen differentially encode instructed motivational outcomes of action. J Neurosci. 2004; 24(14):3500–3510. [PubMed: 15071097]

91. Donahue CH, Seo H. Attaching values to actions: action and outcome encoding in the primate caudate nucleus. J Neurosci. 2008; 28(18):4579–4580. [PubMed: 18448632]

92. Lau B, Glimcher PW. Action and outcome encoding in the primate caudate nucleus. J Neurosci. 2007; 27(52):14502–14514. [PubMed: 18160658]

93. Breiter HC, Aharon I, Kahneman D, Dale A, Shizgal P. Functional imaging of neural responses to expectancy and experience of monetary gains and losses. Neuron. 2001; 30(2):619–639. [PubMed: 11395019]

94. Schonberg T, Daw ND, Joel D, O'Doherty JP. Reinforcement learning signals in the human striatum distinguish learners from nonlearners during reward-based decision making. J Neurosci. 2007; 27(47):12860–12867. [PubMed: 18032658]

95. Mayberg HS, Brannan SK, Mahurin RK, Jerabek PA, Brickman JS, Tekell JL, Silva JA, McGinnis S, Glass TG, Martin CC, Fox PT. Cingulate function in depression: a potential predictor of treatment response. Neuroreport. 1997; 8(4):1057–1061. [PubMed: 9141092]

96. Mulert C, Juckel G, Brunnmeier M, Karch S, Leicht G, Mergl R, Moller HJ, Hegerl U, Pogarell O. Rostral anterior cingulate cortex activity in the theta band predicts response to antidepressive medication. Clin EEG Neurosci. 2007; 38(2):78–81. [PubMed: 17515172]

97. Xue G, Lu Z, Levin IP, Weller JA, Li X, Bechara A. Functional dissociations of risk and reward processing in the medial prefrontal cortex. Cereb Cortex. 2009; 19(5):1019–1027. [PubMed: 18842669]

98. Ino T, Nakai R, Azuma T, Kimura T, Fukuyama H. Differential activation of the striatum for decision making and outcomes in a monetary task with gain and loss. Cortex. 2009

