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

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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.

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

Contrast	Cluster Size (mm³)	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 (mm³)	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.
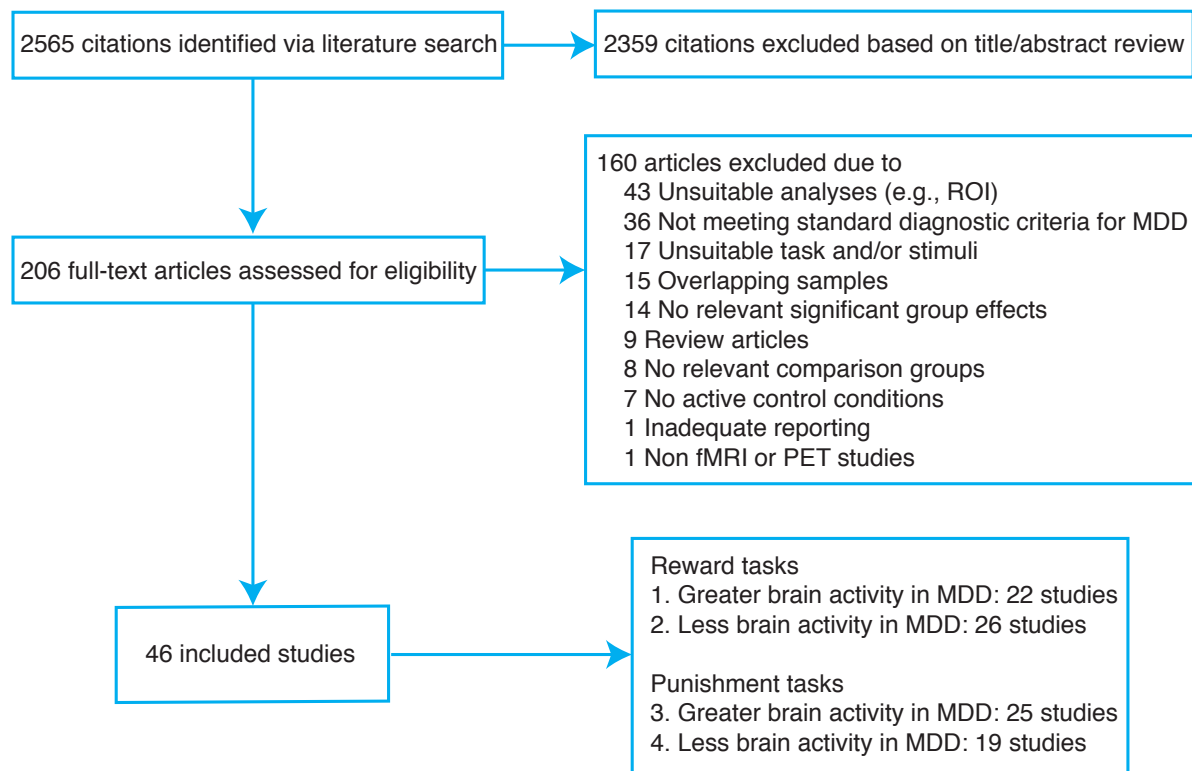
Figure 1. Flowchart of Study Selection. Our systematic literature search identified a total of 46 neuroimaging studies that met our inclusion criteria, yielding 4 coordinate-based meta-analyses with at least 17 independent studies; ROI, region of interest; MDD, major depressive disorder.
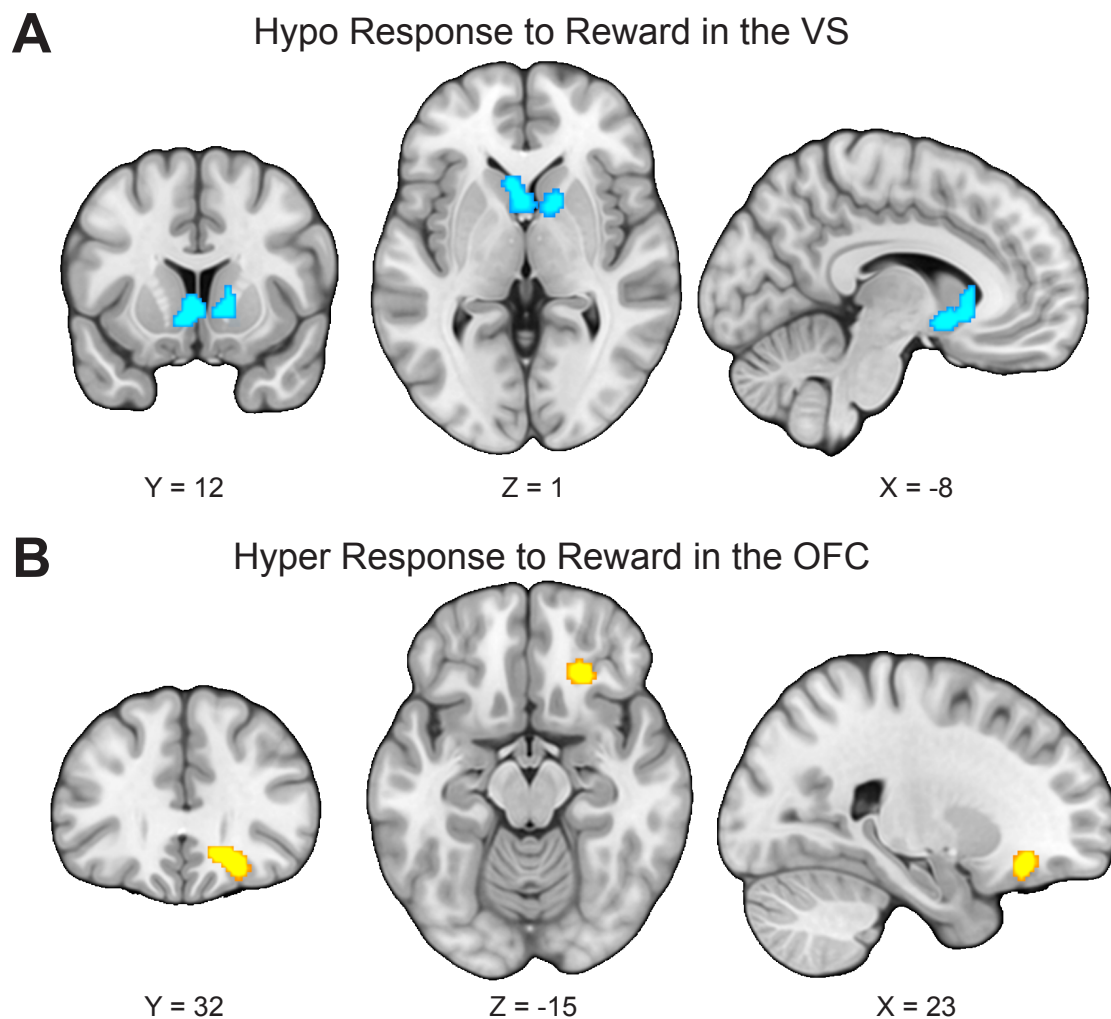
Figure 2. Opposing Abnormalities in the Reward Circuit in Response to Reward in Major Depressive Disorder (MDD). **(A)** To examine regions that consistently showed blunted response to reward, we synthesized 26 studies reporting less activity in response to reward in people with MDD than healthy controls (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.

