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

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Abstract

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 reward-related responses, particularly in the ventral striatum (VS). Yet, the link between MDD and reward-related responses in other regions remains inconclusive, thus limiting our understanding of the pathophysiology of MDD. To address this issue, we performed a coordinate-based meta-analysis of 41 neuroimaging studies encompassing reward-related responses from a total of 794 patients with MDD and 803 healthy controls. Our 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 orbitofrontal cortex. These findings help to reconceptualize our understanding of reward processing abnormalities in MDD and suggest a role for dysregulated corticostriatal connectivity.
**Introduction**

Depression is a prevalent mental disorder ranked as the leading non-fatal cause of disability by the World Health Organization (Friedrich, 2017; World Health Organization, 2017). 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 (Alloy et al., 2016; Heshmati and Russo, 2015; Nusslock and Alloy, 2017; Olino, 2016; Olino et al., 2014, 2011; Pizzagalli, 2014; Robbins, 2016; Treadway and Zald, 2011; Whitton et al., 2015). 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; Arrondo et al., 2015; Knutson et al., 2008; Luking et al., 2016; McCabe et al., 2009; Pizzagalli et al., 2009; Smoski et al., 2009)(Arrondo et al., 2015; Knutson et al., 2008; McCabe et al., 2009; Pizzagalli et al., 2009; Smoski et al., 2009).

The striatum, which can be divided into dorsal and ventral sections, is the primary input zone for basal ganglia (Haber, 2016; Haber and Knutson, 2010). It receives afferent projections from the midbrain, amygdala, and prefrontal cortex (PFC), such as the orbitofrontal cortex (OFC), dorsolateral prefrontal cortex (dLPC), ventromedial prefrontal cortex (vmPFC), and anterior cingulate cortex (ACC; Haber, 2016; Haber and Knutson, 2010). It also projects to such regions as the ventral pallidum, ventral tegmental area, and substantia nigra (Haber and Knutson, 2010). Many of the regions linked to the striatum, particularly prefrontal regions, have been associated with the computation and representation of reward value (Berridge and Kringelbach, 2015; Der-Avakian and Markou, 2012; Kringelbach, 2005; Levy and Glimcher, 2012; Padoa-Schioppa, 2011; Padoa-Schioppa and Conen, 2017; Rangel et al., 2008; Saez et al., 2017; Smith and Delgado, 2015; Smith and Huettel, 2010; Stalnaker et al., 2015; Wang et al., 2016), as well as the regulation of affect.
and reward-related behavior in animals and healthy individuals (Delgado et al., 2016; Ferenczi et al., 2016; Peters and Büchel, 2010; Phelps et al., 2014; Voorn et al., 2004). The striatum also has long been proposed to play an important role in the onset and course of MDD, with longitudinal studies demonstrating that blunted VS activation during reward anticipation predicts the emergence of depressive symptoms and disorder (Morgan et al., 2013; Stringaris et al., 2015) and deep-brain stimulation studies using it as a treatment target for treatment-resistant depression (Dougherty et al., 2015; Malone et al., 2009).

Although blunted striatal response to reward in MDD is a well-established finding in the literature (Groenewold et al., 2013; Hanson et al., 2015; Heshmati and Russo, 2015; Whitton et al., 2015; Zhang et al., 2013), 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 (Forbes et al., 2006; Smoski et al., 2009), dIPFC (Demenescu et al., 2011; Pizzagalli et al., 2009), vmPFC (Keedwell et al., 2005; Rizvi et al., 2013), ACC (Dichter et al., 2012; Mitterschiffthaler et al., 2003), middle frontal gyrus (Dichter et al., 2012; Keedwell et al., 2005), inferior frontal gyrus (Kumari et al., 2003; Mitterschiffthaler et al., 2003), subgenual cingulate (Kumari et al., 2003; Rizvi et al., 2013), and dorsomedial prefrontal cortex (Keedwell et al., 2005) during the processing of rewarding stimuli. In contrast, other studies have reported less activity in MDD in response to reward in the OFC (Dichter et al., 2012; Forbes et al., 2006), ACC (Forbes et al., 2006; Kumari et al., 2003; Pizzagalli et al., 2009; Smoski et al., 2009), middle frontal gyrus (Kumari et al., 2003; Mitterschiffthaler et al., 2003; Smoski et al., 2009), and frontal pole (Dichter et al., 2012). The inconsistencies may be due to a number of factors, such as limited statistical power (Button et al., 2013; Jia et al., 2018; Poldrack et al., 2017) and susceptibility artifacts in the PFC (Andersson et al., 2001; Chase et al., 2015; Delgado et al., 2016; Ojemann et al., 1997). 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, dIPFC, vmPFC and/or ACC).

Inconsistencies in the literature have prompted researchers to conduct coordinate-based meta-analyses to identify common activation patterns implicated in MDD during reward processing (Groenewold et al., 2013; Keren et al., 2018; Zhang et al., 2013). Although prior meta-analytic efforts have shown some overlapping findings in the striatum, we note that there is a striking degree of anatomical disagreement across these efforts, with non-overlapping findings all throughout the brain (see Table S1 and Figure S1 for a complete comparison of findings across studies). The lack of agreement across studies can be due to methodological issues, such as lenient thresholding, overlapping samples, software issues (Eickhoff et al., 2017), and inclusion of region-of-interest (ROI) coordinates, as detailed in a previous review (Muller et al., 2016). For example, two previous meta-analyses (Groenewold et al., 2013; Zhang et al., 2013) corrected for multiple comparisons using the false discovery rate (FDR) approach, which has been shown to be inadequate in controlling the false positives among clusters in neuroimaging meta-analyses (Chumbley and Friston, 2009; Eickhoff et al., 2012) and might have contributed to the lack of agreement across studies.

To address these issues and extend extant work, we performed a coordinate-based meta-analysis following procedures recommended by new guidelines (Barch and Pagliaccio, 2017; Muller et al., 2017, 2016). The current work differed from previous meta-analyses on reward processing in MDD in various aspects, such as only including whole-brain studies to avoid localization bias; only including studies that used an active control condition to isolate reward-related processes; only including independent samples to avoid double counting the same participants; using more stringent thresholding criteria; having the most up-to-date literature search; 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 (Eickhoff et al., 2016).

Our primary hypothesis was that the literature would consistently show 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. To examine these hypotheses, we conducted four separate coordinate-based meta-analyses testing spatial convergence of neuroimaging findings for the following four contrasts: 1) positive valence (reward > punishment/neutral stimuli or neutral stimuli > punishment) for MDD > HC; 2) negative valence (punishment > reward/neutral stimuli or neutral stimuli > reward) for MDD > HC; 3) positive valence for HC > MDD; 4) negative valence for HC > MDD. 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. We aimed to address two main 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?

