Meta-analysis of Reward Processing in Major Depressive Disorder: Distinct Abnormalities within the Reward Circuit?

Tommy H. Ng, Lauren B. Alloy, & David V. Smith
Department of Psychology, Temple University, Philadelphia, PA, USA

Number of Words in the Abstract: 246
Number of Words in the Main Text: 3285
Number of Tables: 2
Number of Figures: 3
Number of Supplemental Information: 1
Short Title: Reward Processing Dysfunction in Depression
Key words: Major depressive disorder; reward; orbitofrontal cortex; ventral striatum; coordinate-based meta-analysis; neuroimaging

Corresponding Author:

David V. Smith, Ph.D.
Assistant Professor of Psychology
Temple University
Weiss Hall, Room 825
1701 North 13th Street
Philadelphia, PA 19122
Office Phone: 215-204-1552
Email: david.v.smith@temple.edu

Abstract

Background: Many neuroimaging studies have investigated reward processing dysfunction in major depressive disorder (MDD). These studies have led to the common idea that MDD is associated with blunted responses within the reward circuit, particularly in the ventral striatum (VS). Yet, the link between MDD and aberrant responses to reward in other brain regions remains inconclusive, thus limiting our understanding of the pathophysiology of MDD.

Methods: We performed a coordinate-based meta-analysis of 46 neuroimaging studies encompassing reward-related responses from a total of 915 patients with MDD and 917 healthy controls (HCs). We only included studies that reported whole-brain results and isolated reward-related processes using an active control condition.

Results: Consistent with the common notion that MDD is characterized by blunted responses to reward, we found that experiments reporting blunted responses for reward in MDD relative to HCs converged in the bilateral VS. In contrast, we found significant convergence among experiments reporting elevated responses for reward in MDD in the right orbitofrontal cortex (OFC). We also found that experiments obtaining greater responses to punishment in MDD converged in the left sublenticular extended amygdala.

Conclusions: Our meta-analytic findings argue against the idea that MDD is linked to a monolithic deficit within the reward system. Instead, our results demonstrate that MDD is associated with opposing abnormalities in the reward circuit: hypo-responses in the VS and hyper-responses in the OFC. These findings help to reconceptualize our understanding of reward-processing abnormalities in MDD, potentially suggesting a role for dysregulated corticostriatal connectivity.

Introduction

Depression is a prevalent mental disorder ranked as the leading cause of disability by the World Health Organization (1). Therefore, it is of paramount importance to understand its underlying neurobiological mechanisms. Over the past decade, theorists have proposed that anhedonia, one of the core symptoms of depression, is linked to reward processing dysfunction (2–11). In particular, many neuroimaging studies have reported reduced activity in the ventral striatum (VS) in response to reward in individuals with major depressive disorder (MDD) as compared with healthy controls (HCs; 12–17) .

The striatum, which can be divided into dorsal and ventral sections, is the primary input zone for basal ganglia (18, 19). It receives afferent projections from the midbrain, amygdala, and prefrontal cortex (PFC), such as the orbitofrontal cortex (OFC), dorsolateral prefrontal cortex (dlPFC), ventromedial prefrontal cortex (vmPFC), and anterior cingulate cortex (ACC; 18, 19). It also projects to such regions as the ventral pallidum, ventral tegmental area, and substantia nigra (19). Many of the regions linked to the striatum, particularly prefrontal regions, have been associated with the computation and representation of reward value (20–31), as well as the regulation of affect and reward-related behavior in animals and healthy individuals (32–36).

Although blunted striatal response to reward in MDD is a well-established finding in the literature (2, 6, 37–39), it is less clear how other regions, particularly the PFC, also may contribute to reward-processing deficits in MDD. For instance, some studies have found that relative to HCs, MDD exhibited greater activation in the OFC (16, 40), dlPFC (15, 41), vmPFC (42, 43), ACC (44, 45), middle frontal gyrus (43, 45), inferior frontal gyrus (44, 46), subgenual cingulate (42, 46), and dorsomedial prefrontal cortex (43) during the processing of rewarding stimuli. In contrast, other studies have reported less activity in MDD in response to reward in the OFC (40, 45), ACC (15, 16, 40, 46), middle frontal gyrus (16, 44, 46), and

frontal pole (45). The inconsistencies may be due to a number of factors, such as limited statistical power (47, 48) and susceptibility artifacts in the PFC (32, 49–51). Therefore, the association between prefrontal regions and MDD remains equivocal, both in terms of the *direction* (i.e., hyper- or hypo-responses) and the *location* of the effect (e.g., OFC, dlPFC, vmPFC and/or ACC).

To address this problem, we performed a coordinate-based meta-analysis of 46 neuroimaging studies containing reward-related responses from a total of 915 patients with MDD and 917 HCs. Our primary hypothesis was that compared with HCs, individuals with MDD would exhibit blunted activation of the striatum and abnormal activation of the prefrontal regions (e.g., the OFC) during the processing of rewarding stimuli. We also explored whether there were consistent neural responses to punishing stimuli in MDD relative to HCs. The comprehensive nature of the current meta-analysis allowed us to investigate whether a quantitative synthesis of neuroimaging studies on reward processing dysfunction in MDD would unveil common activation patterns that may be difficult to discern by individual studies due to inconsistent findings. Our analyses addressed two specific questions. First, which brain regions show consistent hypo-responses to reward-relevant stimuli in MDD relative to HCs? Second, which brain regions show consistent hyper-responses to reward-relevant stimuli in MDD relative to HCs?

Methods and Materials

Study Selection

We conducted a systematic literature search to identify neuroimaging studies on reward processing abnormalities in mood disorders (Figure 1). Potentially eligible studies published between 1/1/1997 and 3/14/2017 were identified by searching the MEDLINE, EMBASE,

PsycINFO, PsycARTICLES, Scopus, and Web of Science using the grouped terms (fMRI* or PET*) AND (depress* OR bipolar* OR mania* OR manic* OR hypomania* OR hypomanic*) AND (reward* OR effort* OR decision* OR reinforce* OR habit* OR discounting* OR "prediction error" OR "delayed gratification" OR "approach motivation" OR "positive valence systems"). To enhance search sensitivity, the reference lists of the retrieved articles and review papers were further checked to identify potentially relevant articles. Although our initial goal was to investigate reward processing dysfunction in both MDD and bipolar disorder, the current meta-analysis only focused on MDD due to an inadequate number of studies on bipolar disorder.

Inclusion Criteria

We included studies that (a) used a reward and/or punishment task, (b) reported comparisons between people with MDD and HCs, (c) used standardized diagnostic criteria (e.g., DSM) to determine psychiatric diagnoses, (d) used fMRI or PET in conjunction with parametric analysis or subtraction methodology contrasting an experimental condition and an active control condition (e.g., a punishment condition, a lower-intensity reward condition, or a neutral condition) to isolate reward-related processes and identify foci of task-related neural changes, (e) reported significant results of whole-brain group analyses, as non-whole-brain coordinates (e.g., region of interest-based coordinates) have been argued to bias coordinate-based meta-analyses (52), (f) reported coordinates in a standard stereotactic space [Talairach or Montreal Neurological Institute (MNI) space], and (g) used independent samples.

The study with the largest sample size was included if there was sample overlap between studies. Reward tasks were operationalized as involving presentation of a rewarding stimulus (e.g., winning money, favorite music, positive faces), whereas punishment tasks were operationalized as involving presentation of a punishing stimulus (e.g., losing money, negative faces).

Coordinate-Based Meta-Analysis

Coordinate-based meta-analyses were performed using GingerALE 2.3.6 (http://brainmap.org), which employs the activation likelihood estimation (ALE) method (53–55). The ALE method tests against the null hypothesis that activation foci reported in a body of studies are uniformly distributed across the brain, as opposed to concentrated in certain regions (53). The method is implemented in the following steps. First, for each included study, a map of the activation likelihood is computed. Second, the maps are aggregated to compute the ALE score for each voxel. The ALE statistic indicates the probability that at least one true peak activation lies in the voxel across the population of all possible studies. Finally, a permutation test is employed to identify voxels in which the ALE statistic is larger than expected by chance (53–56). The ALE method takes into account heterogeneity in spatial uncertainty across studies (53, 55, 56) and differences in number of peak coordinates reported per cluster (55). This approach allows random-effects estimates of ALE, increasing generalizability of the results (56).

Statistical Analysis

Our analysis focused on which brain regions show consistent hypo- or hyper-responses to reward-relevant stimuli in MDD relative to HCs. To ensure adequate statistical power and limit the possibility that a meta-analytic effect is driven by a small set of studies (52, 57), we only conducted a meta-analysis if there was at least 17 independent studies available for analysis. We also took steps to minimize within-group effects on the meta-analyses (55). If a study reported more than one contrast (often referred to as an “experiment” in meta-analyses), the contrasts examining similar processes were pooled together to avoid double counting the same participants in a meta-analysis. For example, when a study reported between-group effects in response to $1.50 and $5 rewards relative to neutral or loss

conditions, the coordinates derived from the two contrasts were coded as a single reward experiment.

All analyses were performed in Montreal Neurological Institute (MNI) space. Coordinates reported in Talairach space were converted to MNI using the "icbm2tal" transformation (58). We assessed statistical significance and corrected for multiple comparisons using the permutation-based approach (N = 1000) recommended by the developers of GingerALE (52, 59). This approach utilized a cluster-forming threshold of $P < 0.001$ (uncorrected) and maintained a cluster-level family-wise error rate of 5% (52).

Results

Given the inconsistency of findings in the literature of reward processing abnormalities in MDD, we used a coordinate-based meta-analytic approach and activation likelihood estimation (53, 56) to examine whether we could identify consistent activation patterns across studies. As shown in Figure 1, our systematic literature search identified a total of 46 neuroimaging studies that met our inclusion criteria, yielding 4 coordinate-based meta-analyses with at least 17 independent experiments. Tables S1 and S2 show the characteristics of the included studies and their samples. In the present meta-analytic dataset, for the MDD group, the mean number of participants was 20.3, the mean age was 35.9, the mean percentage of females was 61.6%, and the mean percentage of medication usage was 36.6%. For the HC group, the mean number of participants was 20.4, the mean age was 34.5, and the mean percentage of females was 60.5%.

Aberrant Reward Responses in MDD

A host of studies have reported blunted responses to reward in MDD. These findings tend to converge on the striatum. We therefore first examined regions that consistently showed

blunted responses to reward. We synthesized results of 26 studies reporting less activity in response to reward in people with MDD than HCs (i.e. HC > MDD for reward > punishment/neutral stimuli or neutral stimuli > punishment). As expected, our results indicated that these studies reliably reported less activation in the bilateral VS in MDD (Table 1; Figure 2a).

As the striatum receives afferent projections from many prefrontal regions, such as the OFC and the vmPFC, we hypothesized that MDD would be associated with abnormal activation of the prefrontal regions (e.g., the OFC) during the processing of rewarding stimuli. To examine this hypothesis, we aggregated results of 22 studies reporting greater activity in response to reward in people with MDD than HCs (i.e. MDD > HC for reward > punishment/neutral stimuli or neutral stimuli > punishment). Importantly, our results indicated that these studies reliably reported greater activation in the right OFC in MDD (Table 1; Figure 2b). Taken together, these results suggest that relative to HCs, people with MDD exhibited hypo-responses in the VS and, more importantly, hyper-responses in the OFC to rewarding stimuli.

