**Online Supplementary Material**

**Neurofunctional mapping of reward anticipation and outcome for major depressive disorder: A voxel-based meta-analysis**

**Supplementary Methods**

*Further details on SDM*

*Sensitivity analyses*

*Subgroup analyses*

*Meta-regression analyses*

**Supplementary Results**

*Sensitivity analyses*

*Subgroup analyses*

*Meta-regression analyses*

**Supplementary Discussion**

*The relationship between distinct reward processes and subjective anhedonia*

*The effect of anxiety comorbidity*

*The effect of medication*

**Supplementary References**

**Supplementary Fig. 1.** Flowchart of the article selection process

**Supplementary Table 1.** Subgroup and jack-knife sensitivity analyses of brain activation differences between MDD patients and HC during the anticipation phase

**Supplementary Table 2.** Subgroup and jack-knife sensitivity analyses of brain activation differences between MDD patients and HC during the outcome phase

**Supplementary Methods**

***Further details on SDM***

Seed-based d mapping (SDM) incorporates and combines the various positive features of activation likelihood estimation (ALE) and multilevel kernel density analysis (MKDA) (Radua & Mataix-Cols, 2009). This software is based and improves upon the many positive features of existing peak probability methods. It enables investigators to combine peak coordinates with statistical parametric maps and uses standard effect size and variance-based meta-analytic calculations (Radua et al., 2012b). Compared with ALE, the advantages of SDM are listed below: First, for the selection of studies, statistical parametric maps can be included in SDM algorithms, constitutes an improvement over ALE. Second, to describe the effect sizes, SDM aims to estimate the effect size rather than the peak likelihood in ALE (Radua et al., 2014). Third, for reduction of the heterogeneity, SDM addresses between-study heterogeneity by reconstructing positive and negative maps in the same image, thus counteracting the effects of studies reporting findings in opposite directions (Radua & Mataix-Cols, 2009, 2012). While ALE is not controlled the residual heterogeneity, and increases and decreases are not counteracted, potentially leading to voxels being detected as increased and decreased. Fourth, for the weighting studies, SDM implements random-effects models in which each study is weighted by the inverse of the sum of its variance and the calculated between-study variance (Radua et al., 2012b). Finally, complementary analyses in SDM, such as jack-knife, subgroup, and meta-regression analyses are useful to assess the reliability and robustness of the findings.

Here, we briefly described the steps of this study. First, peak coordinates and measurements (*z* values, *p* values, *t* values) of brain activity differences were extracted at the whole-brain level, and *p* values or *z* values were converted to *t* values online. Second, we performed the pre-processing step to recreate the effect-size brain maps of each original study independently, and positive and negative coordinates were reconstructed on the same map. Monte Carlo brain maps were created to facilitate the estimation of the null distributions for the subsequent analyses (Radua et al., 2012b). Third, an effect size map was computed for every study. From these single-study maps, a mean map weighted by the square root of the sample size of each study and the inverse of its variance plus the between-study variance accounting for interstudy heterogeneity was calculated. Default SDM kernel size and thresholds (full-width at half-maximum = 20 mm, voxel *p* = 0.005, peak height *Z* = 1, cluster extent = 10 voxels) were used, which have been reported to optimally balance sensitivity and specificity (Radua et al., 2012a; Radua et al., 2012b). In addition, to assess the robustness of the findings, complementary analyses were performed, including jack-knife sensitivity analyses, subgroup analyses and meta-regression analyses.

***Sensitivity analyses***

The robustness and publication bias of the results were assessed using jack-knife sensitivity analyses. The reliability analysis of the pooled analysis results consisted of repeating the main statistical analysis several times, and discarding one different study each time from the analysis (Radua et al., 2012b). Regions resulting from many different combinations of studies are regarded as highly replicable, whereas outlier results disappear as soon as one study is removed from the analysis, indicating a lack of interstudy consistency.