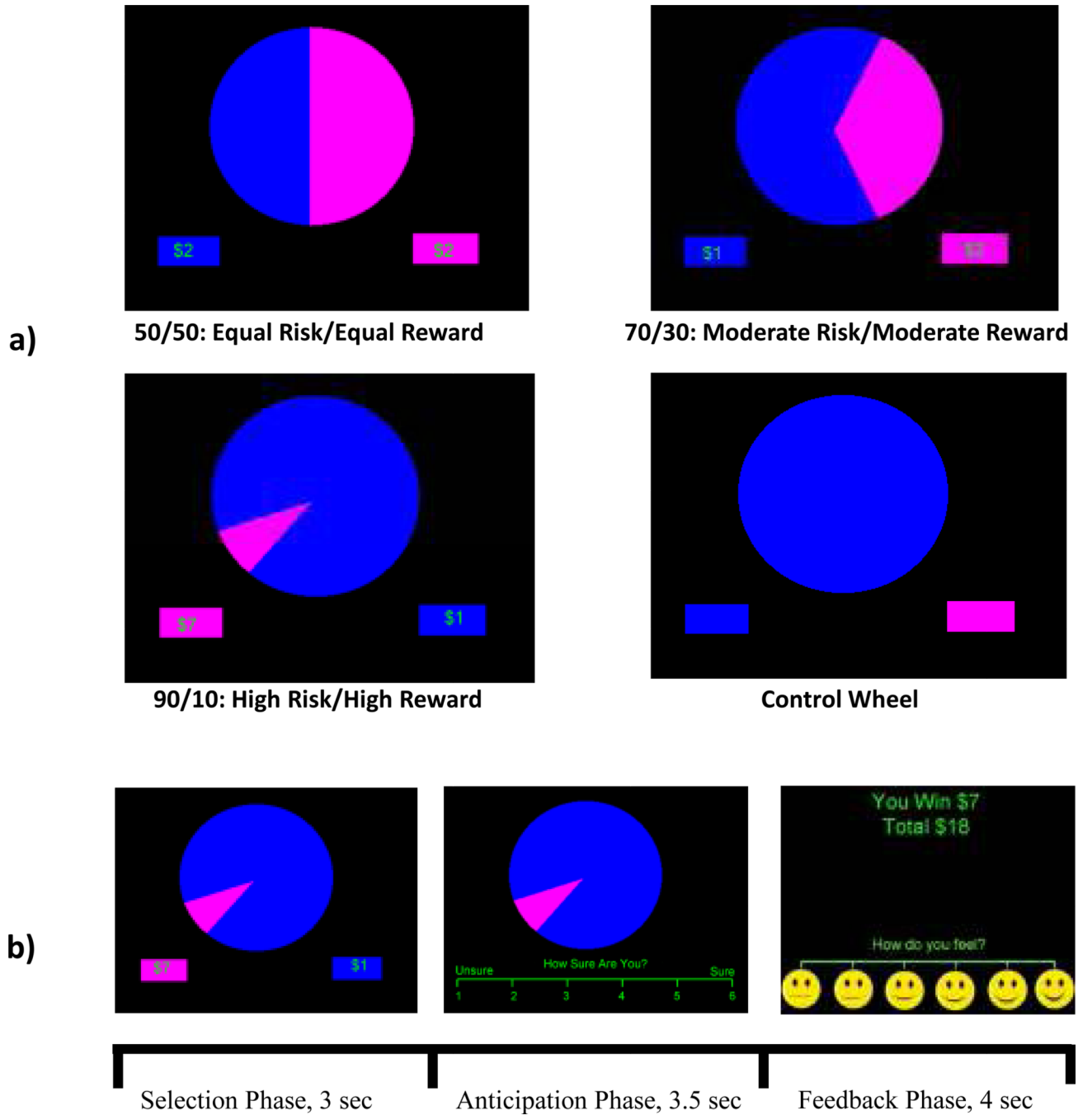

Figure 1.
The Wheel of Fortune task; (a) The four different wheel types; (b) The timing of three task processes, i.e., reward selection, reward anticipation, and reward feedback.

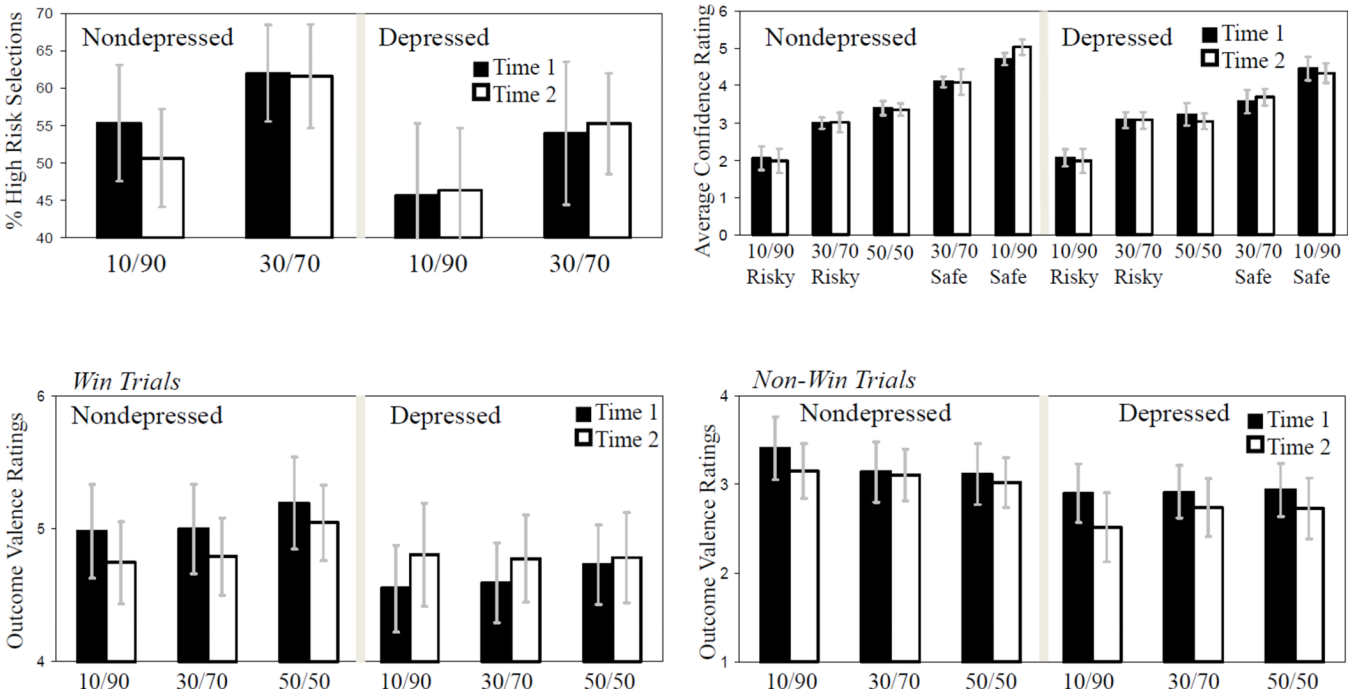

Figure 2.