Hyper Punishment Responses in MDD

We also conducted exploratory analyses to examine which brain regions consistently show aberrant responses to punishment in MDD relative to HCs. First, we meta-analyzed 25 studies reporting greater activity in response to punishment in people with MDD than HCs (i.e. MDD > HC for punishment > reward/neutral stimuli or neutral stimuli > reward). Our results indicated that these studies reliably reported greater activation in the left sublenticular extended amygdala in MDD (Table 2; Figure 3). Second, we synthesized 19 studies reporting less activity in response to punishment in people with MDD than HCs (i.e. HC > MDD for punishment > reward/neutral stimuli or neutral stimuli > reward). Our results indicated that these studies did not report consistent activation patterns. Together, these results suggest that

relative to HCs, people with MDD exhibited hyper-responses in the left sublenticular extended amygdala during processing of punishment-relevant stimuli.

Discussion

A growing number of researchers have studied reward processing dysfunction using neuroimaging methods to enhance our understanding of the underlying pathophysiology of MDD. Many of these studies have shown that patients with MDD exhibit blunted responses to reward in the VS, but more disparate patterns of responses in other brain areas (12–16). Therefore, it remains unclear what brain regions, other than the VS, are most consistently implicated in reward processing among people with MDD. To address this issue, we performed a coordinate-based meta-analysis of 46 neuroimaging studies containing reward-related responses from a total of 915 patients with MDD and 917 HCs. Our meta-analytic findings confirm that reward responses within the VS are consistently blunted in MDD relative to HCs across studies. In contrast, we find that reward responses within the OFC are consistently elevated in MDD. Contrary to the common notion that MDD is characterized by blunted responses to reward, these findings suggest that MDD may be characterized by both hypo- and hyper-responses to reward at the neural level and highlight the need for a more fine-tuned understanding of the various components of reward processing in MDD.

Although our striatal findings are consistent with previous meta-analytic work documenting abnormalities in processing of positive or reward stimuli in MDD (37, 38), we emphasize that our work differs in two key ways. First, our results implicate highly specific—yet distinct—abnormalities in the reward circuit, with hypo-responses to reward in the VS and hyper-responses to reward in the OFC. In sharp contrast, prior meta-analytic work has generally reported distributed patterns of abnormalities, with little anatomical agreement across studies. For instance, although prior meta-analytic efforts have shown some

overlapping findings in parts of the visual cortex, ACC, and basal ganglia, we note that there is a striking degree of disagreement across these efforts, with non-overlapping findings all throughout the brain (see Table S3 for a complete comparison of findings across studies). The lack of agreement across studies can be due potentially to the heterogeneous nature of the disorder and the included studies, as well as methodological problems, such as inclusion of region-of-interest (ROI) coordinates and overlapping samples, inadequate power due to low number of included studies, and differences in inclusion/exclusion criteria (60).

Second, the analysis methods employed in our study are state-of-the-art and more rigorous than prior studies in this area. For instance, the current meta-analysis attempts to minimize methodological issues by using more stringent criteria recommended by new guidelines (60–62), such as only including whole-brain studies that used an active control condition and independent samples, correcting for multiple comparisons, and only conducting a meta-analysis when there were at least 17 eligible experiments to ensure adequate statistical power and restrict excessive contribution of any particular studies to cluster-level thresholding (52). We speculate that the enhanced rigor and methods of our study contributed to our ability to identify highly circumscribed and distinct abnormalities in the reward circuit.

In our view, our most important finding is that studies consistently report that people with MDD exhibit hyper-responses to reward in the OFC. Exposure to rewards (e.g., money and pleasant sights) evokes activity in the OFC (20–22, 24, 25, 63). Therefore, given that MDD is traditionally linked to blunted response to reward or reduced capacity to experience pleasure (6), our finding of hyperactivity of the OFC in response to reward in MDD may seem paradoxical. One interpretation would be that MDD is at least partly characterized by hypersensitivity to reward, which fits with a set of experimental studies reporting that individuals with severe MDD found dextroamphetamine to be more rewarding than did

controls (64–66). Anhedonia, then, may be rooted in decreased connectivity between the prefrontal regions and subcortical regions underlying reward-related behavior, as suggested by previous research (67).

Alternatively, OFC hyperactivity may reflect enhanced inhibitory control over subcortical regions underlying reward-related behavior, causing anhedonia. Optogenetic and neuroimaging studies have revealed that hyperactivity in prefrontal regions (e.g., medial PFC, vmPFC) innervated by glutamatergic neurons may causally inhibit reward-related behavior via suppressing striatal responses to dopamine neurons in the midbrain (4, 33) and increasing connectivity between the medial PFC, lateral OFC, and VS (4, 33). In addition, increased negative effective connectivity between the orbital and medial PFC and amygdala in response to reward has been found in MDD but not bipolar depression or healthy controls (68), suggesting that the OFC might exert over-control over subcortical regions in MDD but not bipolar depression or healthy individuals. The differences in the effects of OFC between the groups might be explained by research demonstrating that stimulation of the medial PFC at different frequencies affect dopamine release in the VS differently. Specifically, although stimulation of the medial PFC at low frequencies (10 Hz), which correspond to the firing rate of PFC neurons during performance of cognitive tasks, decreased dopamine release in the VS, high frequency stimulation (60 Hz) increased dopamine release in the VS (33, 69) and has strong antidepressant effects (70, 71). Taken together, OFC hyperactivity may inhibit reward-related behavior and lead to anhedonia via suppressing striatal responses to dopamine neurons in the midbrain (4, 33) and increasing connectivity between the PFC and the VS in MDD (4, 33).

The role of corticostriatal connectivity during reward processing in MDD remains an open and important question (72). We believe our meta-analytic results will provide a springboard for future studies that seek to understand the role of dysregulated corticostriatal

connectivity in MDD and develop a full picture of the pathophysiology of MDD. These endeavors will require empirical assessments of connectivity within the reward circuit using psychophysiological interaction analysis (73–75) and dynamic causal modeling (76). Such approaches have shown promise for revealing specific patterns of task-dependent corticostriatal interactions in samples containing healthy individuals (77–80), clinical populations (67, 72, 81), or a mix of both (82). Nevertheless, a caveat of such approaches is that dysregulated corticostriatal connectivity may involve modulatory regions, such as the midbrain (83). Taken together, our results help delineate specific abnormalities within the reward circuit and supply a foundation for refining connectivity-based models of psychopathology.

In addition to distinct abnormalities with the reward circuit, our study also finds that MDD is associated with hyper-responses in the left sublenticular extended amygdala in response to punishment. Our finding fits with others in suggesting that amygdala hyperactivation is linked to the processing of affectively salient, especially punishing, stimuli in MDD, and may underlie negativity bias in depression (84, 85). It is also in agreement with a long series of studies indicating that the amygdala may be a key brain region implicated in the pathophysiology of depression (86–88).

Although our meta-analysis reveals circumscribed patterns of abnormal responses to affective stimuli in the amygdala, VS, and OFC, we note that our findings should be interpreted in the context of two limitations. First, heterogeneity across studies may have added noise to our analyses and restricted our capacity for detecting true effects. Specifically, due to the limited number of studies, our analyses collapsed across different reward processes (e.g., anticipation and outcome), reward modalities (e.g., monetary and social), and specific contrasts that would help isolate and differentiate neural responses to salience and valence (31, 89–92). In addition, our analyses also collapsed across different mood states,

psychotropic medication usage, ages, and comorbidities (88, 93, 94). In doing so, important differences in brain activation may be obscured and more specific questions related to brain activation—particularly questions related to neural representations of valence or salience (89, 95–97)—cannot be addressed in our work. Future studies should examine how these factors may affect reward processing in MDD. Nevertheless, we highlight that the convergence of findings despite the heterogeneity of the included studies is striking and suggests that the current findings may reflect trait abnormalities of MDD. Second, many included studies have relatively small sample sizes and report coordinates that are not corrected for multiple comparisons, which may lead to biased results (47, 48). The validity of a meta-analysis hinges on the validity of the included studies (98). Future work should follow the most updated guidelines for best practices in the field to avoid generating biased findings (99).

Notwithstanding these caveats, our meta-analysis shows that MDD is consistently associated with opposing abnormalities in the reward circuit in response to reward: hypo-response in the VS and hyper-response in the OFC. Our meta-analytic results therefore argue against the common notion that MDD is only associated with blunted responses to reward. Our findings suggest that MDD may be tied to opposing abnormalities in the OFC and VS, which may suggest MDD stems, in part, from dysregulated connectivity between these regions. We believe our findings will help lay a foundation towards developing a more refined understanding and treatment of MDD and its comorbid psychiatric disorders, particularly ones that involve persistent maladaptive behavior (100). For example, a more refined understanding of the abnormalities in the reward circuitry in MDD may help distinguish other disorders exhibiting reward processing abnormalities, such as bipolar disorder and schizophrenia (6). Finally, given that previous treatment targets for deep brain

stimulation for treatment-resistant depression have yielded mixed results (101–110), the portion of OFC implicated by our results could be a promising treatment target.

Acknowledgements

This work was supported, in part, by a grant from the National Institutes of Health (R21-MH113917 to DVS). We note that the manuscript was posted on bioRxiv as a preprint. Study materials are available on Open Science Framework at https://osf.io/sjb4d. Images are available on the NeuroVault repository at https://neurovault.org/collections/3884.

Disclosures

All authors report no biomedical financial interests or potential conflicts of interest.

References

1. World Health Organization (2017): *Depression and other common mental disorders: global health estimates*. .

2. Heshmati M, Russo SJ (2015): Anhedonia and the brain reward circuitry in depression. *Curr Behav Neurosci Rep*. 2: 146–153.

3. Pizzagalli DA (2014): Depression, stress, and anhedonia: toward a synthesis and integrated model. *Annu Rev Clin Psychol*. 10: 393–423.

4. Robbins TW (2016): Illuminating anhedonia. *Science*. 351: 24–25.

5. Treadway MT, Zald DH (2011): Reconsidering Anhedonia in Depression: Lessons from Translational Neuroscience. *Neurosci Biobehav Rev*. 35: 537–555.

6. Whitton AE, Treadway MT, Pizzagalli DA (2015): Reward processing dysfunction in major depression, bipolar disorder and schizophrenia. *Curr Opin Psychiatry*. 28: 7–12.

7. Nusslock R, Alloy LB (2017): Reward Processing and Mood-Related Symptoms: An RDoC and Translational Neuroscience Perspective. *J Affect Disord*. 216: 3–16.

8. Alloy LB, Olino T, Freed RD, Nusslock R (2016): Role of Reward Sensitivity and Processing in Major Depressive and Bipolar Spectrum Disorders. *Behav Ther*. 47: 600–621.

9. Olino TM (2016): Future Research Directions in the Positive Valence Systems: Measurement, Development, and Implications for Youth Unipolar Depression. *J Clin Child Adolesc Psychol Off J Soc Clin Child Adolesc Psychol Am Psychol Assoc Div 53*. 45: 681–705.

10. Olino TM, McMakin DL, Morgan JK, Silk JS, Birmaher B, Axelson DA, *et al*. (2014): Reduced reward anticipation in youth at high-risk for unipolar depression: A

preliminary study. *Dev Cogn Neurosci*, Developmental Social and Affective Neuroscience. 8: 55–64.