Materials and Methods

Study Selection

The current coordinate-based meta-analysis primarily followed the guidelines for meta-analyses, whenever applicable (Moher et al., 2009; Muller et al., 2017). 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 8/7/2018 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 (the search identified 23 studies on bipolar disorder across positive and negative valence contrasts, yielding fewer than 17 experiments for each targeted meta-analysis).

- 3206 citations identified via literature search
- 2977 citations excluded based on title/abstract review
- 229 full-text articles assessed for eligibility
- 188 articles excluded due to
  - 63 Unsuitable analyses (e.g., ROI, SVC)
  - 42 Not meeting standard diagnostic criteria for MDD
  - 18 Unsuitable task and/or stimuli
  - 17 No relevant significant group effects
  - 15 Review articles
  - 14 Overlapping samples
  - 8 No relevant comparison groups
  - 8 No active control conditions
  - 2 Inadequate reporting
  - 1 Non fMRI or PET studies

- 41 included studies
- Reward tasks
  1. Greater brain activity in MDD: 18 studies
  2. Less brain activity in MDD: 22 studies
- Punishment tasks
  3. Greater brain activity in MDD: 24 studies
  4. Less brain activity in MDD: 17 studies
**Figure 1.** Flowchart of study selection. Our systematic literature search identified a total of 41 neuroimaging studies that met our inclusion criteria, yielding 4 coordinate-based meta-analyses with at least 17 independent studies; ROI, region of interest; SVC, small volume correction; MDD, major depressive 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-IV, DSM-IV-TR, ICD-10) 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 without small volume corrections (SVC), as non-whole-brain coordinates [e.g., region of interest (ROI)-based coordinates] and analyses involving SVC have been argued to bias coordinate-based meta-analyses (Eickhoff et al., 2016; Muller et al., 2017), (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). The stimuli used in the included studies of the meta-analysis reflect both a reward-punishment continuum and a positive-negative continuum. For example, although positive faces are traditionally considered only as positive stimuli, we considered them as
rewards, based on previous research showing that positive faces activate the reward circuitry, that they are discounted as a function of time, that they are tradable for other rewards (e.g., money), that they reinforce work, and that people are willing to work to view positive faces and exert more effort for more positive faces (e.g., Hayden et al., 2007; Krach et al., 2010; Tsukiura and Cabeza, 2008).

**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 (Eickhoff et al., 2012; Laird et al., 2005; Turkeltaub et al., 2012). The ALE method aims to identify regions showing spatial convergence between experiments and tests against the null hypothesis that the foci of experiments are uniformly and randomly distributed across the brain (Eickhoff et al., 2012). It treats foci from individual experiments as centers for 3D Gaussian probability distributions representing spatial uncertainty. The width of these distributions was determined based on between-subject and between-template variability (Eickhoff et al., 2009). The ALE algorithm weighs the between-subject variability by the number of participants for each study, based on the idea that experiments of larger sample sizes are more likely to reliably report true activation effects. Therefore, experiments with larger sample sizes are modeled by smaller Gaussian distributions, resulting in a stronger influence on ALE scores, which indicate the probability that at least one true peak activation lies in the voxel across the population of all possible studies (Eickhoff et al., 2009).

The ALE 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. Finally, a permutation test is employed to identify voxels in which the ALE statistic is larger than expected by chance (Eickhoff et al., 2009, 2012; Laird et al., 2005; Turkeltaub et al., 2012). The ALE method takes into account
heterogeneity in spatial uncertainty across studies (Eickhoff et al., 2009, 2012; Turkeltaub et al., 2012) and differences in number of peak coordinates reported per cluster (Turkeltaub et al., 2012). This approach allows random-effects estimates of ALE, increasing generalizability of the results (Eickhoff et al., 2009).

It is important to note that coordinate-based meta-analyses represent a departure from traditional meta-analyses (Fox et al., 1998; Muller et al., 2017). Specifically, whereas traditional meta-analyses aim to calculate pooled effect sizes to determine the direction and magnitude of an effect based on a body of literature, coordinate-based meta-analyses evaluate whether the location of an effect is consistent within a body of literature (e.g., whether studies that examined blunted responses to reward in MDD consistently implicate the VS). In other words, coordinate-based meta-analyses are blind to effect size magnitude, but direction is tied to the analysis (Fox et al., 1998; Muller et al., 2017).

**Statistical Analysis**

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 (Eickhoff et al., 2012, 2009) to examine whether we could identify consistent activation patterns across studies. Our main analyses focused on examining which brain regions show consistent hypo- or hyper-responses to reward in MDD relative to HCs. We also conducted exploratory analyses to investigate which brain regions consistently show aberrant responses to punishment in MDD relative to HCs. Our analyses were limited to four independent contrasts: 1) positive valence (reward > punishment/neutral stimuli or neutral stimuli > punishment) for MDD > HC; 2) negative valence (punishment > reward/neutral stimuli or neutral stimuli > reward) for MDD > HC; 3) positive valence for HC > MDD; 4) negative valence for HC > MDD. Assessing these contrasts in separate coordinate-based meta-analyses is essential for characterizing reward-processing abnormalities in MDD.
Indeed, this approach is adopted by many ALE meta-analyses of studies that compare a psychiatric group with a healthy control group (e.g., Delvecchio et al., 2013; Muller et al., 2016; Zhang et al., 2013).

To ensure adequate statistical power and limit the possibility that a meta-analytic effect is driven by a small set of studies (Eickhoff et al., 2016; Smith and Delgado, 2017), 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 (Turkeltaub et al., 2012). 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 (Lancaster et al., 2007). We assessed statistical significance and corrected for multiple comparisons using the permutation-based approach (N = 1000) recommended by the developers of GingerALE (Eickhoff et al., 2016, 2017). This approach utilized a cluster-forming threshold of $P < 0.001$ (uncorrected) and maintained a cluster-level family-wise error rate of 5% (Eickhoff et al., 2016). To capture anatomical variation between individual human brains (Mazziotta et al., 1995), we show probabilistic anatomical labels for the locations of the maximum ALE values using the Harvard–Oxford cortical and subcortical atlases (Desikan et al., 2006). For transparency, all of our statistical maps (thresholded and unthresholded) derived from the meta-analyses are publicly available on NeuroVault.
(https://neurovault.org/collections/3884/). Readers are free to access these maps and define these regions using their own labels.