Top Left: Percentage of high risk selections (i.e., smaller pie slices) for the 10/90 and 30/70 conditions for both diagnostic groups at both timepoints. **Top Right**. Average confidence ratings (range = 1 to 6) for both diagnostic groups at both timepoints. Note that the unequal wheels are subdivided based on selection selections on a trial-by-trial basis (i.e., “risky” or “safe” selections). **Bottom Left:** Ratings of feedback valence for win trials for both diagnostic groups at both timepoints. On win trails, the range and direction of the ratings were 1 = Neutral, 6 = Very Happy, whereas on no-win trials, the range and direction of the ratings were 1 = Very Sad, 6 = Neutral. **Bottom Right:** Ratings of feedback valence for non-win trials for both diagnostic groups at both timepoints. On win trails, the range and direction of the ratings were 1 = Neutral, 6 = Very Happy, whereas on no-win trials, the range and direction of the ratings were 1 = Very Sad, 6 = Neutral.

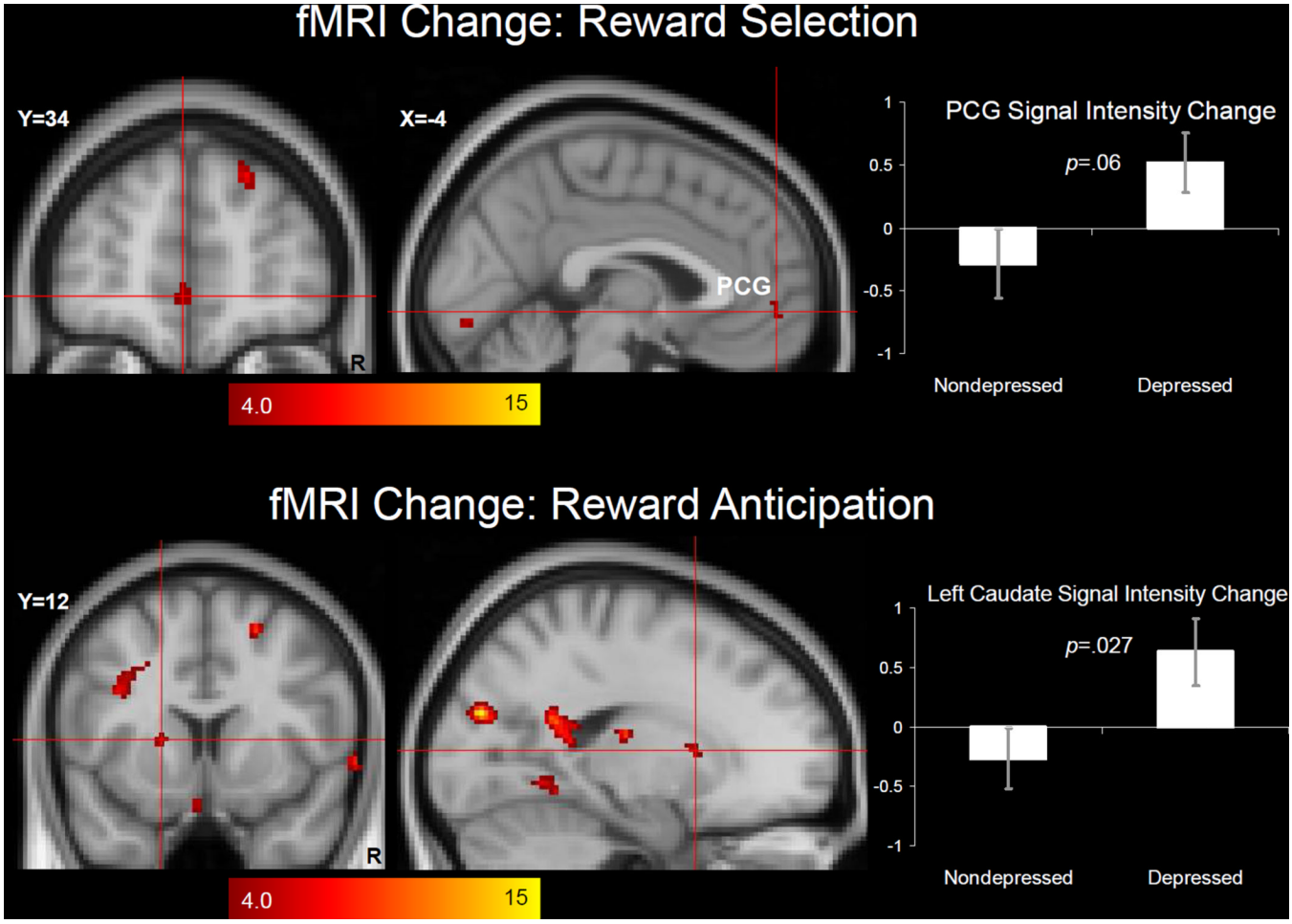

Figure 3.

Reward selection (**top**) and anticipation (**bottom**) fMRI results (money vs. control). Activation images denote voxels with significant Group (Depressed, Nondepressed) X Time (Time 1, Time 2) interactions. Neurological convention (right on right) is used and coordinates are in MNI space. Signal intensity is T statistic units.

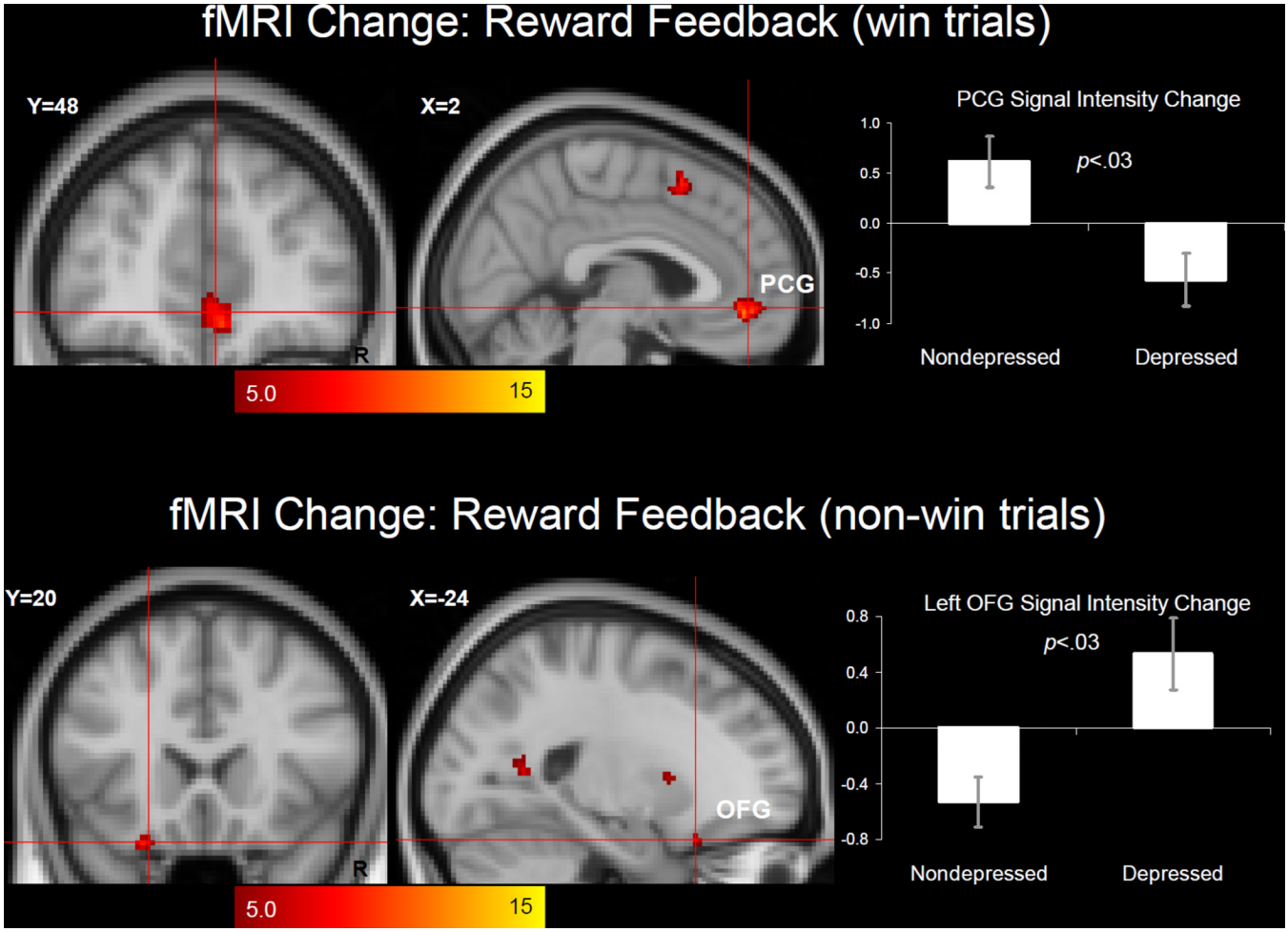

Figure 4.