11. Olino TM, McMakin DL, Dahl RE, Ryan ND, Silk JS, Birmaher B, *et al*. (2011): "I won, but I'm not getting my hopes up": Depression moderates the relationship of outcomes and reward anticipation. *Psychiatry Res Neuroimaging*. 194: 393–395.
12. Arrondo G, Segarra N, Metastasio A, Ziauddeen H, Spencer J, Reinders NR, *et al*. (2015): Reduction in ventral striatal activity when anticipating a reward in depression and schizophrenia: a replicated cross-diagnostic finding. *Front Psychol*. 6. doi: 10.3389/fpsyg.2015.01280.
13. Knutson B, Bhanji JP, Cooney RE, Atlas LY, Gotlib IH (2008): Neural responses to monetary incentives in major depression. *Biol Psychiatry*. 63: 686–692.
14. McCabe C, Cowen PJ, Harmer CJ (2009): Neural representation of reward in recovered depressed patients. *Psychopharmacology (Berl)*. 205: 667–677.
15. Pizzagalli DA, Holmes AJ, Dillon DG, Goetz EL, Birk JL, Bogdan R, *et al*. (2009): Reduced Caudate and Nucleus Accumbens Response to Rewards in Unmedicated Subjects with Major Depressive Disorder. *Am J Psychiatry*. 166: 702–710.
16. Smoski MJ, Felder J, Bizzell J, Green SR, Ernst M, Lynch TR, Dichter GS (2009): FMRI of Alterations in Reward Selection, Anticipation, and Feedback in Major Depressive Disorder. *J Affect Disord*. 118: 69–78.
17. Luking KR, Pagliaccio D, Luby JL, Barch DM (2016): Reward Processing and Risk for Depression Across Development. *Trends Cogn Sci*. 20: 456–468.
18. Haber SN (2016): Corticostriatal circuitry. *Dialogues Clin Neurosci*. 18: 7–21.
19. Haber SN, Knutson B (2010): The reward circuit: Linking primate anatomy and human imaging. *Neuropsychopharmacology*. 35: 4–26.

20. Berridge KC, Kringelbach ML (2015): Pleasure Systems in the Brain. *Neuron*. 86: 646–664.

21. Der-Avakian A, Markou A (2012): The neurobiology of anhedonia and other reward-related deficits. *Trends Neurosci*. 35: 68–77.

22. Kringelbach ML (2005): The human orbitofrontal cortex: linking reward to hedonic experience. *Nat Rev Neurosci*. 6: 691–702.

23. Levy DJ, Glimcher PW (2012): The root of all value: a neural common currency for choice. *Curr Opin Neurobiol*. 22: 1027–1038.

24. Padoa-Schioppa C (2011): Neurobiology of economic choice: A good-based model. *Annu Rev Neurosci*. 34: 333–359.

25. Padoa-Schioppa C, Conen KE (2017): Orbitofrontal Cortex: A Neural Circuit for Economic Decisions. *Neuron*. 96: 736–754.

26. Rangel A, Camerer C, Montague PR (2008): A framework for studying the neurobiology of value-based decision making. *Nat Rev Neurosci*. 9: 545–556.

27. Saez RA, Saez A, Paton JJ, Lau B, Salzman CD (2017): Distinct Roles for the Amygdala and Orbitofrontal Cortex in Representing the Relative Amount of Expected Reward. *Neuron*. 95: 70-77.e3.

28. Smith DV, Delgado MR (2015): Reward Processing. In: Toga AW, editor. *Brain Mapp Encycl Ref*, 1st ed. Waltham, MA: Academic Press, pp 361–366.

29. Smith DV, Huettel SA (2010): Decision Neuroscience: Neuroeconomics. *Wiley Interdiscip Rev Cogn Sci*. 1: 854–871.

30. Stalnaker TA, Cooch NK, Schoenbaum G (2015): What the orbitofrontal cortex does not do. *Nat Neurosci*. 18: 620–627.

31. Wang KS, Smith DV, Delgado MR (2016): Using fMRI to study reward processing in humans: past, present, and future. *J Neurophysiol*. 115: 1664–1678.

32. Delgado MR, Beer JS, Fellows LK, Huettel SA, Platt ML, Quirk GJ, Schiller D (2016, November 29): Viewpoints: Dialogues on the functional role of the ventromedial prefrontal cortex. *Nat Neurosci*. News. doi: 10.1038/nn.4438.

33. Ferenczi EA, Zalocusky KA, Liston C, Grosenick L, Warden MR, Amatya D, *et al*. (2016): Prefrontal cortical regulation of brainwide circuit dynamics and reward-related behavior. *Science*. 351: aac9698.

34. Peters J, Büchel C (2010): Neural representations of subjective reward value. *Behav Brain Res*. 213: 135–141.

35. Phelps EA, Lempert KM, Sokol-Hessner P (2014): Emotion and decision making: multiple modulatory neural circuits. *Annu Rev Neurosci*. 37: 263–287.

36. Voorn P, Vanderschuren LJMJ, Groenewegen HJ, Robbins TW, Pennartz CMA (2004): Putting a spin on the dorsal-ventral divide of the striatum. *Trends Neurosci*. 27: 468–474.

37. Zhang WN, Chang SH, Guo LY, Zhang KL, Wang J (2013): The neural correlates of reward-related processing in major depressive disorder: A meta-analysis of functional magnetic resonance imaging studies. *J Affect Disord*. 151: 531–539.

38. Groenewold NA, Opmeer EM, de Jonge P, Aleman A, Costafreda SG (2013): Emotional valence modulates brain functional abnormalities in depression: Evidence from a meta-analysis of fMRI studies. *Neurosci Biobehav Rev*. 37: 152–163.

39. Hanson JL, Hariri AR, Williamson DE (2015): Blunted ventral striatum development in adolescence reflects emotional neglect and predicts depressive symptoms. *Biol Psychiatry*. 78: 598–605.

40. Forbes EE, May JC, Siegle GJ, Ladouceur CD, Ryan ND, Carter CS, *et al*. (2006): Reward-Related Decision-Making in Pediatric Major Depressive Disorder: An fMRI Study. *J Child Psychol Psychiatry*. 47: 1031–1040.

41. Demenescu LR, Renken R, Kortekaas R, van Tol M-J, Marsman JBC, van Buchem MA, *et al*. (2011): Neural correlates of perception of emotional facial expressions in out-patients with mild-to-moderate depression and anxiety. A multicenter fMRI study. *Psychol Med*. 41: 2253–2264.

42. Rizvi SJ, Salomons TV, Konarski JZ, Downar J, Giacobbe P, McIntyre RS, Kennedy SH (2013): Neural response to emotional stimuli associated with successful antidepressant treatment and behavioral activation. *J Affect Disord*. 151: 573–581.

43. Keedwell PA, Andrew C, Williams SCR, Brammer MJ, Phillips ML (2005): A double dissociation of ventromedial prefrontal cortical responses to sad and happy stimuli in depressed and healthy individuals. *Biol Psychiatry*. 58: 495–503.

44. Mitterschiffthaler MT, Kumari V, Malhi GS, Brown RG, Giampietro VP, Brammer MJ, *et al*. (2003): Neural response to pleasant stimuli in anhedonia: an fMRI study. *Neuroreport*. 14: 177–182.

45. Dichter GS, Kozink RV, McClernon FJ, Smoski MJ (2012): Remitted major depression is characterized by reward network hyperactivation during reward anticipation and hypoactivation during reward outcomes. *J Affect Disord*. 136: 1126–1134.

46. Kumari V, Mitterschiffthaler MT, Teasdale JD, Malhi GS, Brown RG, Giampietro V, *et al*. (2003): Neural abnormalities during cognitive generation of affect in treatment-resistant depression. *Biol Psychiatry*. 54: 777–791.

47. Button KS, Ioannidis JPA, Mokrysz C, Nosek BA, Flint J, Robinson ESJ, Munafò MR (2013): Power failure: why small sample size undermines the reliability of neuroscience. *Nat Rev Neurosci*. 14: 365–376.

48. Jia X-Z, Zhao N, Barton B, Burciu R, Carriere N, Cerasa A, *et al*. (2018): Small effect size leads to reproducibility failure in resting-state fMRI studies. *bioRxiv*. 285171.

49. Andersson JL, Hutton C, Ashburner J, Turner R, Friston K (2001): Modeling geometric deformations in EPI time series. *NeuroImage*. 13: 903–919.

50. Chase HW, Kumar P, Eickhoff SB, Dombrovski AY (2015): Reinforcement learning models and their neural correlates: An activation likelihood estimation meta-analysis. *Cogn Affect Behav Neurosci*. 15: 435–459.

51. Ojemann JG, Akbudak E, Snyder AZ, McKinstry RC, Raichle ME, Conturo TE (1997): Anatomic localization and quantitative analysis of gradient refocused echo-planar fMRI susceptibility artifacts. *NeuroImage*. 6: 156–167.

52. Eickhoff SB, Nichols TE, Laird AR, Hoffstaedter F, Amunts K, Fox PT, *et al*. (2016): Behavior, sensitivity, and power of activation likelihood estimation characterized by massive empirical simulation. *NeuroImage*. 137: 70–85.

53. Eickhoff SB, Bzdok D, Laird AR, Kurth F, Fox PT (2012): Activation Likelihood Estimation meta-analysis revisited. *Neuroimage*. 59: 2349–2361.

54. Laird AR, Fox PM, Price CJ, Glahn DC, Uecker AM, Lancaster JL, *et al*. (2005): ALE meta-analysis: controlling the false discovery rate and performing statistical contrasts. *Hum Brain Mapp*. 25: 155–164.

55. Turkeltaub PE, Eickhoff SB, Laird AR, Fox M, Wiener M, Fox P (2012): Minimizing within-experiment and within-group effects in Activation Likelihood Estimation meta-analyses. *Hum Brain Mapp*. 33: 1–13.

56. Eickhoff SB, Laird AR, Grefkes C, Wang LE, Zilles K, Fox PT (2009): Coordinate-based activation likelihood estimation meta-analysis of neuroimaging data: a random-effects approach based on empirical estimates of spatial uncertainty. *Hum Brain Mapp*. 30: 2907–2926.

57. Smith DV, Delgado MR (2017): Meta-analysis of psychophysiological interactions: Revisiting cluster-level thresholding and sample sizes. *Hum Brain Mapp*. 38: 588–591.

58. Lancaster JL, Tordesillas-Gutiérrez D, Martinez M, Salinas F, Evans A, Zilles K, *et al*. (2007): Bias between MNI and Talairach coordinates analyzed using the ICBM-152 brain template. *Hum Brain Mapp*. 28: 1194–1205.

59. Eickhoff SB, Laird AR, Fox PM, Lancaster JL, Fox PT (2017): Implementation Errors in the GingerALE Software: Description and Recommendations. *Hum Brain Mapp*. 38: 7–11.

60. Muller VI, Cieslik EC, Serbanescu I, Laird AR, Fox PT, Eickhoff SB (2016): Altered Brain Activity in Unipolar Depression Revisited: Meta-analyses of Neuroimaging Studies. *JAMA Psychiatry*. . doi: 10.1001/jamapsychiatry.2016.2783.

61. Muller VI, Cieslik EC, Laird AR, Fox PT, Radua J, Mataix-Cols D, *et al*. (2017): Ten simple rules for neuroimaging meta-analysis. *Neurosci Biobehav Rev*. . doi: 10.1016/j.neubiorev.2017.11.012.

62. Barch DM, Pagliaccio D (2017): Consistency, Replication, and Meta-analyses of Altered Brain Activity in Unipolar Depression. *JAMA Psychiatry*. 74: 56–57.

63. Rolls ET (2017): The orbitofrontal cortex and emotion in health and disease, including depression. *Neuropsychologia*. . doi: 10.1016/j.neuropsychologia.2017.09.021.

64. Tremblay LK, Naranjo CA, Graham SJ, Herrmann N, Mayberg HS, Hevenor S, Busto UE (2005): Functional Neuroanatomical Substrates of Altered Reward Processing in Major Depressive Disorder Revealed by a Dopaminergic Probe. *Arch Gen Psychiatry*. 62: 1228–1236.