**Results**

As shown in Figure 1, our systematic literature search identified a total of 41 neuroimaging studies that met our inclusion criteria, yielding 4 coordinate-based meta-analyses with at least 17 independent experiments. Tables S2 and S3 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 19.9, the mean age was 36.4, the mean percentage of females was 60.9%, and the mean percentage of medication usage was 36.6%. For the HC group, the mean number of participants was 20.1, the mean age was 34.9, and the mean percentage of females was 60.3%. Types of reward or punishment used by the included studies encompass money, points, or voucher (41.5%; 17/41); faces (34.1%; 14/41); pictures (12.2%; 5/41); words, statements, captions, or paragraphs (12.2%; 5/41); and autobiographical memory (4.9%; 2/41). 41.5% (17/41) of studies reported both reward and punishment contrasts; 29.3% (12/41) of studies reported punishment contrasts only; and 26.8% (11/41) of studies reported reward contrasts only.

**Aberrant Reward and Punishment Responses in MDD**

We first synthesized results of 22 studies reporting less activity in response to reward in people with MDD than HC’s (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 a single cluster extending bilaterally across the VS and including part of the subcallosal cortex in MDD (Table 1; Figure 2a).

In addition to examining which regions consistently showed hypo-responses to reward, we also examined which, if any, brain regions showed consistent hyper-responses to reward-relevant stimuli. We aggregated results of 18 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.

We conducted sensitivity analyses to examine whether excluding studies that used neutral stimuli > punishment as a reward contrast would affect the main results related to reward responses in MDD. The analyses revealed that the results remained the same (see supplementary materials for details). We also conducted exploratory analyses to examine which brain regions consistently show aberrant responses to punishment in MDD relative to HCs. Results are detailed in supplementary materials.

**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         | 912                   | Frontal Orbital Cortex (26%), Frontal Pole (13%)      | 20  | 32  | -12  |
| HC > MDD         | 1768                  | Subcallosal Cortex (14%)                              | -2  | 8   | -4   |
|                  |                       | Caudate (32.1%), Accumbens (11.1%)                    | 8   | 6   | -2   |

Coordinates are x,y,z values of the locations of the maximum activation likelihood estimation (ALE) values in MNI space. Probabilistic labels reflect the probability that a coordinate belongs to a given region derived from the Harvard-Oxford probabilistic atlas. For clarity, we only report labels whose likelihood exceeds 5%. MDD, major depressive disorder; HC, healthy controls.
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 22 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 ventral striatum (VS) in MDD. (B) To identify regions that consistently showed hyper-responses to reward, we meta-analyzed 18 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.
Discussion

A growing number of researchers have used 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 in the VS, but more disparate patterns of responses in other brain areas (Arrondo et al., 2015; Hamilton et al., 2012; Knutson et al., 2008; McCabe et al., 2009; Miller et al., 2015; Palmer et al., 2014; Pizzagalli et al., 2009; Smoski et al., 2009)(Arrondo et al., 2015; Knutson et al., 2008; McCabe et al., 2009; Pizzagalli et al., 2009; Smoski et al., 2009). Therefore, it remains unclear what brain regions, other than the VS, are most consistently implicated in people with MDD, particularly during reward processing (See Table S1 and Figure S1). To address this issue, we performed a coordinate-based meta-analysis of 41 neuroimaging studies containing reward-related responses from a total of 794 patients with MDD and 803 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 blunted striatal findings are consistent with previous meta-analytic work documenting reward processing abnormalities in MDD (Groenewold et al., 2013; Keren et al., 2018; Zhang et al., 2013), 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, previous meta-analyses have generally reported distributed patterns of abnormalities, with little anatomical agreement across studies (see Table S1 and Figure S1).
Second, to minimize bias, our study employed more stringent analysis methods than prior studies in this area, following recommendations by new guidelines (Barch and Pagliaccio, 2017; Muller et al., 2017, 2016). For example, instead of using the FDR approach which has been shown to be inadequate in controlling the false positives among clusters in neuroimaging meta-analyses (Chumbley and Friston, 2009; Eickhoff et al., 2012), we corrected for multiple comparisons using the permutation-based approach. We also excluded ROI- or SVC-based studies and only included whole-brain studies that used an active control condition and independent samples. In addition, we only conducted 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 (Eickhoff et al., 2016). 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.

A prior meta-analysis using similarly rigorous methods revealed no significant convergence of findings among neuroimaging studies comparing MDD and HCs (Muller et al., 2016); nevertheless, we note that the previous meta-analysis differed from the current meta-analysis in at least four key ways. First, whereas the previous meta-analysis focused on emotional or cognitive processing, the current meta-analysis focused solely on reward processing. Second, the previous meta-analysis excluded participants younger than 18 years old; in contrast, the current meta-analysis included participants of all ages, boosting our power and ability to generalize our findings to MDD across ages. Third, the previous meta-analysis included studies up until October 2015, whereas our meta-analysis included studies until August 2018. Finally, the previous meta-analysis excluded MDD participants in remission, whereas the current meta-analysis included them, allowing us to begin to address the question of whether reward processing dysfunction is not simply a state, but a trait of MDD. Our ability to identify significant convergence highlights the significance of reward
processing dysfunction in MDD and might indicate the literature on reward processing in MDD is more homogeneous than that on emotional or cognitive processing in MDD.

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, which has been associated with the computation and representation of reward value (Berridge and Kringelbach, 2015; Der-Avakian and Markou, 2012; Kringelbach, 2005; Padoa-Schioppa, 2011; Padoa-Schioppa and Conen, 2017; Rolls, 2017). Therefore, given that MDD is traditionally linked to blunted response to reward or reduced capacity to experience pleasure (Whitton et al., 2015), 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 hyper-responses 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 (Naranjo et al., 2001; Tremblay et al., 2005, 2002). Anhedonia, then, may be rooted in decreased connectivity between the prefrontal regions and subcortical regions underlying reward-related behavior, as suggested by previous research (Young et al., 2016).

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 (Ferenczi et al., 2016; Robbins, 2016) and increasing connectivity between the medial PFC, lateral OFC, and VS (Ferenczi et al., 2016; Robbins, 2016). 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 (Almeida et al., 2009).
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 affects 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 (Ferenczi et al., 2016; Jackson et al., 2001) and has strong antidepressant effects (Covington et al., 2010; Steinberg et al., 2015). Taken together, OFC hyperactivity may inhibit reward-related behavior and lead to anhedonia via suppressing striatal responses to dopamine neurons in the midbrain (Ferenczi et al., 2016; Robbins, 2016) and increasing connectivity between the PFC and the VS in MDD (Ferenczi et al., 2016; Robbins, 2016).