Reward feedback fMRI results for win (**top**) and non-win (**bottom**) trials, relative to control feedback. Activation images denote voxels with significant Group (Depressed, Nondepressed) X Time (Time 1, Time 2) interactions. Neurological convention (right on right) is used and coordinates are in MNI space. Signal intensity is T statistic units.

Table 1

Means (SDs) of demographics and symptom profiles of participants at both timepoints.

	MDD (n = 12)		Control (n=15)						
	Time 1	**Time 2**	**Time 1**	**Time 2**	**Time 1 Group *p***	**Time 2 Group *p***	**MDD Time *p***	**Control Time *p***	**Group X Time *p***
HAM-D	23.8 (2.3)	8.7 (9.4)	0.2 (0.6)	0.5 (1.1)	<.0001	.0002	<.003	0.217	<.0001
BDI	27.1 (5.1)	11.6 (8.6)	0.7 (1.2)	1.0 (1.4)	<.0001	<.0001	<.0001	0.265	<.0001
JAM*	10.8 (5.1)	12.9 (4.8)	14.7 (2.4)	14.9 (2.8)	0.016	*ns*	*ns*	*ns*	*ns*
BAS Drive*	8.7 (2.1)	9.5 (1.8)	10.5 (2.2)	11.1 (1.8)	0.048	*ns*	*ns*	*ns*	*ns*
BAS Fun-seeking*	9.1 (3.8)	10.5 (3.4)	11.3 (2.1)	11.3 (2.1)	0.072	*ns*	*ns*	*ns*	*ns*
BAS Reward Responsiveness*	15.5 (2.2)	16.3 (2.2)	16.5 (1.7)	16.7 (1.9)	*ns*	*ns*	*ns*	*ns*	*ns*
BIS*	23.5 (4.2)	23.3 (4.0)	18.1 (2.0)	19.1 (3.1)	<0.0001	0.006	*ns*	*ns*	*ns*

Note: HAM-D: Hamilton Rating Scale for Depression (57), 17-item version; BDI: Beck Depression Inventory (58); JAM: Jackson Appetitive Motivation Scale (59); BAS: Behavioral Activation Scale; BIS: Behavioral Inhibition Scale (60). Time 1: Day of pre-treatment scan; Time 2: Day of post-treatment scan.

*Data are missing for one depressed male participant at Time 1

Biol Psychiatry. Author manuscript; available in PMC 2013 May 20.

Table 2

Clusters showing significant Group (Depressed, Nondepressed) X Time (Time 1, Time 2) interactions during monetary **selections** (money vs control). The last columns represent two-tailed paired t-tests (i.e., Time 2 – Time 1) conducted on signal intensity z-values from depressed participants on voxels identified as significant from the interaction tests. Positive t values denote a significant increase in the MDD group after psychotherapy and that negative t values denote a significant decrease in the MDD group after psychotherapy.

Region	Brodmann Area	Size (mm^3)	Z max	Coordinates			Effect of BATD: *t*(p)
				X	Y	Z	
Amygdala (Left)		208	9.1	−14	−8	−12	−3.64 (0.001)
Caudate							
Left		160	6.63	−6	6	2	0.47 (0.64)
Right *		280	6.54	20	22	0	0.66 (0.52)
Right *		280	7.23	12	14	14	1.12 (0.28)
Right *		336	8.02	10	10	2	1.30 (0.21)
Frontal Gyrus (Inferior)							
Left	45	168	5.7	−46	30	8	0.30 (0.77)
Right	46	144	6.29	52	34	10	1.27 (0.22)
Frontal Gyrus (Middle, Right) *	8	680	7.2	48	26	38	.79 (0.087)
Frontal Gyrus (Superior) *							
Left	6	256	9.03	−12	30	58	−3.20 (0.004)
Right	6	640	9.56	18	26	60	1.85 (0.077)
Frontal Orbital Cortex							
Left *	47	384	8.01	−46	26	−8	1.03 (0.31)
Right	47	176	7.96	36	28	−20	0.51 (0.62)
Frontal Pole *							
Left		160	6.86	−16	66	2	0.33 (0.74)
Left	9	664	14.46	−18	62	22	1.46 (0.16)
Right	10	200	9.25	36	66	−4	0.76 (0.46)
Right	46	376	6.71	46	44	−2	1.08 (0.29)
Right	9	1344	13.26	22	44	34	1.76 (0.093)
Hippocampus (Right)	35	232	6.79	−30	−16	−24	1.74 (0.096)
Intracalcarine Cortex (Right)	18	664	7.95	8	−82	2	−1.98 (0.061)