65. Tremblay LK, Naranjo CA, Cardenas L, Herrmann N, Busto UE (2002): Probing Brain Reward System Function in Major Depressive Disorder: Altered Response to Dextroamphetamine. *Arch Gen Psychiatry*. 59: 409–416.

66. Naranjo CA, Tremblay LK, Busto UE (2001): The role of the brain reward system in depression. *Prog Neuropsychopharmacol Biol Psychiatry*. 25: 781–823.

67. Young KD, Bodurka J, Drevets WC (2016): Differential neural correlates of autobiographical memory recall in bipolar and unipolar depression. *Bipolar Disord*. 18: 571–582.

68. Almeida JRC de, Versace A, Mechelli A, Hassel S, Quevedo K, Kupfer DJ, Phillips ML (2009): Abnormal amygdala-prefrontal effective connectivity to happy faces differentiates bipolar from major depression. *Biol Psychiatry*. 66: 451–459.

69. Jackson ME, Frost AS, Moghaddam B (2001): Stimulation of prefrontal cortex at physiologically relevant frequencies inhibits dopamine release in the nucleus accumbens. *J Neurochem*. 78: 920–923.

70. Steinberg EE, Christoffel DJ, Deisseroth K, Malenka RC (2015): Illuminating circuitry relevant to psychiatric disorders with optogenetics. *Curr Opin Neurobiol*. 0: 9–16.

71. Covington HE, Lobo MK, Maze I, Vialou V, Hyman JM, Zaman S, *et al*. (2010): Antidepressant effect of optogenetic stimulation of the medial prefrontal cortex. *J Neurosci Off J Soc Neurosci*. 30: 16082–16090.

72. Admon R, Pizzagalli DA (2015): Dysfunctional Reward Processing in Depression. *Curr Opin Psychol*. 4: 114–118.

73. Friston KJ, Buechel C, Fink GR, Morris J, Rolls E, Dolan RJ (1997): Psychophysiological and Modulatory Interactions in Neuroimaging. *NeuroImage*. 6: 218–229.

74. McLaren DG, Ries ML, Xu G, Johnson SC (2012): A generalized form of context-dependent psychophysiological interactions (gPPI): a comparison to standard approaches. *NeuroImage*. 61: 1277–1286.

75. Smith DV, Gseir M, Speer ME, Delgado MR (2016): Toward a cumulative science of functional integration: A meta-analysis of psychophysiological interactions. *Hum Brain Mapp*. 37: 2904–2917.

76. Friston KJ, Harrison L, Penny W (2003): Dynamic causal modelling. *NeuroImage*. 19: 1273–1302.

77. Chatham CH, Frank MJ, Badre D (2014): Corticostriatal Output Gating during Selection from Working Memory. *Neuron*. 81: 930–942.

78. Smith DV, Rigney AE, Delgado MR (2016): Distinct Reward Properties are Encoded via Corticostriatal Interactions. *Sci Rep*. 6: 20093.

79. Wimmer GE, Daw ND, Shohamy D (2012): Generalization of value in reinforcement learning by humans. *Eur J Neurosci*. 35: 1092–1104.

80. Wimmer GE, Shohamy D (2012): Preference by Association: How Memory Mechanisms in the Hippocampus Bias Decisions. *Science*. 338: 270–273.

81. Admon R, Pizzagalli DA (2015): Corticostriatal pathways contribute to the natural time course of positive mood. *Nat Commun*. 6: 10065.

82. Hanson JL, Knodt AR, Brigidi BD, Hariri AR (2017): Heightened connectivity between the ventral striatum and medial prefrontal cortex as a biomarker for stress-related psychopathology: understanding interactive effects of early and more recent stress. *Psychol Med*. 1–9.

83. Murty VP, Shermohammed M, Smith DV, Carter RM, Huettel SA, Adcock RA (2014): Resting state networks distinguish human ventral tegmental area from substantia nigra. *NeuroImage*. 100: 580–589.

84. Roiser JP, Elliott R, Sahakian BJ (2012): Cognitive Mechanisms of Treatment in Depression. *Neuropsychopharmacology*. 37: 117–136.

85. Eshel N, Roiser JP (2010): Reward and Punishment Processing in Depression. *Biol Psychiatry*, Vascular Function in Depression in Older Adults. 68: 118–124.

86. Price JL, Drevets WC (2010): Neurocircuitry of Mood Disorders. *Neuropsychopharmacology*. 35: 192–216.

87. Rive MM, van Rooijen G, Veltman DJ, Phillips ML, Schene AH, Ruhé HG (2013): Neural correlates of dysfunctional emotion regulation in major depressive disorder. A systematic review of neuroimaging studies. *Neurosci Biobehav Rev*. 37: 2529–2553.

88. Phillips ML, Drevets WC, Rauch SL, Lane R (2003): Neurobiology of emotion perception II: Implications for major psychiatric disorders. *Biol Psychiatry*. 54: 515–528.

89. Bartra O, McGuire JT, Kable JW (2013): The valuation system: A coordinate-based meta-analysis of BOLD fMRI experiments examining neural correlates of subjective value. *NeuroImage*. 76: 412–427.

90. Clithero JA, Rangel A (2014): Informatic parcellation of the network involved in the computation of subjective value. *Soc Cogn Affect Neurosci*. 9: 1289–1302.

91. O'Doherty JP (2014): The problem with value. *Neurosci Biobehav Rev*. 43: 259–268.

92. Zald DH, Treadway MT (2017): Reward Processing, Neuroeconomics, and Psychopathology. *Annu Rev Clin Psychol*. 13: 471–495.

93. Drevets WC (2007): Orbitofrontal Cortex Function and Structure in Depression. *Ann N Y Acad Sci*. 1121: 499–527.

94. Hafeman DM, Chang KD, Garrett AS, Sanders EM, Phillips ML (2012): Effects of medication on neuroimaging findings in bipolar disorder: an updated review. *Bipolar Disord*. 14: 375–410.

95. Cooper JC, Knutson B (2008): Valence and salience contribute to nucleus accumbens activation. *NeuroImage*. 39: 538–547.

96. Kahnt T, Park SQ, Haynes J-D, Tobler PN (2014): Disentangling neural representations of value and salience in the human brain. *Proc Natl Acad Sci U S A*. 111: 5000–5005.

97. Litt A, Plassmann H, Shiv B, Rangel A (2011): Dissociating Valuation and Saliency Signals during Decision-Making. *Cereb Cortex*. 21: 95–102.

98. Akobeng AK (2005): Understanding systematic reviews and meta-analysis. *Arch Dis Child*. 90: 845–848.

99. Nichols TE, Das S, Eickhoff SB, Evans AC, Glatard T, Hanke M, *et al*. (2017): Best practices in data analysis and sharing in neuroimaging using MRI. *Nat Neurosci*. 20: 299–303.

100. Diehl MM, Lempert K, Parr AC, Ballard I, Steele VR, Smith DV (2018): Toward an Integrative Perspective on the Neural Mechanisms Underlying Persistent Maladaptive Behaviors. *PsyArXiv*. . doi: 10.17605/OSF.IO/YVDS9.

101. Naesström M, Blomstedt P, Bodlund O (2016): A systematic review of psychiatric indications for deep brain stimulation, with focus on major depressive and obsessive-compulsive disorder. *Nord J Psychiatry*. 70: 483–491.

102. Jiménez F, Velasco F, Salin-Pascual R, Hernández JA, Velasco M, Criales JL, Nicolini H (2005): A Patient with a Resistant Major Depression Disorder Treated with Deep Brain Stimulation in the Inferior Thalamic Peduncle. *Neurosurgery*. 57: 585–593.

103. Lozano AM, Giacobbe P, Hamani C, Rizvi SJ, Kennedy SH, Kolivakis TT, *et al*. (2012): A multicenter pilot study of subcallosal cingulate area deep brain stimulation for treatment-resistant depression. *J Neurosurg*. 116: 315–322.

104. Malone DA, Dougherty DD, Rezai AR, Carpenter LL, Friehs GM, Eskandar EN, *et al*. (2009): Deep Brain Stimulation of the Ventral Capsule/Ventral Striatum for Treatment-Resistant Depression. *Biol Psychiatry*. 65: 267–275.

105. Bewernick BH, Hurlemann R, Matusch A, Kayser S, Grubert C, Hadrysiewicz B, *et al*. (2010): Nucleus Accumbens Deep Brain Stimulation Decreases Ratings of Depression and Anxiety in Treatment-Resistant Depression. *Biol Psychiatry*, Stimulating Research on the Treatment of Depression: Electroconvulsive Therapy, Transcranial Magnetic Stimulation, and Deep Brain Stimulation. 67: 110–116.

106. Schlaepfer TE (2015): Deep Brain Stimulation for Major Depression—Steps on a Long and Winding Road. *Biol Psychiatry*, Depression. 78: 218–219.

107. Schlaepfer TE, Bewernick BH, Kayser S, Mädler B, Coenen VA (2013): Rapid effects of deep brain stimulation for treatment-resistant major depression. *Biol Psychiatry*. 73: 1204–1212.

108. Puigdemont D, Pérez-Egea R, Portella MJ, Molet J, de Diego-Adeliño J, Gironell A, *et al*. (2012): Deep brain stimulation of the subcallosal cingulate gyrus: further evidence in treatment-resistant major depression. *Int J Neuropsychopharmacol*. 15: 121–133.

109. Holtzheimer PE, Husain MM, Lisanby SH, Taylor SF, Whitworth LA, McClintock S, *et al*. (2017): Subcallosal cingulate deep brain stimulation for treatment-resistant depression: a multisite, randomised, sham-controlled trial. *Lancet Psychiatry*. . doi: 10.1016/S2215-0366(17)30371-1.

110. Holtzheimer PE, Kelley ME, Gross RE, Filkowski MM, Garlow SJ, Barrocas A, *et al*. (2012): Subcallosal cingulate deep brain stimulation for treatment-resistant unipolar and bipolar depression. *Arch Gen Psychiatry*. 69: 150–158.

Table 1. Peak Coordinates of Group Differences in Neural Responses to Reward.

Contrast	Cluster Size (mm^3)	Probabilistic Anatomical Label	x	y	z
MDD > HC	848	Frontal Orbital Cortex (23%), Frontal Pole (12%)	20	32	-12
HC > MDD	3032	Subcallosal Cortex (11%)	-2	8	-4
		Lateral Ventricle (65%), Caudate (20%)	-6	18	4
		Pallidum (17%), Caudate (8%)	12	8	-2
		Putamen (86%)	16	8	-8
		Accumbens (73%), Caudate (24%)	10	16	-4
		Caudate (97%)	14	14	10

Coordinates are in MNI space. Probabilistic labels reflect the probability that a coordinate belongs to a given region. For clarity, we only report labels whose likelihood exceeds 5%. MDD, major depressive disorder; HC, healthy controls.

Table 2. Peak Coordinates of Group Differences in Neural Responses to Punishment.

Contrast	Cluster Size (mm^3)	Probabilistic Anatomical Label	x	y	z
MDD > HC	1096	Amygdala (82%)	-26	-8	-14
		Amygdala (57%)	-16	-2	-18

Coordinates are in MNI space. Probabilistic labels reflect the probability that a coordinate belongs to a given region. For clarity, we only report labels whose likelihood exceeds 5%. MDD, major depressive disorder; HC, healthy controls.