The role of corticostriatal connectivity during reward processing in MDD remains an open and important question (Admon and Pizzagalli, 2015a; Drysdale et al., 2017; Kaiser et al., 2015). Previous meta-analyses indicate that at least some people with MDD exhibit dysfunction in resting-state corticostriatal connectivity (Drysdale et al., 2017; Kaiser et al., 2015). We believe our meta-analytic results will provide a springboard for future studies that seek to develop a full picture of the pathophysiology of MDD and understand the role of dysregulated corticostriatal connectivity in MDD, particularly in the context of reward processing. These endeavors will require empirical assessments of connectivity within the reward circuit using psychophysiological interaction analysis (Friston et al., 1997; McLaren et al., 2012; Smith et al., 2016a) and dynamic causal modeling (Friston et al., 2003). Such approaches have shown promise for revealing specific patterns of task-dependent corticostriatal interactions in samples containing healthy individuals (Chatham et al., 2014; Smith et al., 2016b; Wimmer et al., 2012; Wimmer and Shohamy, 2012), clinical populations
(Admon and Pizzagalli, 2015a, 2015b; Young et al., 2016), or a mix of both (Hanson et al., 2017). Nevertheless, a caveat of such approaches is that dysregulated corticostriatal connectivity may involve modulatory regions, such as the midbrain (Murty et al., 2014). In addition, although reinforcement learning models, such as actor-critic models and prediction error models have been utilized to understand the pathophysiology of several psychiatric disorders (e.g., schizophrenia and addiction), research on their application on MDD has been scant (Gold et al., 2012; Maia and Frank, 2011). Our results help delineate specific abnormalities within the reward circuit and supply a foundation for refining connectivity-based and computational models of MDD.

Even though our meta-analysis reveals circumscribed patterns of abnormal responses to reward in the VS and OFC, we note that our findings should be interpreted in the context of their 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 (Bartra et al., 2013; Clithero and Rangel, 2014; O’Doherty, 2014; Wang et al., 2016; Zald and Treadway, 2017). Our analyses also collapsed across different mood states, psychotropic medication usage, ages, and comorbidities (Drevets, 2007; Hafeman et al., 2012; Phillips et al., 2003). 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 (Bartra et al., 2013; Cooper and Knutson, 2008; Kahnt et al., 2014; Litt et al., 2011)—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 (Button et al., 2013; Jia et al., 2018). The validity of a meta-analysis hinges on the validity of the included studies (Akobeng, 2005). Future work should follow the most updated guidelines for best practices in the field to avoid generating biased findings (Nichols et al., 2017). Third, most of the included studies only recruited adults with acute major depression. More studies on other ages (e.g., pre-adolescents, adolescents) and mood states (e.g., remission) are needed. Fourth, we note that the search criteria were designed to focus on studies on reward and might not identify some studies on punishment. Therefore, the analyses and results in relation to punishment are exploratory in nature and should be interpreted with caution. Fifth, the ALE method, by nature, cannot incorporate null results (Muller et al., 2017). As a result, the current findings could be confounded by publication bias. Sixth, it is important to acknowledge that reward processing is complex, and the receipt of reward can be linked to both affective and informative signals (Smith et al., 2016b). Finally, it is important to note that some patients in the included studies were medicated. The normalizing effects of treatment could obscure differences between MDD and HCs, increasing the probability of type II errors (Delaveau et al., 2011; Dichter et al., 2009).

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 abnormal reward processing (Diehl et al., 2018). For example, a more refined understanding of the abnormalities in the reward circuitry in MDD may help distinguish it from other disorders exhibiting reward processing abnormalities, such as bipolar disorder, schizophrenia, and substance use disorder (Batalla et al., 2017; Whitton et al., 2015). Finally, given that previous treatment targets for deep brain stimulation for treatment-resistant depression have yielded mixed results (Bewernick et al., 2010; Holtzheimer et al., 2012, 2017; Jiménez et al., 2005; Lozano et al., 2012; Malone et al., 2009; Naesström et al., 2016; Puigdemont et al., 2012; Schlaepfer et al., 2013; Schlaepfer, 2015), the portion of OFC implicated by our results could be a promising treatment target.
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Disclosures

All authors report no biomedical financial interests or potential conflicts of interest.
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Meta-analysis of Reward Processing in Major Depressive Disorder Reveals Distinct Abnormalities within the Reward Circuit

Supplemental Information

Supplementary Results and Discussion

Aberrant Reward Responses in Major Depressive Disorder (MDD)—Excluding Neutral Stimuli > Punishment Contrast

As a significant result for the contrast of neutral stimuli > punishment could be due to positive reward salience (i.e., reward > neutral stimuli > punishment) or negative reward salience (i.e., neutral stimuli > reward/punishment), we conducted sensitivity analyses to examine whether excluding studies that used neutral stimuli > punishment as a reward contrast would affect our main results related to reward responses in MDD. After excluding the 2 experiments of neutral stimuli > punishment (1, 2), the results remained the same: We found significant convergence among experiments reporting blunted responses for reward in MDD relative to HCs in the VS, as well as significant convergence among experiments reporting elevated responses for reward in MDD relative to HCs in the OFC (See Table S4).

Hyper Punishment Responses in Major Depressive Disorder (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 24 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 S5; Figure S2). Second, we synthesized 17 studies reporting less activity in response to punishment in people with MDD than HCs (i.e. HC > MDD for punishment >
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.

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 (3, 4). It is also in agreement with a meta-analysis indicating increased activation in the amygdala in response to negative stimuli in MDD relative to HCs (5) and a long series of studies indicating that the amygdala may be a key brain region implicated in the pathophysiology of depression (6–8). Interestingly, longitudinal studies have reported that amygdala reactivity, potentially in combination with life stress, prospectively predicts internalizing (e.g., depressive and anxiety) symptoms (9, 10), highlighting the importance of amygdala reactivity in the course of depression.
### Table S1. Comparison of Findings on Reward Responses (i.e., Reward > Punishment/Neutral) in Previous Meta-analyses.

| Brain Region               | MNI Coordinates | TAL Coordinates |
|----------------------------|-----------------|-----------------|
|                            | x   | y   | z   | x   | y   | z   |
| **Groenewold et al. (50)** |     |     |     |     |     |     |
| **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 |     |     |     |
| **Zhang et al. (51)**      |     |     |     |     |     |     |
| **MDD > HC**               |     |     |     |     |     |     |
| Cuneus                     | 4   | -86 | 18  |     |     |     |
| Cuneus                     | -6  | -86 | 22  |     |     |     |
| Frontal Lobe               | 20  | 30  | -6  |     |     |     |
| Brain Region         | Coordinates |   |   |
|----------------------|-------------|---|---|
| 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**

| Brain Region         | Coordinates |   |   |
|----------------------|-------------|---|---|
| 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|

**Keren et al. (52)**

| Brain Region         | Coordinates |   |   |
|----------------------|-------------|---|---|
| Caudate Body         | 12          | 14 | 14 |
| Caudate Head         | 6           | 2  | -2 |
| Caudate Body         | -8          | -2 | -18|