Region	Brodmann Area	Size (mm^3)	Z max	Coordinates			Effect of BATD: *t*(p)
				X	Y	Z	
Lateral Occipital Cortex (Superior, Left)	19	352	8.07	−16	−58	72	−2.12 (0.046)
Lingual Gyrus							
Left	18	136	6.53	−2	−84	−8	1.10 (0.28)
Right *	30	200	6.26	4	−62	6	−1.32 (0.20)
Occipital Pole *							
Left	19	192	8.25	−16	−90	32	−2.51 (0.02)
Left	17	200	8.16	−10	−90	12	−1.52 (0.14)
Paracingulate Gyrus							
Left	32	256	5.72	−2	52	−2	1.98 (0.06)
Left *	6	168	7.02	−10	14	50	1.18 (0.25)
Parietal Lobule (Superior, Right)	7	152	8.31	12	−56	72	−1.49 (0.15)
Postcentral Gyrus (Left) *	4	160	7.07	−56	−12	50	−3.12 (0.005)
Precentral Gyrus							
Left *	6	120	8.06	−28	−8	50	1.14 (0.27)
Left *	6	664	10.85	−12	−28	78	−3.00 (0.007)
Right	6	352	8.57	26	−14	62	1.50 (0.15)
Right	4	392	8.41	44	−10	44	1.13 (0.27)
Precuneous (Left) *	23	504	7.87	−10	−64	18	−1.59 (0.13)
Putamen (Left)		288	6.14	−32	−16	−8	2.56 (0.018)
Supramarginal Gyrus							
Right	40	248	6.03	66	−28	34	2.21 (0.038)
Left	40	288	7.32	−66	−38	38	−2.50 (0.02)
Supramarginal Gyrus (Posterior, Right) *	13	480	5.98	50	−42	30	2.11 (0.047)
Temporal (Posterior Inferior)							
Left	21	152	5.43	−60	−24	−6	2.03 (0.054)
Right	20	208	7.42	46	−34	−18	1.21 (0.24)
Left	20	488	7.64	−62	−18	−20	1.53 (0.14)
Temporal Fusiform (Posterior, Left) *	36	448	6.75	−30	−34	−18	2.18 (0.04)
Temporal Gyrus (Inferior)							

Region	Brodmann Area	Size (mm^3)	Z max	Coordinates			Effect of BATD: *t*(p)
				X	Y	Z	
Right	20	168	6.38	50	−18	−34	1.63 (0.12)
Right		920	8.73	42	−60	−2	−2.08 (0.049)
Temporal Gyrus (Posterior Superior, Left)	42	152	6.77	−62	−28	6	2.05 (0.052)

*Identifies overlap with regions that differentiated groups at baseline (25)

Table 3

Clusters showing significant Group (Depressed, Nondepressed) X Time (Time 1, Time 2) interactions during monetary **anticipation** (money vs control). The last columns represent two-tailed paired *ttests* (i.e., Time 2 – Time 1) conducted on signal intensity z-values from depressed participants on voxels identified as significant from the interaction tests. Positive t values denote a significant increase in the MDD group after psychotherapy and that negative t values denote a significant decrease in the MDD group after psychotherapy.