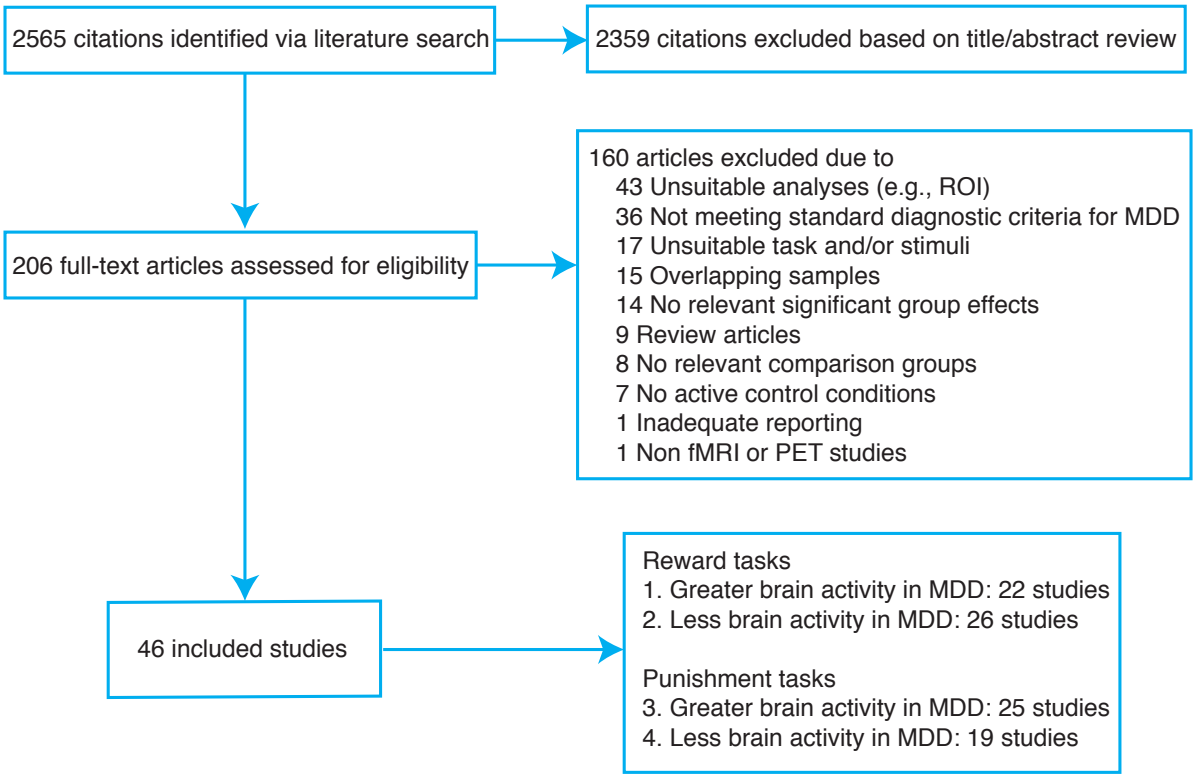

Figure 1. Flowchart of Study Selection. Our systematic literature search identified a total of 46 neuroimaging studies that met our inclusion criteria, yielding 4 coordinate-based meta-analyses with at least 17 independent studies; ROI, region of interest; MDD, major depressive disorder.

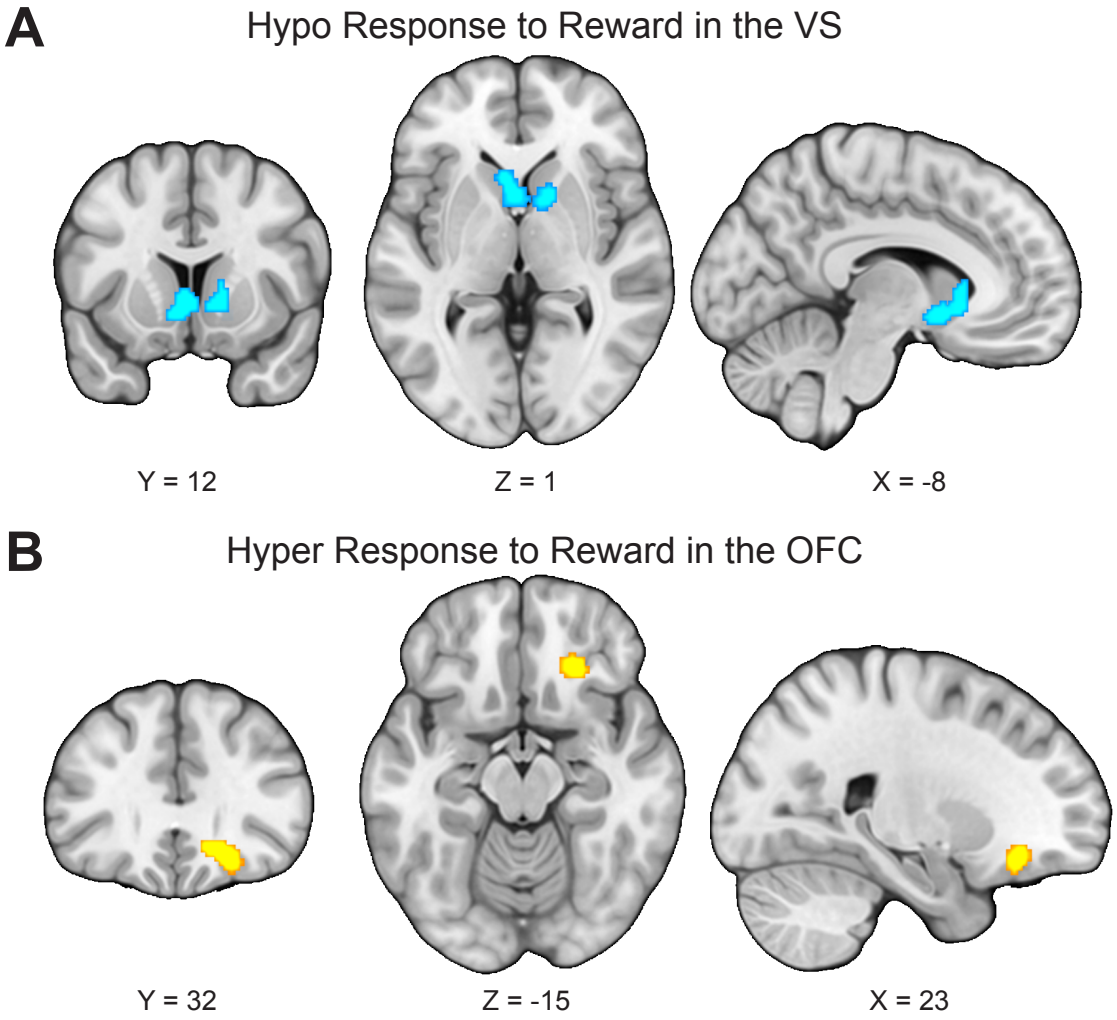

Figure 2. Opposing Abnormalities in the Reward Circuit in Response to Reward in Major Depressive Disorder (MDD). **(A)** To examine regions that consistently showed blunted response to reward, we synthesized 26 studies reporting less activity in response to reward in people with MDD than healthy controls (HCs). Our results indicated that these studies reliably report less activation in the bilateral ventral striatum (VS) in MDD. **(B)** To identify regions that consistently showed hyper-responses to reward, we meta-analyzed 22 studies reporting greater activity in response to reward in people with MDD than HCs. Our results indicated that these studies reliably report greater activation in the right orbitofrontal cortex (OFC) in MDD.

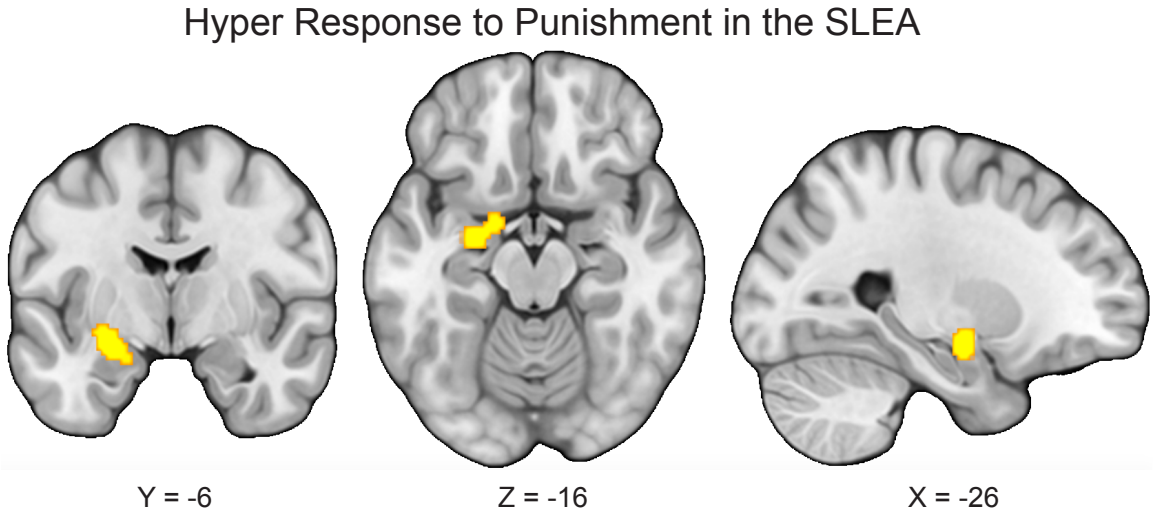

Figure 3. Hyper Response to Punishment in the Sublenticular Extended Amygdala (SLEA) in Major Depressive Disorder (MDD). To conduct exploratory analyses to examine which brain regions consistently show elevated response to punishment in MDD relative to healthy controls (HCs), we meta-analyzed 25 studies reporting greater activity in response to punishment in people with MDD than HCs. Our results indicated that these studies reliably report greater activation in the left SLEA in MDD.

Meta-analysis of Reward Processing in Major Depressive Disorder: Distinct Abnormalities within the Reward Circuit?

Supplemental Information

Table S1. Characteristics of the Study Samples Included in the Meta-Analysis.

	MDD Patients						Healthy Controls		
Study	*n*	Age	% Female	% Medicated	Mood States	Comorbidity	*n*	Age	%Female
Arnone *et al*. (1)	Depressed = 38; remitted = 24	Depressed = 36.1; remitted = 33.8	Depressed = 12%; remitted = 6%	0.0%	Depressed and Remitted	Exclusion of a concurrent comorbid axis I psychiatric disorder or primary cluster A or B axis II disorder.	54	32.4	20.0%
Arrondo *et al*. (2)	24	33.1	29.2%	54.2%	Depressed	Exclusion of alcohol or drug dependence.	21	34.3	23.5%
Bremner *et al*. (3)	18	40	66.7%	0.0%	Depressed	Exclusion of organic mental disorders or comorbid psychotic disorders, post-traumatic stress disorder, childhood trauma, alcohol or substance abuse or dependence, or dyslexia. No current or past history of comorbid psychiatric disorders.	9	35	77.8%
Burger *et al*. (4)	36	40.7	61.1%	100.0%	Depressed	Exclusion of substance dependence. Inclusion of PD, agoraphobia, generalized anxiety disorder, social phobia, obsessive compulsive disorder, post-traumatic stress disorder, somatoform disorder, eating	36	41.3	52.8%