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).
Table S2. Characteristics of the Study Samples Included in the Meta-Analysis.

| Study               | Diagnostic Criteria | MDD Patients | Healthy Controls |
|---------------------|---------------------|--------------|-----------------|
|                      | n       | Age  | % Female | % Medicated | Mood States | Comorbidity |
| Arrondo et al. (11) | DSM-IV  | 24   | 33.1    | 29.2%       | 54.2%       | D           | Exclusion of alcohol or drug dependence. |
| Bremner et al. (12) | DSM-IV  | 18   | 40      | 66.7%       | 0.0%        | D           | 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. |
| Burger et al. (13)  | DSM-IV  | 36   | 40.7    | 61.1%       | 100.0%      | D           | Exclusion of substance dependence. Inclusion of PD, agoraphobia, generalized anxiety disorder, social phobia, obsessive compulsive disorder, post-traumatic stress disorder, somatoform disorder, eating disorder, dysthymia, alcohol abuse, and substance abuse. |
| Chantiluke et al. (14) | DSM-IV | 20   | 16.2    | 50.0%       | 0.0%        | D           | Exclusion of major psychiatric disorders. |
| Chase et al. (15)   | DSM-IV  | 40   | 31      | 77.5%       | 77.5%       | D           | No exclusion of psychiatric comorbidities. Inclusion of lifetime comorbid anxiety |
| Study                  | Methodology | N  | Mean Age | 66.1% | 23.7% | Exclusion Criteria                                                                                                                                 |
|-----------------------|-------------|----|----------|-------|-------|--------------------------------------------------------------------------------------------------------------------------------------------------|
| Demenescu et al. (1)  | DSM-IV      | 59 | 36.2     |       |       | Disorders and substance use disorders. Exclusion of axis I disorders, such as psychotic disorder or dementia, current alcohol or substance abuse.       |
| Dichter et al. (16)   | DSM-IV      | 19 | 23.6     | 78.9% | 0.0%  | Exclusion of current axis I psychopathology. Exclusion of current comorbid anxiety disorders, substance abuse or dependence, bipolar disorder, or other psychiatric diagnoses. Inclusion of past history of PD and bulimia. |
| Elliott et al. (17)   | DSM-IV      | 10 | 42.2     | 70.0% | 100.0%| Exclusion of current comorbid anxiety disorders, substance abuse or dependence, bipolar disorder, or other psychiatric diagnoses. Inclusion of past history of PD and bulimia. |
| Engelmann et al. (18) | DSM-IV      | 19 | 37.6     | 52.6% | 0.0%  | Exclusion of lifetime bipolar disorder, psychotic disorder, obsessive-compulsive disorder, tic disorder, eating disorder, cognitive disorder, substance abuse or dependence in the previous 6 months or positive urine drug screen, or clinically significant suicidal ideation. |
| Fournier et al. (19)  | DSM-IV      | 26 | 30.6     | 69.0% | 69.2% | Exclusion of bipolar disorder, borderline personality disorder, and alcohol/substance use                                                                 |
disorder within 2 months before the scan. Inclusion of history of anxiety disorder and substance abuse.

| Study                | DSM Version | N  | Mean | Rate | Rate |
|----------------------|-------------|----|------|------|------|
| Fu et al. (20) and (21) | DSM-IV | 19 | 43.2 | 68.4% | 100.0% |
| Exclusion of current axis I disorder and history of substance abuse within 2 months of study participation. | | | | | |
| Fu et al. (22) | DSM-IV | 16 | 40 | 81.3% | 0.0% |
| Exclusion of other axis I disorder, including anxiety disorder or history of substance within 2 months of study participation. | | | | | |
| Gotlib et al. (23) | DSM-IV | 18 | 35.2 | 72.2% | 50.0% |
| Exclusion of psychotic ideation, social phobia, PD, mania, or substance abuse in the past 6 months or behavioral indications of possible impaired mental status. | | | | | |
| Gradin et al. (24) | DSM-IV | 25 | 25.5 | 68.0% | 0.0% |
| Hall et al. (25) | DSM-IV | 29 | 37.4 | 55.2% | 51.7% |
| Johnston et al. (26) | DSM-IV/ICD-10 | 19 | 50.8 | 78.9% | 85.0% |
| Exclusion of other primary psychiatric disorder and substance misuse. | | | | | |
| Keedwell et al. (27) | ICD-10 | 12 | 43 | 66.7% | 66.7% |
| Exclusion of other axis I disorder. | | | | | |
| Knutson et al. (28) | DSM-III-R | 14 | 30.7 | 64.3% | 0.0% |
| Exclusion of other current axis I disorder. | | | | | |