Region	Brodmann Area	Size (mm^3)	Z max	Coordinates			Effect of BATD: t (p)
				X	Y	Z	
Caudate (Left) *		200	9.1	−18	−18	24	2.36 (0.027)
Cingulate Gyrus (Left)		184	7.6	−10	0	40	2.13 (0.045)
Frontal Gyrus (Middle) *							
Left	9	200	7.3	−36	14	28	1.75 (0.094)
Left	9	1016	13	−28	26	28	3.48 (0.002)
Left	6	184	7.1	−34	14	50	1.44 (0.164)
Frontal Gyrus (Inferior, Left)	13	424	11	−44	24	4	0.57 (0.57)
Frontal Gyrus (Superior, Left)	6	544	10	−16	2	60	2.75 (0.012)
Frontal Orbital Cortex							
Right	47	528	11	38	26	0	0.92 (0.37)
Left	47	136	7.5	−40	30	−10	0.70 (0.49)
Hippocampus (Left) *		408	10	−24	−24	−18	1.98 (0.06)
Insular Cortex (Right)	13	368	11	36	−18	2	2.41 (0.025)
Lingual Gyrus							
Right *	19	600	11	20	−56	−8	1.85 (0.078)
Left	19	2104	11	−20	−56	−10	2.20 (0.038)
Occipital Cortex (Lateral)							
Right	18	720	16	18	−82	24	2.01 (0.057)
Left *	19	192	8.9	−34	−82	20	2.08 (0.049)
Occipital Cortex (Superior, Lateral)							
Right	19	400	7.9	30	−74	44	1.88 (0.073)
Left *	19	168	8	−30	−76	50	2.36 (0.027)
Occipital Fusiform Gyrus (Left) *	18	168	7	−30	−70	−2	1.46 (0.16)
Parahippocampal Gyrus (Posterior, Left)	35	168	8.2	−10	−40	−6	2.69 (0.013)

Region	Brodmann Area	Size (mm^3)	Z max	Coordinates			Effect of BATD: t (p)
				X	Y	Z	
Planum Polare (Right)	38	560	8	46	4	−12	2.00 (0.058)
Postcentral Gyrus							
Right*	5	392	8.5	12	−40	58	1.45 (0.16)
Left	5	1808	11	−8	−40	58	1.52 (0.14)
Precentral Gyrus*							
Right		632	8.9	36	6	30	1.07 (0.30)
Right	4	152	7.7	36	−12	44	2.75 (0.012)
Left	4	208	12	−8	−30	74	1.69 (0.10)
Left	6	152	6.5	−64	2	10	2.14 (0.044)
Precuneous*							
Right	23	1448	11	18	−50	20	2.74 (0.012)
Right	7	384	11	6	−52	68	−1.99 (0.06)
Subcallosal Cortex (Right)	25	256	10	2	8	−18	2.22 (0.037)
Supramarginal Gyrus (Anterior, Right)	40	168	8.5	60	−28	46	−1.92 (0.068)
Supramarginal Gyrus (Posterior, Right)	41	256	7.6	42	−38	6	1.06 (0.30)
Temporal Fusiform Cortex (Posterior)							
Right	20	888	11	40	−12	−24	3.59 (0.002)
Right	36	200	8.2	26	−36	−18	1.03 (0.31)
Temporal Gyrus (Anterior Inferior, Left)	20	192	7.4	−52	−10	−32	−2.87 (0.009)
Temporal Gyrus (Anterior Middle, Right)	21	408	11	64	0	−16	−1.62 (0.12)
Temporal Gyrus (Middle)							
Right	22	1392	10	60	−44	0	0.38 (0.71)
Left	21	128	7.9	−60	−18	−8	1.42 (0.17)
Temporal Gyrus (Posterior Middle, Left)	20	136	7.3	54	−10	−20	0.61 (0.55)
Temporal Pole*							
Left	21	168	11	−58	6	−26	3.23 (0.004)
Left	38	648	8.3	−44	4	−12	2.79 (0.011)
Thalamus*		576	9.6	18	−20	14	1.82 (0.082)

*Identifies overlap with regions that differentiated groups at baseline (25)

Biol Psychiatry. Author manuscript; available in PMC 2013 May 20.

Table 4

Clusters showing significant Group (Depressed, Nondepressed) X Time (Time 1, Time 2) interactions during monetary **feedback**. The last columns represent two-tailed paired ttests (i.e., Time 2 – Time 1) conducted on signal intensity z-values from depressed participants on voxels identified as significant from the interaction tests. Positive t values denote a significant increase in the MDD group after psychotherapy and that negative t values denote a significant decrease in the MDD group after psychotherapy.