						disorder, dysthymia, alcohol abuse, and substance abuse.			
Chantiluke *et al*. (5)	20	16.2	50.0%	0.0%	Depressed	Exclusion of major psychiatric disorders.	21	16.3	52.4%
Chase *et al*. (6)	40	31	77.5%	77.5%	Depressed	No exclusion of psychiatric comorbidities. Inclusion of lifetime comorbid anxiety disorders and substance use disorders.	37	33.1	67.6%
Davey *et al*. (7)	19	18.6	64.7%	52.9%	Depressed	Exclusion of psychotic disorder, substance dependence, pervasive developmental disorder, or intellectual disability. Inclusion of anxiety disorders.	20	19.3	63.2%
Demenescu *et al*. (8)	59	36.2	66.1%	23.7%	Depressed	Exclusion of axis I disorders, such as psychotic disorder or dementia, current alcohol or substance abuse.	56	39.8	60.7%
Dichter *et al*. (9)	19	23.6	78.9%	0.0%	Remitted	Exclusion of current axis I psychopathology.	19	27.9	63.2%
Elliott *et al*. (10)	10	42.2	70.0%	100.0%	Depressed	Exclusion of current comorbid anxiety disorders, substance abuse or dependence, bipolar disorder, or other psychiatric diagnoses. Inclusion of past history of PD and bulimia.	11	37.6	72.7%
Epstein *et al*. (11)	10	35.6	90.0%	0.0%	Depressed	Exclusion of major psychiatric disorders and substance abuse.	12	32	58.3%
Fournier *et al*. (12)	26	30.6	69.0%	69.2%	Depressed	Exclusion of bipolar disorder, borderline personality disorder, and alcohol/substance use	28	32.6	57.0%

						disorder within 2 months before the scan. Inclusion of history of anxiety disorder and substance abuse.			
Fu *et al*. (13) and (14)	19	43.2	68.4%	100.0%	Depressed	Exclusion of current axis I disorder and history of substance abuse within 2 months of study participation.	19	42.8	57.9%
Fu *et al*. (15)	16	40	81.3%	0.0%	Depressed	Exclusion of other axis I disorder, including anxiety disorder or history of substance within 2 months of study participation.	16	39.2	81.3%
Gorka *et al*. (16)	MDD only = 9; MDD+PD = 13	MDD only = 25.4; MDD+PD = 39.1	MDD only = 66.7%; MDD+PD = 76.9%	MDD only = 11.1%; MDD+PD = 30.8%	Depressed	All participants: Exclusion of lifetime psychotic disorder or bipolar disorder and inclusion of past alcohol/substance abuse/dependence; MDD only: exclusion of lifetime anxiety disorder; MDD+PD: inclusion of PD, social phobia, specific phobia, post-traumatic stress disorder, generalized anxiety disorder, and obsessive compulsive disorder.	18	29.5	72.2%
Gotlib *et al*. (17)	18	35.2	72.2%	50.0%	Depressed	Exclusion of psychotic ideation, social phobia, PD, mania, or substance abuse in the past 6 months or behavioral indications of possible impaired mental status.	18	30.8	72.2%
Gradin *et al*. (18)	25	25.5	68.0%	0.0%	Depressed	Unspecified	25	25.4	68.0%

Hall *et al*. (19)	29	37.4	55.2%	51.7%	Depressed	Exclusion of history of alcohol or substance abuse.	25	37.7	55.2%
Johnston *et al*. (20)	19	50.8	78.9%	85.0%	Depressed	Exclusion of other primary psychiatric disorder and substance misuse.	21	46.1	71.4%
Keedwell *et al*. (21)	12	43	66.7%	66.7%	Depressed	Exclusion of other axis I disorder.	12	36	66.7%
Knutson *et al*. (22)	14	30.7	64.3%	0.0%	Depressed	Exclusion of other current axis I disorder.	12	28.7	66.7%
Kumar *et al*. (23)	15	45.3	60.0%	100.0%	Depressed	Exclusion of other axis I or II disorders and a history of substance or alcohol misuse.	18	42	61.1%
Kumari *et al*. (24)	6	47	100.0%	Unspecified	Depressed	Unspecified	6	44	100.0%
Laurent *et al*. (25)	11	24.1 (whole sample)	100.0%	23.1%	Depressed	No exclusion of psychiatric comorbidities. Inclusion of past substance abuse/dependence, anxiety disorders, and eating disorder.	11	24.1 (whole sample)	100.0%
Mitterschiffthaler *et al*. (26)	17	39.3	82.4%	0.0%	Depressed	Exclusion of comorbid axis I disorder and substance/alcohol abuse within 2 months prior to study participation.	17	39.4	82.4%
Murrough *et al*. (27)	20	38.1	44.4%	0.0%	Depressed	Exclusion of lifetime history of psychotic illness or bipolar disorder and current alcohol or substance abuse.	20	35	45.0%
Osuch *et al*. (28)	16	22.6	68.8%	6.3%	Depressed	Unspecified	15	23.5	73.3%
Pizzagalli *et al*. (29)	30	43.2	50.0%	0.0%	Depressed	Exclusion of other axis I disorder except for anxiety disorders.	31	38.8	41.9%

Remijnse *et al*. (30)	20	35	40.0%	0.0%	Depressed	Exclusion of current alcohol or substance abuse at the time of study participation. Inclusion of social anxiety disorder, generalized anxiety disorder, PD without agoraphobia, PD, and cannabis abuse in early and sustained full remission.	27	32	70.4%
Rizvi *et al*. (31)	21	38.9	66.7%	0.0%	Depressed	Exclusion of other primary axis I disorder, lifetime history of hypomania/mania, psychosis, obsessive compulsive disorder, or eating disorder, and substance abuse or dependence (except nicotine or caffeine) within the last 3 months.	18	36.2	66.7%
Rosenblau *et al*. (32)	12	43.5	41.7%	0.0%	Depressed	Exclusion of other axis I or II disorders.	12	45.8	41.7%
Scheuerecker *et al*. (33)	13	37.9	23.1%	0.0%	Depressed	Exclusion of past alcohol or substance abuse, other mental illnesses, and personality disorders.	15	35.5	33.3%
Schiller *et al*. (34)	19	23.6	78.9%	0.0%	Remitted	Exclusion of current axis I psychopathology.	19	27.9	63.2%
Segarra *et al*. (35)	24	33.1	29.2%	54.0%	Depressed	Exclusion of dependence on alcohol or recreational drugs.	21	34.3	19.0%
Sharp *et al*. (36)	14	13.4	100.0%	Unspecified	Depressed	Exclusion of current use of nicotine, illicit drugs, psychotic disorders, bipolar I disorder, learning disabilities, and mental retardation.	19	13.7	100.0%

Smoski *et al*. *(37)*	14	34.8	50.0%	0.0%	Depressed	Exclusion of current mood disorder, anxiety disorder, psychotic disorder, substance abuse, or active suicidal ideation and history of psychosis or mania.	15	30.8	60.0%
Smoski *et al*. (38)	9	34.4	Unspecifie d	44.4%	Depressed	Inclusion of generalized anxiety disorder and binge eating disorder.	13	26.2	Unspecifi ed
Surguladze *et al*. (39)	16	42.3	37.5%	100.0%	Depressed	Exclusion of illicit substance abuse.	14	35.1	42.9%
Surguladze *et al*. (40)	9	42.8	44.4%	100.0%	Depressed	Exclusion of illicit substance abuse and other axis I disorders.	9	39.7	44.4%
Townsend *et al*. (41)	15	45.6	40.0%	0.0%	Depressed	Exclusion of comorbid axis I disorder.	15	44.8	40.0%
Wagner *et al*. (42)	19	39.9	55.0%	100.0%	Depressed	Exclusion of current comorbid axis I disorder and a history of manic episodes.	20	34.1	60.0%
Wang *et al*. (43)	12	69.1	58.3%	91.7%	Depressed	Exclusion of another major psychiatric disorder and alcohol/drug abuse/dependence. Inclusion of generalized anxiety disorder.	20	73.1	60.0%
Young *et al*. (44)	16	37.1	87.5%	0.0%	Depressed	Exclusion of serious suicidal ideation, psychosis, drug/alcohol abuse in the past year and dependence (except for nicotine) in their lifetime.	16	37.8	87.5%
Zhang *et al*. (45)	21	43.8	38.1%	100.0%	Depressed	Exclusion of illicit substance use or substance use disorders.	25	39.3	36.0%

Zhong *et al*. (46)	29	20.5	55.2%	0.0%	Depressed	Exclusion of lifetime substance dependence and substance abuse in the last 6 months.	31	20.8	51.6%

MDD, major depressive disorder; PD, panic disorder.

Table S2. Study Characteristics.

Study	fMRI or PET	Design	Space	Paradigm	Stimuli	Contrast
Arnone *et al*. (1)	fMRI	Block	MNI	Viewing faces with happy, sad, fearful, and neutral emotions	Faces	MDD > HC, Outcome: Negative > Neutral HC > MDD, Outcome: Negative > Neutral MDD > HC, Outcome: Positive > Neutral
Arrondo *et al*. (2)	fMRI	Event-related	MNI	Modified monetary incentive delay task	Money	HC > MDD, Anticipation: Reward > Non-Reward
Bremner *et al*. (3)	PET	Block	MNI	Verbal declarative memory tasks with neutral paragraph encoding compared to a control condition and sad word pair retrieval compared to a control condition.	Words and paragraphs	MDD > HC, Outcome: Negative > Neutral HC > MDD, Outcome: Negative > Neutral
Burger *et al*. (4)	fMRI	Event-related	MNI	Face matching paradigm	Faces	HC > MDD, Outcome: Negative > Neutral HC > MDD, Outcome: Positive > Neutral
Chantiluke *et al*. (5)	fMRI	Event-related	TAL	Reward continuous performance task	Money	MDD > HC, Outcome: Reward > Non-Reward HC > MDD, Outcome: Reward > Non-Reward
Chase *et al*. (6)	fMRI	Event-related	MNI	Card guessing paradigm	Money	MDD > HC, Anticipation: Reward > Non-Reward HC > MDD, Anticipation: Reward > Non-Reward MDD > HC, Anticipation: Reward Expectancy HC > MDD, Anticipation: Reward Expectancy MDD > HC, Outcome: Prediction Error
Davey *et al*. (7)	fMRI	Block	MNI	Viewing faces giving positive or control feedback	Faces	MDD > HC, Outcome: Reward > Non-Reward
Demenescu *et al*. (8)	fMRI	Event-related	MNI	Viewing faces with angry, fearful, sad, happy, and neutral expressions and scrambled faces; rating gender or pressing buttons in conformity with the instruction presented on the screen	Faces	MDD > HC, Outcome: Positive > Scrambled Face
Dichter *et al*. (9)	fMRI	Event-related	MNI	Modified monetary incentive delay task	Money	MDD > HC, Anticipation: Reward > Non-Reward MDD > HC, Outcome: Reward > Non-Reward

						HC > MDD, Outcome: Reward > Non-Reward
Elliott *et al*. (10)	fMRI	Block	MNI	Affective go/no go task	Words	MDD > HC, Outcome: Negative > Positive HC > MDD, Outcome: Positive > Negative
Epstein *et al*. (11)	fMRI	Block	MNI	Viewing positive, negative, and neutral words	Words	MDD > HC, Outcome: Negative > Neutral HC > MDD, Outcome: Negative > Neutral HC > MDD, Outcome: Positive > Neutral
Fournier *et al*. (12)	fMRI	Block	MNI	Labeling a color flash superimposed upon neutral faces that gradually morphed into angry, fearful, sad, or happy faces	Faces	MDD > HC, Outcome: Negative > Neutral MDD > HC, Outcome: Positive > Neutral
Fu *et al*. (13) and (14)	fMRI	Event-related	TAL	Indicating the sex of faces morphed to represent low, medium, and high intensities of sadness	Faces	MDD > HC, Outcome: Negative (low, medium, and high intensity) HC > MDD, Outcome: Positive (low, medium, and high intensity)
Fu *et al*. (15)	fMRI	Event-related	TAL	Indicating the sex of faces morphed to represent low, medium, and high intensities of sadness	Faces	MDD > HC, Outcome: Negative (low, medium, and high intensity) HC > MDD, Outcome: Negative (low, medium, and high intensity)
Gorka *et al*. (16)	fMRI	Block	MNI	Passive slot machine task	Money	MDD > HC, Anticipation: Reward > Non-Reward HC > MDD, Anticipation: Reward > Non-Reward
Gotlib *et al*. (17)	fMRI	Block	MNI	Indicating the sex of faces that were fearful, angry, sad, happy, neutral, or scrambled	Faces	MDD > HC, Outcome: Negative > Neutral HC > MDD, Outcome: Negative > Neutral MDD > HC, Outcome: Positive > Neutral HC > MDD, Outcome: Positive > Neutral
Gradin *et al*. (18)	fMRI	Event-related	MNI	Ultimatum game	Money	HC > MDD, Outcome: Increasing fairness (decreasing inequality) MDD > HC, Outcome: Increasing inequality (decreasing fairness)
Hall *et al*. (19)	fMRI	Event-related	TAL	Contingency reversal reward paradigm	Money	HC > MDD, Outcome: Magnitude of Loss: Large Loss > Small Loss HC > MDD, Outcome: Magnitude of Reward: Large Reward > Small Reward