19 42.8 57.9%

16 39.2 81.3%

18 30.8 72.2%

25 25.4 68.0%

25 37.7 55.2%

21 46.1 71.4%

12 36 66.7%

12 28.7 66.7%
| Study                  | DSM Version | Sample Size | Gender | Presence | Diagnosis | Unspecified Comorbidities                                                                 |
|-----------------------|-------------|-------------|--------|----------|-----------|-----------------------------------------------------------------------------------------|
| Kumari et al. (29)    | DSM-IV      | 6           | 47     | 100.0%   | Unspecified | No exclusion of psychiatric comorbidities. Inclusion of past substance abuse/dependence, anxiety disorders, and eating disorder. |
| Laurent et al. (30)   | DSM-IV      | 11          | 24.1   | 100.0%   | 23.1%     | No exclusion of psychiatric comorbidities. Inclusion of past substance abuse/dependence, anxiety disorders, and eating disorder. |
| Liu et al. (31)       | DSM-IV      | 21          | 30.7   | 57.1%    | 0.0%      | Exclusion of axis I disorders (other than anxiety) and psychotic features and lifetime substance abuse or dependence. |
| Murrough et al. (32)  | DSM-IV      | 20          | 38.1   | 44.4%    | 0.0%      | Exclusion of lifetime history of psychotic illness or bipolar disorder and current alcohol or substance abuse. |
| Pizzagalli et al. (33)| DSM-IV      | 30          | 43.2   | 50.0%    | 0.0%      | Exclusion of other axis I disorder except for anxiety disorders. |
| Remijnse et al. (34)  | DSM-IV      | 20          | 35     | 40.0%    | 0.0%      | 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. |
| Rizvi et al. (35)     | DSM-IV      | 21          | 38.9   | 66.7%    | 0.0%      | Exclusion of other primary axis I disorder, lifetime history of |
| Study                  | DSM Version | Sample Size | Gender | Ethnicity | Age | Other Exclusions                                                                                                                                 |
|------------------------|-------------|-------------|--------|-----------|-----|------------------------------------------------------------------------------------------------------------------------------------------------|
| Rosenblau et al. (36)  | DSM-IV      | 12          | 43.5   | 41.7%     | 0.0%| Exclusion of hypomania/mania, psychosis, obsessive compulsive disorder, or eating disorder, and substance abuse or dependence (except nicotine or caffeine) within the last 3 months. |
| Scheuerecker et al. (37)| DSM-IV      | 13          | 37.9   | 23.1%     | 0.0%| Exclusion of past alcohol or substance abuse, other mental illnesses, and personality disorders.                                           |
| Schiller et al. (38)   | DSM-IV      | 19          | 23.6   | 78.9%     | 0.0%| Exclusion of current axis I psychopathology.                                                                                          |
| Segarra et al. (39)    | DSM-IV      | 24          | 33.1   | 29.2%     | 54.0%| Exclusion of dependence on alcohol or recreational drugs.                                                                             |
| Sharp et al. (40)      | DSM-IV      | 14          | 13.4   | 100.0%    | Unspecified| Exclusion of current use of nicotine, illicit drugs, psychotic disorders, bipolar I disorder, learning disabilities, and mental retardation. |
| Smoski et al. (41)     | DSM-IV      | 14          | 34.8   | 50.0%     | 0.0%| Exclusion of current mood disorder, anxiety disorder, psychotic disorder, substance abuse, or active suicidal ideation and history of psychosis or mania. |
| Study                        | Scale     | N  | Age  | Gender | Diagnosis                                      | Other Exclusions                                                                 |
|------------------------------|-----------|----|------|--------|-----------------------------------------------|--------------------------------------------------------------------------------|
| Smoski et al. (42)           | DSM-IV    | 9  | 34.4 | Unspecified | 44.4%                                      | Inclusion of generalized anxiety disorder and binge eating disorder. |
| Surguladze et al. (43)       | DSM-IV    | 16 | 42.3 | 37.5%  | 100.0%                                      | Exclusion of illicit substance abuse.                                           |
| Surguladze et al. (44)       | DSM-IV    | 9  | 42.8 | 44.4%  | 100.0%                                      | Exclusion of illicit substance abuse and other axis I disorders.         |
| Townsend et al. (45)         | DSM-IV    | 15 | 45.6 | 40.0%  | 0.0%                                        | Exclusion of comorbid axis I disorder.                                        |
| Young et al. (47)            | DSM-IV-TR | 16 | 37.1 | 87.5%  | 0.0%                                        | Exclusion of serious suicidal ideation, psychosis, drug/alcohol abuse in the past year and dependence (except for nicotine) in their lifetime. |
| Wang et al. (46)             | DSM-IV    | 12 | 69.1 | 58.3%  | 91.7%                                      | Exclusion of another major psychiatric disorder and alcohol/drug abuse/dependence. Inclusion of generalized anxiety disorder. |
| Zhang et al. (48)            | ICD-10    | 21 | 43.8 | 38.1%  | 100.0%                                      | Exclusion of illicit substance use or substance use disorders.                  |
| Zhong et al. (49)            | DSM-IV    | 29 | 20.5 | 55.2%  | 0.0%                                        | Exclusion of lifetime substance dependence and                                |
substance abuse in the last 6 months.