Win vs control trials

Region	Brodmann Area	Size (mm^3)	Z Max	Coordinates			Effect of BATD t (p)
				X	Y	Z	
Caudate (Left)		1128	11.41	−16	14	6	−2.16 (0.042)
Cingulate Gyrus (Posterior, Left)	30	120	7.11	−6	−52	18	−2.13 (0.045)
Frontal Gyrus (Superior)							
Left	6	120	8.05	−12	20	66	−1.16 (0.26)
Right	6	528	9.44	2	14	56	−1.3 (0.21)
Insular Cortex (Left)	13	312	10.59	−34	8	−14	−1 (0.33)
Intracalcarine Cortex (Left)	18	184	7.45	−8	−84	8	1.5 (0.15)
Lingual Gyrus (Left)	18	248	10.05	−8	−70	0	1.95 (0.064)
Occipital Cortex (Lateral superior, Right)*	19	120	7.46	30	−72	34	2.64 (0.015)
Paracingulate Gyrus (Right)	24	1968	11.51	4	44	−8	−2.32 (0.03)
Parahippocampal Gyrus (Posterior, Right)	37	536	10.34	18	−40	−16	1.65 (0.11)
Planum Temporale (Left)	21	360	8.43	−40	−4	−18	2.55 (0.018)
Postcentral Gyrus (Left)	2	160	7.64	−58	−18	42	−2.64 (0.015)
Precentral Gyrus (Left)	6	376	12.85	−50	0	48	−1.29 (0.21)
Supramarginal Gyrus (Posterior, Left)	40	120	6.66	−64	−40	28	−1.45 (0.16)
Temporal Fusiform Cortex (Posterior, Right)	20	544	12.83	40	−42	−26	2.24 (0.036)
Temporal Gyrus (Middle posterior, Left)	20	120	8.42	−64	−8	−24	−1.94 (0.066)

Non-win vs control trials

Region	Brodmann Area	Size (mm^3)	Z Max	Coordinates			Effect of BATD t (p)
				X	Y	Z	
Angular Gyrus (Left)	13	1224	9.35	−48	−46	22	3.85 (0.00087)
Frontal Gyrus (Inferior pars opercularis, Right)	44	152	6.91	52	12	2	−0.45 (0.66)
Frontal Gyrus (Superior, Right)	6	168	6.7	4	14	62	−1.66 (0.11)

Non-win vs control trials

Region	Brodmann Area	Size (mm^3)	Z Max	Coordinates			Effect of BATD t (p)
				X	Y	Z	
Frontal Operculum Cortex (Right)	13	344	9.49	30	24	12	1.38 (0.18)
Frontal Orbital Cortex							
Left	47	120	9.02	−24	20	−22	2.42 (0.024)
Left	11	248	8.47	−26	42	−16	−1.71 (0.1)
Lingual Gyrus							
Left	18	208	7.14	−14	−72	0	2.83 (0.0096)
Right*	19	160	8.15	10	−54	−8	1.55 (0.14)
Occipital Cortex (Lateral superior)							
Left	18	424	10.72	−36	−68	22	1.82 (0.082)
Left	19	344	9.7	−38	−78	34	−0.18 (0.86)
Left †	19	448	10.55	−36	−62	46	−2.46 (0.022)
Occipital Fusiform Gyrus (Left)	19	168	9.85	−18	−80	−16	−1.09 (0.29)
Parahippocampal Gyrus (Posterior, Right)	36	288	8.28	18	−38	−16	1.03 (0.32)
Parietal Lobule (Superior, Left)	40	168	6.31	−36	−38	48	−1.88 (0.073)
Planum Polare (Right)	13	960	9.65	44	−12	−6	3.6 (0.0016)
Precentral Gyrus							
Left	6	304	11.01	−50	2	48	−1.72 (0.1)
Left	4	208	6.89	−38	−14	60	−2.1 (0.048)
Right	4	200	8.75	8	−26	78	1.48 (0.15)
Precuneous (Left)	30	480	7.19	−22	−58	10	0.62 (0.54)
Putamen (Left)*		176	7.27	−20	10	6	−2.03 (0.055)
Subcallosal Cortex (Left)	25	152	8.56	−2	8	−6	0.8 (0.43)
Supramarginal Gyrus (Anterior, Left)	40	208	10.06	−60	−32	44	−2.54 (0.019)
Temporal Gyrus (Superior anterior)							
Left	21	184	6.72	−62	2	−12	2.33 (0.029)
Left	21	1424	10.75	−56	−28	−2	2.61 (0.016)
Left	42	208	9.25	−68	−20	6	1.5 (0.15)
Right	21	200	7.69	56	−18	−8	1.89 (0.072)
Right	22	688	10.79	54	−32	2	1.99 (0.06)
Right	22	176	8.52	68	−36	12	2.46 (0.022)

Non-win vs control trials

Region	Brodmann Area	Size (mm^3)	Z Max	Coordinates			Effect of BATD t (p)
				X	Y	Z	
Temporal Pole (Right) *	38	1208	7.94	58	8	−18	3.12 (0.005)

* Identifies overlap with regions that differentiated groups at baseline (25)