						MDD > HC, Outcome: Reward Acquisition > Punishment Reversal HC > MDD, Outcome: Reward Acquisition > Punishment Reversal
Johnston *et al.* (20)	fMRI	Event-related	MNI	Modified Pessiglione task	Voucher	MDD > HC, Outcome: Loss > Non-Loss HC > MDD, Outcome: Loss > Non-Loss MDD > HC, Outcome: Reward > Non-Reward HC > MDD, Outcome: Reward > Non-Reward
Keedwell *et al.* (21)	fMRI	Block	TAL	Being exposed to happy, sad, or neutral autobiographical memory prompts and facial expressions	Autobiographical memory and faces	MDD > HC, Outcome: Negative > Neutral HC > MDD, Outcome: Negative > Neutral MDD > HC, Outcome: Positive > Neutral HC > MDD, Outcome: Positive > Neutral
Knutson *et al.* (22)	fMRI	Event-related	TAL	Monetary incentive delay task	Money	MDD > HC, Anticipation: Reward > Non-Reward HC > MDD, Anticipation: Reward > Non-Reward HC > MDD, Outcome: Non-Loss > Loss HC > MDD, Outcome: Reward > Non-Reward
Kumar *et al.* (23)	fMRI	Event-related	MNI	Pavlovian reward-learning paradigm	Water	MDD > HC, Outcome: Prediction Error HC > MDD, Outcome: Prediction Error
Kumari *et al.* (24)	fMRI	Block	TAL	Viewing positive or negative pictures with a caption	Pictures and captions	HC > MDD, Outcome: Negative > Neutral MDD > HC, Outcome: Negative > Neutral HC > MDD, Outcome: Positive > Neutral MDD > HC, Outcome: Positive > Neutral HC > MDD, Outcome: Positive > Negative MDD > HC, Outcome: Positive > Negative
Laurent *et al.* (25)	fMRI	Event-related	MNI	Seeing own infant vs. other infant distress faces	Faces	HC > MDD, Outcome: Very negative > Negative
Mitterschiffthaler *et al.* (26)	fMRI	Block	MNI	Naming the color of negative and neutral words	Words	MDD > HC, Outcome: Negative > Neutral
Murrough *et al.* (27)	fMRI	Event-related	MNI	Rating emotional valence of happy, sad, or neutral faces	Faces	HC > MDD, Outcome: 100% Positive > Neutral
Osuch *et al.* (28)	fMRI	Block	MNI	Listening to favorite vs. neutral music	Music	HC > MDD, Outcome: Favorite Music > Neutral Music

Pizzagalli *et al.* (29)	fMRI	Event-related	MNI	Monetary incentive delay task	Money	MDD > HC, Anticipation: Loss > Non-Loss HC > MDD, Anticipation: Loss > Non-Loss MDD > HC, Anticipation: Reward > Non-Reward HC > MDD, Anticipation: Reward > Non-Reward MDD > HC, Outcome: Loss > Non-Loss HC > MDD, Outcome: Loss > Non-Loss MDD > HC, Outcome: Reward > Non-Reward HC > MDD, Outcome: Reward > Non-Reward
Remijnse *et al.* (30)	fMRI	Event-related	MNI	Reversal learning task	Points	MDD > HC, Outcome: Loss > Baseline HC > MDD, Outcome: Loss > Baseline MDD > HC, Outcome: Reward > Baseline
Rizvi *et al.* (31)	fMRI	Blocked	MNI	Viewing IAPS pictures that elicit positive, negative or neutral affective states	Pictures	MDD > HC, Outcome: Positive > Neutral MDD > HC, Outcome: Negative > Neutral
Rosenblau *et al.* (32)	fMRI	Event-related	MNI	Viewing IAPS pictures that elicit positive, negative or neutral affective states with and without cues indicating their emotional valence	Pictures	MDD > HC, Anticipation: Negative > Neutral MDD > HC, Outcome: Negative > Neutral
Scheuerecker *et al.* (33)	fMRI	Block	MNI	Face matching paradigm	Faces	MDD > HC, Outcome: Negative > Neutral
Schiller *et al.* (34)	fMRI	Event-related	MNI	Monetary incentive delay task	Money	HC > MDD, Anticipation: Loss > Non-Loss HC > MDD, Outcome: Loss > Non-Loss
Segarra *et al.* (35)	fMRI	Event-related	MNI	Simulated slot-machine game	Money	HC > MDD, Outcome: Unexpected Reward > Full Miss
Sharp *et al.* (36)	fMRI	Event-related	TAL	Card guessing paradigm	Money	HC > MDD, Outcome: Reward > Non-Reward
Smoski *et al.* (38)	fMRI	Event-related	MNI	Modified monetary incentive delay task	Money	MDD > HC, Anticipation: Money > Control HC > MDD, Anticipation: Money > Control MDD > HC, Outcome: Non-Win > Control HC > MDD, Outcome: Non-Win > Control MDD > HC, Outcome: Winning > Control HC > MDD, Outcome: Winning > Control

						MDD > HC, Selection: Money > Control HC > MDD, Selection: Money > Control
Smoski *et al.* *(37)*	fMRI	Event-related	MNI	Wheel of fortune task	Money	HC > MDD, Anticipation: Reward > Non-Reward HC > MDD, Outcome: Reward > Non-Reward
Surguladze *et al.* (40)	fMRI	Event-related	TAL	Indicating the sex of neutral faces and faces morphed to represent mild and high intensities of fear and disgust	Faces	HC > MDD, Outcome: Increasing intensities of happy faces MDD > HC, Outcome: Increasing intensities of sad faces
Surguladze *et al.* (39)	fMRI	Event-related	TAL	Indicating the sex of neutral faces and faces morphed to represent mild and high intensities of sadness and happiness	Faces	MDD > HC, Outcome: Differential response to 100% disgust HC > MDD, Outcome: Differential response to 50% fear
Townsend *et al.* (41)	fMRI	Block	MNI	Face matching paradigm	Faces	HC > MDD, Outcome: Negative > Neutral
Wagner *et al.* (42)	fMRI	Event-related	MNI	Self-referential processing task	Statements	MDD > HC, Outcome: Neutral > Negative MDD > HC, Outcome: Neutral > Positive
Wang *et al.* (43)	fMRI	Event-related	MNI	Emotional oddball task	Pictures	MDD > HC, Outcome: Negative > Neutral
Young *et al.* (44)	fMRI	Event-related	TAL	Autobiographical memory task	Words and autobiographical memories	HC > MDD, Outcome: Very Positive > Positive HC > MDD, Outcome: Very Negative > Negative MDD > HC, Outcome: Very Negative > Negative
Zhang *et al.* (45)	fMRI	Event-related	MNI	Viewing IAPS positive, neutral, and negative pictures with or without valence cues	Pictures	MDD > HC, Outcome: Reward > Non-Reward
Zhong *et al.* (46)	fMRI	Block	MNI	Face matching paradigm	Faces	MDD > HC, Outcome: Negative > Neutral HC > MDD, Outcome: Negative > Neutral

MNI, Montreal Neurological Institute space; TAL, Talairach space; IAPS, International Affective Picture System; MDD, major depressive disorder; HC, healthy controls

Table S3. Comparison of Findings on Reward Responses (i.e., Reward > Punishment/Neutral) in Previous Meta-analyses.

Brain Region	MNI Coordinates		
	x	y	z
Groenewold et al. 2013 (47)			
MDD > HC			
Lingual Gyrus	26	-92	-14
Olfactorius Cortex	4	22	-14
Middle Orbitofrontal	2	26	-14
Rectus	2	30	-24
Middle Orbitofrontal	0	26	-12
Rectus	0	24	-24
HC > MDD			
Cerebellum	-16	-74	-28
Lingual Gyrus	-18	-62	-6
Fusiform Gyrus	-22	-74	-14
Inferior Occipital Gyrus	-30	-80	-12
Rolandic Operculum	-40	-24	20
Insula	-36	-24	22
Superior Temporal Gyrus	-40	-36	12
Heschl Gyrus	-46	-16	12
Postcentral Gyrus	-50	-18	18
Supramarginal Gyrus	-50	-22	18
Anterior Cingulate Cortex	-2	28	16
Anterior Cingulate Cortex	4	32	14
Lingual Gyrus	-18	-62	-6
Cerebellum	-6	-58	-4
Calcarine Sulcus	-20	-54	4
Fusiform Gyrus	-26	-58	-12
Precuneus	-20	-52	2
Pallidum	18	0	-4
Putamen	28	-4	8
Thalamus	14	-8	0
Insula	38	10	-12
Amygdala	30	-2	-12
Caudate	16	26	6
Fusiform	44	-62	-20
Crus Cerebellum	44	-64	-20
Brain Region	TAL Coordinates		
	x	y	z
Zhang et al. 2013 (48)			
MDD > HC			
Cuneus	4	-86	18
Cuneus	-6	86	22
Frontal Lobe	20	30	-6
Middle Frontal Gyrus	40	28	38
Superior Frontal Gyrus	-4	48	32
Fusiform Gyrus	-48	-74	-12

Middle Frontal Gyrus	-48	14	30
Lingual Gyrus	12	-52	4
Lingual Gyrus	14	-54	0
HC > MDD			
Caudate	-6	18	4
Caudate	-8	-8	10
Thalamus	-10	-12	8
Thalamus	-14	-14	16
Caudate	-12	-4	20
Cerebellum	4	-36	-4
Cerebellum	-4	-42	4
Putamen	14	8	2
Caudate	14	14	10
Anterior Cingulate	-8	30	10
Insula	34	-4	16
Cerebellum	-6	-60	-20

MNI, Montreal Neurological Institute space; MDD, major depressive disorder; HC, healthy controls; TAL, Talairach space. Ventral striatum is the only area implicated in reward processing in MDD relative to HCs across the two previous meta-analyses and the current meta-analysis (see Table 1 for peak coordinates of group differences in neural responses to reward found in the current meta-analysis).

Supplementary References

1. Arnone D, McKie S, Elliott R, Thomas EJ, Downey D, Juhasz G, *et al*. (2012): Increased amygdala responses to sad but not fearful faces in major depression: relation to mood state and pharmacological treatment. *Am J Psychiatry*. 169: 841–850.

2. Arrondo G, Segarra N, Metastasio A, Ziauddeen H, Spencer J, Reinders NR, *et al*. (2015): Reduction in ventral striatal activity when anticipating a reward in depression and schizophrenia: a replicated cross-diagnostic finding. *Front Psychol*. 6. doi: 10.3389/fpsyg.2015.01280.