Hyper Response to Punishment in the SLEA

Y = -6   Z = -16   X = -26
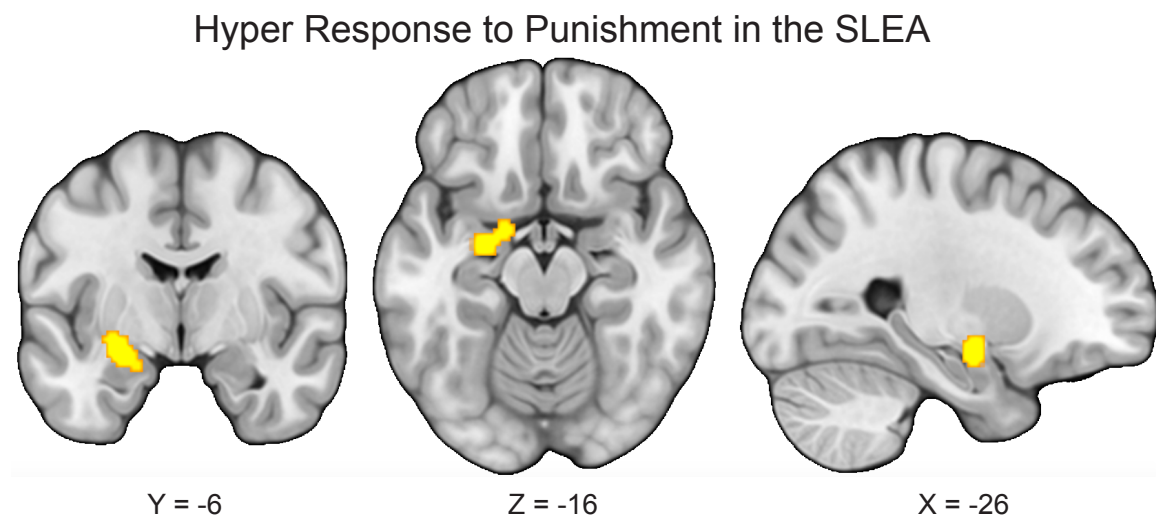
Figure 3. Hyper Response to Punishment in the Sublenticular Extended Amygdala (SLEA) in Major Depressive Disorder (MDD). To conduct exploratory analyses to examine which brain regions consistently show elevated response to punishment in MDD relative to healthy controls (HCs), we meta-analyzed 25 studies 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.

| Study	MDD Patients						Healthy Controls		
	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%

Study	N	Age	%	%	Status	Exclusion/Inclusion Criteria	N	Age	%
						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%

Study									
						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%

Study	N	Age	%	%	Group	Exclusion criteria	N	Age	%
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%

Study	n	Age	% Female	%	Mood state	Exclusion criteria	n	Age	% Female
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%

Study	N					Criteria	N		
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	Unspecified	44.4%	Depressed	Inclusion of generalized anxiety disorder and binge eating disorder.	13	26.2	Unspecified
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

Elliott *et al*. (10)	fMRI	Block	MNI	Affective go/no go task	Words	HC > MDD, Outcome: Reward > Non-Reward 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).

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