MDD, major depressive disorder; D, depressed; R, remitted; PD, panic disorder.
| Study                | Design or PET | Design          | Space | Paradigm                                                                 | Correction          | Stimuli     | Contrast                                      |
|---------------------|---------------|-----------------|-------|--------------------------------------------------------------------------|---------------------|-------------|-----------------------------------------------|
| Arrondo et al. (11) | fMRI          | Event-related   | MNI   | Modified monetary incentive delay task Verbal declarative memory tasks with neutral paragraph encoding compared to a control condition and sad word pair retrieval compared to a control condition. | Uncorrected         | Money       | HC > MDD, Anticipation: Reward > Non-Reward   |
|                     | PET           | Block           | MNI   |                                                                          |                      |             | MDD > HC, Outcome: Negative > Neutral         |
|                     |               |                 |       |                                                                          |                      |             | HC > MDD, Outcome: Positive > Neutral         |
| Bremner et al. (12) |               |                 |       |                                                                          | Uncorrected at p < .005 | Words and paragraphs | HC > MDD, Outcome: Negative > Neutral |
| Burger et al. (13)  | fMRI          | Event-related   | MNI   | Face matching paradigm                                                   | Corrected at p < .05 (TFCE) | Faces       | HC > MDD, Outcome: Negative > Neutral         |
| Chantiluke et al. (14) | fMRI        | Event-related   | TAL   | Reward continuous performance task                                       | Uncorrected at p < .05 | Money       | MDD > HC, Outcome: Reward > Non-Reward        |
|                     |               |                 |       |                                                                          |                      |             | HC > MDD, Outcome: Reward > Non-Reward        |
|                     |               |                 |       |                                                                          |                      |             | MDD > HC, Outcome: Reward Expectancy          |
| Chase et al. (15)   | fMRI          | Event-related   | MNI   | Card guessing paradigm                                                   | Voxel-wise corrected at p < .05 and cluster-wise corrected at p < .01 | Money       | MDD > HC, Anticipation: Reward > Non-Reward   |
|                     |               |                 |       |                                                                          |                      |             | HC > MDD, Anticipation: Reward Expectancy     |
|                     |               |                 |       |                                                                          |                      |             | MDD > HC, Anticipation: Reward Expectancy     |
|                     |               |                 |       |                                                                          |                      |             | MDD > HC, Outcome: Prediction Error           |
| Study                          | Task Type | Task Description                                                                                                                                                                                                 | Correction          | Outcome                                                                                     |
|-------------------------------|-----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|--------------------------------------------------------------------------------------------|
| **Demenescu et al. (1)**      | 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 | Cluster-wise corrected at p < .05 | Faces MDD > HC, Outcome: Positive > Scrambled Face                                          |
| **Dichter et al. (16)**       | fMRI      | Event-related MNI Modified monetary incentive delay task                                                                                                                                                    | Uncorrected at p < .005, k ≥ 10 | Money MDD > HC, Anticipation: Reward > Non-Reward MDD > HC, Outcome: Reward > Non-Reward HC > MDD, Outcome: Reward > Non-Reward |
| **Elliott et al. (17)**       | fMRI      | Block MNI Affective go/no go task                                                                                                                                                                               | Uncorrected at p < .001 | Words MDD > HC, Outcome: Negative > Positive HC > MDD, Outcome: Positive > Negative          |
| **Engelmann et al. (18)**     | fMRI      | Event-related MNI Economic decision-making task                                                                                                                                                                | Cluster-wise corrected at p < .05 | Money MDD > HC, Outcome: Negative > Positive MDD > HC, Outcome: Negative > Neutral MDD > HC, Outcome: Positive > Neutral |
| **Fournier et al. (19)**      | fMRI      | Block MNI Labeling a color flash superimposed upon neutral faces that gradually morphed into angry, fearful, sad, or happy faces                                                                                                                                 | Uncorrected at p < .001, k > 20 | Faces MDD > HC, Outcome: Negative > Neutral MDD > HC, Outcome: Positive > Neutral              |
| **Fu et al. (20) and (21)**   | fMRI      | Event-related TAL Indicating the sex of faces morphed to represent low,                                                                                                                                          | Cluster-wise corrected at p < .005 | Faces MDD > HC, Outcome: Negative (low, medium, and high intensity)                           |
| Study               | Method | Design  | Space  | Task/Procedure                                                                 | Correction                | Outcome | Group 1                      | Comparison | Group 2                      | Outcome | Group 3                      | Comparison |
|---------------------|--------|---------|--------|--------------------------------------------------------------------------------|---------------------------|---------|------------------------------|------------|------------------------------|---------|------------------------------|------------|
| Fu et al. (22)      | fMRI   | Event-related | TAL    | Indicating the sex of faces morphed to represent low, medium, and high intensities of sadness | Unspecified                | Faces   | MDD > HC                      | HC > MDD   | Positive (low, medium, and high intensity) |
| Gotlib et al. (23)  | fMRI   | Block   | MNI    | Indicating the sex of faces that were fearful, angry, sad, happy, neutral, or scrambled | Uncorrected at p < .001, k > 5 | Faces   | MDD > HC, Outcome: Negative > Neutral | HC > MDD, Outcome: Negative > Neutral | Faces   | MDD > HC, Outcome: Positive > Neutral | HC > MDD, Outcome: Increasing fairness (decreasing inequality) |
| Gradin et al. (24)  | fMRI   | Event-related | MNI    | Ultimatum game                                                                 | Cluster-wise corrected at p < .05 | Money   | HC > MDD, Outcome: Increasing fairness (decreasing inequality) | MDD > HC, Outcome: Increasing inequality (decreasing fairness) |
| Hall et al. (25)    | fMRI   | Event-related | TAL    | Contingency reversal reward paradigm                                           | Voxel-wise corrected at p < .05 | Money   | HC > MDD, Outcome: Magnitude of Loss: Large Loss > Small Loss | MDD > HC, Outcome: Magnitude of Reward: Large Reward > Small Reward | HC > MDD, Outcome: Reward Acquisition > Punishment Reversal |
| Study                | Imaging Modality | Task Type      | Task Description                                           | Correction          | Outcome Comparison                                                                 |
|---------------------|------------------|----------------|------------------------------------------------------------|---------------------|-----------------------------------------------------------------------------------|
| Johnston et al. (26) | fMRI             | Event-related MNI | Modified Pessiglione task                                 | Cluster-wise correct at p < .01 | MDD > HC, Outcome: Reward Acquisition > Punishment Reversal                      |
|                     |                  |                |                                                            |                     | HC > MDD, Outcome: Loss > Non-Loss                                                |
|                     |                  |                |                                                            |                     | HC > MDD, Outcome: Loss > Non-Loss                                                |
|                     |                  |                |                                                            |                     | MDD > HC, Outcome: Reward > Non-Reward                                             |
| Keedwell et al. (27) | fMRI             | Block TAL      | Being exposed to happy, sad, or neutral autobiographical memory prompts and facial expressions | Cluster-wise correct at p < .01 | 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. (28)  | fMRI             | Event-related TAL | Monetary incentive delay task                         | Uncorrected at p < .05 | Money                                                                                 |
|                     |                  |                |                                                            |                     | MDD > HC, Anticipation: Reward > Non-Reward                                       |
|                     |                  |                |                                                            |                     | HC > MDD, Anticipation: Reward > Non-Reward                                       |
|                     |                  |                |                                                            |                     | HC > MDD, Outcome: Non-Loss > Loss                                                |
| Kumari et al. (29)   | fMRI             | Block TAL      | Viewing positive or negative pictures with a caption      | Cluster-wise correct at p < .005 | Pictures and captions                                                              |
|                     |                  |                |                                                            |                     | MDD > HC, Outcome: Negative > Neutral                                             |
|                     |                  |                |                                                            |                     | MDD > HC, Outcome: Negative > Neutral                                             |
| Study               | Imaging | Task Type       | Condition(s) | Event-related | MNI Space | fMRI-related Task Description                                                                 | Cluster-wise Correction | Outcome(s)                                                                 |
|---------------------|---------|----------------|--------------|---------------|-----------|-----------------------------------------------------------------------------------------------|------------------------|---------------------------------------------------------------------------|
| Laurent et al. (30) | fMRI    | Event-related  | MNI          | Seeing own infant vs. other infant distress faces | Clustering-wise corrected at p < .05 | Faces                                                                                           | HC > MDD, Outcome: Very negative > Negative |
| Liu et al. (31)     | fMRI    | Event-related  | MNI          | Instrumental probabilistic reward- and punishment-based associative learning task | Clustering-wise corrected at p < .05 | Money                                                                                          | MDD > HC, Outcome: Negative > Neutral |
| Murrough et al. (32)| fMRI    | Event-related  | MNI          | Rating emotional valence of happy, sad, or neutral faces | Clustering-wise corrected at p < .05 | Faces                                                                                          | HC > MDD, Outcome: 100% Positive > Neutral |
| Pizzagalli et al. (33)| fMRI | Event-related  | MNI          | Monetary incentive delay task | Uncorrected at p < .005 | Money                                                                                          | MDD > HC, Anticipation: Loss > Non-Loss |

HC > MDD, Outcome: Positive > Neutral
MDD > HC, Outcome: Positive > Neutral
HC > MDD, Outcome: Positive > Negative
MDD > HC, Outcome: Positive > Negative
HC > MDD, Outcome: Loss > Non-Loss
MDD > HC, Outcome: Loss > Non-Loss
HC > MDD, Outcome: Loss > Non-Loss
| Study            | Design | Task/Paradigm | Analysis | Outcome/Comparison |
|------------------|--------|---------------|----------|-------------------|
| Remijnse *et al.* (34) | fMRI Event-related MNI | Reversal learning task | Uncorrected p < .001 | Points |
| Rizvi *et al.* (35) | fMRI Blocked MNI | Viewing IAPS pictures that elicit positive, negative or neutral affective states | Cluster-wise corrected at p < .05 | Pictures |
| Rosenblau *et al.* (36) | fMRI Event-related MNI | Viewing IAPS pictures that elicit positive, negative or neutral affective states with and without cues indicating their emotional valence | Uncorrected at p < .05 or p < .005 | Pictures |
| Scheuerecker *et al.* (37) | fMRI Block MNI | Face matching paradigm task | Uncorrected at p < .001 | Faces |
| Schiller *et al.* (38) | fMRI Event-related MNI | Monetary incentive delay task | Cluster-wise corrected at p < .05 | Money |
| Segarra *et al.* (39) | fMRI Event-related MNI | Simulated slot-machine game | Cluster-wise corrected at p < .05 | Money |
| Sharp *et al.* (40) | fMRI Event-related TAL | Card guessing paradigm | Uncorrected at p < .005 | Money |