3. Bremner JD, Vythilingam M, Vermetten E, Charney DS (2007): Effects of antidepressant treatment on neural correlates of emotional and neutral declarative verbal memory in depression. *J Affect Disord*. 101: 99–111.

4. Bürger C, Redlich R, Grotegerd D, Meinert S, Dohm K, Schneider I, *et al*. (2017): Differential Abnormal Pattern of Anterior Cingulate Gyrus Activation in Unipolar and Bipolar Depression: an fMRI and Pattern Classification Approach. *Neuropsychopharmacology*. 42: 1399–1408.

5. Chantiluke K, Halari R, Simic M, Pariante CM, Papadopoulos A, Giampietro V, Rubia K (2012): Fronto-Striato-Cerebellar Dysregulation in Adolescents with Depression During Motivated Attention. *Biol Psychiatry*, Molecular Substrates of Neuroplasticity in Depression. 71: 59–67.

6. Chase HW, Nusslock R, Almeida JRC, Forbes EE, LaBarbara EJ, Phillips ML (2013): Dissociable patterns of abnormal frontal cortical activation during anticipation of an uncertain reward or loss in bipolar versus major depression. *Bipolar Disord*. 15: 839–854.

7. Davey CG, Allen NB, Harrison BJ, Yücel M (2011): Increased amygdala response to positive social feedback in young people with major depressive disorder. *Biol Psychiatry*. 69: 734–741.

8. Demenescu LR, Renken R, Kortekaas R, van Tol M-J, Marsman JBC, van Buchem MA, *et al*. (2011): Neural correlates of perception of emotional facial expressions in out-patients with mild-to-moderate depression and anxiety. A multicenter fMRI study. *Psychol Med*. 41: 2253–2264.

9. Dichter GS, Kozink RV, McClernon FJ, Smoski MJ (2012): Remitted major depression is characterized by reward network hyperactivation during reward anticipation and hypoactivation during reward outcomes. *J Affect Disord*. 136: 1126–1134.

10. Elliott R, Rubinsztein JS, Sahakian BJ, Dolan RJ (2002): The Neural Basis of Mood-Congruent Processing Biases in Depression. *Arch Gen Psychiatry*. 59: 597–604.

11. Epstein J, Pan H, Kocsis JH, Yang Y, Butler T, Chusid J, *et al*. (2006): Lack of ventral striatal response to positive stimuli in depressed versus normal subjects. *Am J Psychiatry*. 163: 1784–1790.

12. Fournier JC, Keener MT, Mullin BC, Hafeman DM, LaBarbara EJ, Stiffler RS, *et al*. (2013): Heterogeneity of Amygdala Response in Major Depressive Disorder: The Impact of Lifetime Sub-Threshold Mania. *Psychol Med*. 43: 293–302.

13. Fu CHY, Williams SCR, Cleare AJ, Brammer MJ, Walsh ND, Kim J, *et al*. (2004): 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*. 61: 877–889.

14. Fu CHY, Williams SCR, Brammer MJ, Suckling J, Kim J, Cleare AJ, *et al*. (2007): Neural responses to happy facial expressions in major depression following antidepressant treatment. *Am J Psychiatry*. 164: 599–607.

15. Fu CHY, Williams SCR, Cleare AJ, Scott J, Mitterschiffthaler MT, Walsh ND, *et al*. (2008): Neural responses to sad facial expressions in major depression following cognitive behavioral therapy. *Biol Psychiatry*. 64: 505–512.

16. Gorka SM, Huggins AA, Fitzgerald DA, Nelson BD, Phan KL, Shankman SA (2014): Neural response to reward anticipation in those with depression with and without panic disorder. *J Affect Disord*. 164: 50–56.

17. Gotlib IH, Sivers H, Gabrieli JDE, Whitfield-Gabrieli S, Goldin P, Minor KL, Canli T (2005): Subgenual anterior cingulate activation to valenced emotional stimuli in major depression. *Neuroreport*. 16: 1731–1734.

18. Gradin VB, Pérez A, MacFarlane JA, Cavin I, Waiter G, Engelmann J, *et al*. (2015): Abnormal brain responses to social fairness in depression: an fMRI study using the Ultimatum Game. *Psychol Med*. 45: 1241–1251.

19. Hall GBC, Milne AMB, MacQueen GM (2014): An fMRI study of reward circuitry in patients with minimal or extensive history of major depression. *Eur Arch Psychiatry Clin Neurosci*. 264: 187–198.

20. Johnston BA, Tolomeo S, Gradin V, Christmas D, Matthews K, Steele JD (2015): Failure of hippocampal deactivation during loss events in treatment-resistant depression. *Brain J Neurol*. 138: 2766–2776.

21. Keedwell PA, Andrew C, Williams SCR, Brammer MJ, Phillips ML (2005): A double dissociation of ventromedial prefrontal cortical responses to sad and happy stimuli in depressed and healthy individuals. *Biol Psychiatry*. 58: 495–503.

22. Knutson B, Bhanji JP, Cooney RE, Atlas LY, Gotlib IH (2008): Neural responses to monetary incentives in major depression. *Biol Psychiatry*. 63: 686–692.

23. Kumar P, Waiter G, Ahearn T, Milders M, Reid I, Steele JD (2008): Abnormal temporal difference reward-learning signals in major depression. *Brain*. 131: 2084–2093.

24. Kumari V, Mitterschiffthaler MT, Teasdale JD, Malhi GS, Brown RG, Giampietro V, *et al*. (2003): Neural abnormalities during cognitive generation of affect in treatment-resistant depression. *Biol Psychiatry*. 54: 777–791.

25. Laurent HK, Ablow JC (2013): A Face a Mother Could Love: Depression-Related Maternal Neural Responses to Infant Emotion Faces. *Soc Neurosci*. 8: 228–239.

26. Mitterschiffthaler MT, Williams SCR, Walsh ND, Cleare AJ, Donaldson C, Scott J, Fu CHY (2008): Neural basis of the emotional Stroop interference effect in major depression. *Psychol Med*. 38: 247–256.

27. Murrough JW, Collins KA, Fields J, DeWilde KE, Phillips ML, Mathew SJ, *et al*. (2015): Regulation of neural responses to emotion perception by ketamine in individuals with treatment-resistant major depressive disorder. *Transl Psychiatry*. 5: e509.

28. Osuch EA, Bluhm RL, Williamson PC, Théberge J, Densmore M, Neufeld RWJ (2009): Brain activation to favorite music in healthy controls and depressed patients. *Neuroreport*. 20: 1204–1208.

29. Pizzagalli DA, Holmes AJ, Dillon DG, Goetz EL, Birk JL, Bogdan R, *et al*. (2009): Reduced Caudate and Nucleus Accumbens Response to Rewards in Unmedicated Subjects with Major Depressive Disorder. *Am J Psychiatry*. 166: 702–710.

30. Remijnse PL, Nielen MMA, van Balkom AJLM, Hendriks G-J, Hoogendijk WJ, Uylings HBM, Veltman DJ (2009): Differential frontal-striatal and paralimbic activity during reversal learning in major depressive disorder and obsessive-compulsive disorder. *Psychol Med*. 39: 1503–1518.

31. Rizvi SJ, Salomons TV, Konarski JZ, Downar J, Giacobbe P, McIntyre RS, Kennedy SH (2013): Neural response to emotional stimuli associated with successful antidepressant treatment and behavioral activation. *J Affect Disord*. 151: 573–581.

32. Rosenblau G, Sterzer P, Stoy M, Park S, Friedel E, Heinz A, *et al*. (2012): Functional neuroanatomy of emotion processing in major depressive disorder is altered after successful antidepressant therapy. *J Psychopharmacol (Oxf)*. 26: 1424–1433.

33. Scheuerecker J, Meisenzahl EM, Koutsouleris N, Roesner M, Schöpf V, Linn J, *et al*. (2010): Orbitofrontal volume reductions during emotion recognition in patients with major depression. *J Psychiatry Neurosci JPN*. 35: 311–320.

34. Schiller CE, Minkel J, Smoski MJ, Dichter GS (2013): Remitted Major Depression is Characterized by Reduced Prefrontal Cortex Reactivity to Reward Loss. *J Affect Disord*. 151: 756–762.

35. Segarra N, Metastasio A, Ziauddeen H, Spencer J, Reinders NR, Dudas RB, *et al*. (2016): Abnormal Frontostriatal Activity During Unexpected Reward Receipt in Depression and Schizophrenia: Relationship to Anhedonia. *Neuropsychopharmacology*. 41: 2001–2010.

36. Sharp C, Kim S, Herman L, Pane H, Reuter T, Strathearn L (2014): Major depression in mothers predicts reduced ventral striatum activation in adolescent female offspring with and without depression. *J Abnorm Psychol*. 123: 298–309.

37. Smoski MJ, Rittenberg A, Dichter GS (2011): Major depressive disorder is characterized by greater reward network activation to monetary than pleasant image rewards. *Psychiatry Res*. 194: 263–270.

38. Smoski MJ, Felder J, Bizzell J, Green SR, Ernst M, Lynch TR, Dichter GS (2009): FMRI of Alterations in Reward Selection, Anticipation, and Feedback in Major Depressive Disorder. *J Affect Disord*. 118: 69–78.

39. Surguladze SA, El-Hage W, Dalgleish T, Radua J, Gohier B, Phillips ML (2010): Depression is associated with increased sensitivity to signals of disgust: a functional magnetic resonance imaging study. *J Psychiatr Res*. 44: 894–902.

40. Surguladze SA, Brammer MJ, Keedwell P, Giampietro V, Young AW, Travis MJ, *et al*. (2005): A differential pattern of neural response toward sad versus happy facial expressions in major depressive disorder. *Biol Psychiatry*. 57: 201–209.

41. Townsend JD, Eberhart NK, Bookheimer SY, Eisenberger NI, Foland-Ross LC, Cook IA, *et al*. (2010): fMRI activation in amygdala and orbitofrontal cortex in unmedicated subjects with major depressive disorder. *Psychiatry Res*. 183: 209–217.

42. Wagner G, Schachtzabel C, Peikert G, Bär K-J (2015): The neural basis of the abnormal self-referential processing and its impact on cognitive control in depressed patients. *Hum Brain Mapp*. 36: 2781–2794.

43. Wang L, Krishnan KR, Steffens DC, Potter GG, Dolcos F, McCarthy G (2008): Depressive state- and disease-related alterations in neural responses to affective and executive challenges in geriatric depression. *Am J Psychiatry*. 165: 863–871.

44. Young KD, Bodurka J, Drevets WC (2016): Differential neural correlates of autobiographical memory recall in bipolar and unipolar depression. *Bipolar Disord*. 18: 571–582.

45. Zhang B, Li S, Zhuo C, Li M, Safron A, Genz A, *et al*. (2017): Altered task-specific deactivation in the default mode network depends on valence in patients with major depressive disorder. *J Affect Disord*. 207: 377–383.

46. Zhong M, Wang X, Xiao J, Yi J, Zhu X, Liao J, *et al*. (2011): Amygdala hyperactivation and prefrontal hypoactivation in subjects with cognitive vulnerability to depression. *Biol Psychol*. 88: 233–242.

47. Groenewold NA, Opmeer EM, de Jonge P, Aleman A, Costafreda SG (2013): Emotional valence modulates brain functional abnormalities in depression: Evidence from a meta-analysis of fMRI studies. *Neurosci Biobehav Rev*. 37: 152–163.

48. Zhang WN, Chang SH, Guo LY, Zhang KL, Wang J (2013): The neural correlates of reward-related processing in major depressive disorder: A meta-analysis of functional magnetic resonance imaging studies. *J Affect Disord*. 151: 531–539.