MDD > HC, Outcome: Reward > Non-Reward
HC > MDD, Outcome: Reward > Non-Reward
MDD > HC, Outcome: Loss > Baseline
HC > MDD, Outcome: Loss > Baseline
MDD > HC, Outcome: Reward > Baseline
MDD > HC, Outcome: Positive > Neutral
MDD > HC, Outcome: Negative > Neutral
MDD > HC, Anticipation: Negative > Neutral
MDD > HC, Outcome: Negative > Neutral
MDD > HC, Outcome: Reward > Non-Reward
| Study                      | Approach  | Task Description                                                                 | Analysis Type                  | Condition Comparison                          |
|---------------------------|-----------|----------------------------------------------------------------------------------|--------------------------------|-----------------------------------------------|
| Smoski et al. (42)        | fMRI      | Event-related MNI Modified monetary incentive delay task                           | Cluster-wise corrected         | 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          |
| Surguladze et al. (44)    | fMRI      | Event-related TAL Indicating the sex of neutral faces and faces morphed to represent mild and high intensities of fear and disgust | Cluster-wise corrected at p < .001 | Faces                                         |
|                           |           |                                                                                  |                                | HC > MDD, Outcome: Increasing intensities of happy faces |
|                           |           |                                                                                  |                                | MDD > HC, Outcome: Increasing intensities of sad faces |
|                           |           |                                                                                  |                                | Differential response to 100% disgust         |
|                           |           |                                                                                  |                                | HC > MDD, Outcome: Differential response to 50% fear |
| Surguladze et al. (43)    | fMRI      | Event-related TAL Indicating the sex of neutral faces and faces morphed to represent mild and high intensities of sadness and happiness | Cluster-wise corrected at p < .001 | Faces                                         |
|                           |           |                                                                                  |                                | MDD > HC, Outcome: Differential response to 100% disgust |
|                           |           |                                                                                  |                                | HC > MDD, Outcome: Differential response to 50% fear |
| Study                | Design     | Imaging | Space | Task                                | Correction                        | Outcome                      |
|---------------------|------------|---------|-------|-------------------------------------|-----------------------------------|------------------------------|
| Townsend et al. (45)| fMRI       | Block   | MNI   | Face matching paradigm              | Cluster-wise corrected at p < .05 | Faces                        |
| Wagner et al. (48)  | fMRI       | Event-related | MNI | Self-referential processing task    | Cluster-wise corrected at p < .05 |                              |
| Wang et al. (46)    | fMRI       | Event-related | MNI | Emotional oddball task              | Uncorrected at p < .001, k = 5    | Pictures                     |
| Young et al. (47)   | fMRI       | Event-related | TAL | Autobiographical memory task        | Cluster-wise corrected at p < .05, k > 30 | Words and autobiographical memories |
| Zhang et al. (48)   | fMRI       | Event-related | MNI | Viewing IAPS positive, neutral, and negative pictures with or without valence cues | Cluster-wise corrected at p < .05, k > 157 | Pictures                     |
| Zhong et al. (49)   | fMRI       | Block   | MNI   | Face matching paradigm              | Uncorrected at p < .005, k = 8    |                              |

fMRI, functional magnetic resonance imaging; PET, positron emission tomography; MNI, Montreal Neurological Institute space; SVC, small volume correction; MDD, major depressive disorder; HC, healthy controls; TFCE, threshold-free cluster enhancement; TAL, Talairach space; VS, ventral striatum; dACC, dorsal anterior cingulate cortex; rACC, rostral anterior cingulate cortex; ACC, anterior cingulate cortex; mPFC, medial prefrontal cortex; mOFC, medial orbitofrontal cortex; IAPS, International Affective Picture System.
Table S4. Peak Coordinates of Group Differences in Neural Responses to Reward (Excluding Neutral Stimuli > Punishment).

| Contrast        | Cluster Size (mm$^3$) | Probabilistic Anatomical Label                                      | x   | y   | z   |
|-----------------|-----------------------|---------------------------------------------------------------------|-----|-----|-----|
| MDD > HC        | 968                   | Frontal Orbital Cortex (26%), Frontal Pole (13%)                   | 20  | 32  | -12 |
| HC > MDD        | 1784                  | Subcallosal Cortex (14%)                                           | -2  | 8   | -4  |
|                 |                       | Caudate (32.1%), Accumbens (11.1%)                                 | 8   | 6   | -2  |

Coordinates are x,y,z values of the locations of the maximum activation likelihood estimation (ALE) values in MNI space. Probabilistic labels reflect the probability that a coordinate belongs to a given region derived from the Harvard-Oxford probabilistic atlas. For clarity, we only report labels whose likelihood exceeds 5%. MDD, major depressive disorder; HC, healthy controls.
Table S5. Peak Coordinates of Group Differences in Neural Responses to Punishment.

| Contrast       | Cluster Size (mm$^3$) | Probabilistic Anatomical Label | x   | y   | z   |
|----------------|-----------------------|--------------------------------|-----|-----|-----|
| MDD > HC       | 1104                  | Amygdala (85.4%)              | -26 | -8  | -14 |
|                |                       | Amygdala (61.4%)              | -16 | -2  | -18 |

Coordinates are x,y,z values of the locations of the maximum activation likelihood estimation (ALE) values in MNI space. Probabilistic labels reflect the probability that a coordinate belongs to a given region derived from the Harvard-Oxford probabilistic atlas. For clarity, we only report labels whose likelihood exceeds 5%. MDD, major depressive disorder; HC, healthy controls.
Figure S1. Illustration of Findings of Previous Meta-analyses on Reward Processing in Unipolar Depression. There is a striking degree of anatomical disagreement across these meta-analyses, with non-overlapping findings all throughout the brain. Blue represents Groenewold et al. (50). Green represents Keren et al. (52). Red represents Zhang et al. (51). (A) Previous meta-analyses examining convergence among studies reporting hypo-responses to reward include Groenewold et al. (50), Keren et al. (52), and Zhang et al. (51). (B) Previous meta-analyses examining convergence among studies reporting hyper-responses to reward include Groenewold et al. (50) and Zhang et al. (51).
Figure S2. Hyper-responses 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 24 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.
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