***Subgroup analyses***

To control for any possible sample and methodological differences observed among the studies, several subgroup meta-analyses were conducted to assess the reliability of our results during the two stages separately. In order to control for any possible differences observed between the studies, the analyses were repeated several times to include only those studies that were methodologically homogenous. Therefore, the analyses were repeated for studies of patients with comorbid anxiety, and for studies using 3.0 T magnetic resonance imaging (MRI) scanner. To observe the potential effect of medication on the monetary incentive delay task (MID) related to brain changes, it is better to compare treated patients directly to treatment-naïve individuals, compare pre-treatment and post-treatment results, or compare treatment and placebo conditions. We compared these results with a subgroup analysis of major depressive disorder (MDD) patients who underwent a wash-out period before MRI scanning, given that there were insufficient data to perform the above medication-related comparisons.

***Meta-regression analyses***

Meta-regression analyses were conducted to examine the potential variables contributing to the heterogeneity of the findings. The regression needed to be detected both in the slope and in one of the extremes of the regressors, and analyses were restricted to brain regions identified in the primary meta-analysis comparing patients and controls. The threshold for meta-regression analysis was set at *p* < 0.0005, and findings in regions other than those detected in the main analyses were discarded (Radua et al., 2012b). Several relevant demographic and clinical factors, including the percentage of female patients (a ratio of the number of females to the total number of patients), mean age of patients, illness duration, number of past depressive episodes, onset of age, severity of depression (the Beck Depression Inventory (BDI) and the Hamilton Depression Rating scale (HAMD)), degree of anhedonia (the Snaith-Hamilton Pleasure Scale (SHAPS) and total score of items (item 4, item 12, and item 21) on the BDI) (Fan et al., 2021). For depression severity, we used the BDI scores from each study and translated the HAMD into the BDI-II for those studies that provided only HAMD scores (Furukawa et al., 2019).

**Supplementary Results**

***Sensitivity analyses***

Regarding the anticipation stage, when whole-brain jack-knife sensitivity analyses were performed for the anticipation meta-analysis, the main findings during the anticipation stage remained highly duplicated. The detailed data are shown in Table S1. Hyperactivation in the left inferior frontal gyrus (IFG) and left postcentral gyrus (PoCG) were preserved in all included studies. Hyperactivation in the bilateral medial prefrontal cortex (mPFC), anterior cingulate cortex (ACC), median cingulate cortex (MCC), right middle frontal gyrus (MFG) and left middle temporal gyrus (MTG), and hypoactivation in the right striatum and IFG maintained significance in all but one combination. Hypoactivation in the right cerebellum remained significant in all but two combinations.

As shown in Table S2, whole-brain jack-knife sensitivity analyses demonstrated a high duplication during the feedback stage. Hypoactivation in the bilateral ACC, MCC, left caudate, right striatum, and IFG was preserved in all included studies. Hyperactivation in the left inferior temporal gyrus (ITG) and hypoactivation in the left thalamus, right insula (extending to the temporal pole) and MFG remained significant in all but one combination. Hypoactivation in the left precentral gyrus and cerebellum remained significant in all but two combinations.

***Subgroup analyses***

Within the reward anticipation meta-analysis, subgroup analyses were performed for studies in which patients with/without comorbid anxiety, for studies in which patients had wash-out periods before MRI scanning, and for studies using 3.0 T MRI scanner. Most of the results of the wash-out subgroup analysis were consistent with the pooled analysis, except for the blunted response to reward in the right striatum and IFG. For studies including MDD patients with anxiety comorbidities, compared to healthy controls (HC), MDD patients showed increased in the bilateral mPFC, ACC, MCC, right MFG, and decreased in the left striatum and right cerebellum. For studies using 3.0 T MRI scanner, we found hyperactivation in the bilateral mPFC, MCC, and right MFG and hypoactivation in the right cerebellum, striatum and IFG in depressed individuals (see Table S1).

The subgroup analyses for the outcome meta-analysis were repeated several times as with the anticipation stage (see Table S2). For studies including patients with comorbid anxiety, the analysis revealed that MDD patients had a decreased response in the bilateral striatum, ACC, MCC, right IFG, insula (extending to the temporal pole left precentral gyrus, cerebellum and thalamus. The results of the wash-out subgroup analyses remained unchanged during outcome stage. For the studies using 3.0 T MRI scanner (n=6), the analysis revealed that MDD patients showed decreased reward response in the bilateral ACC, MCC, right IFG, insula (extending to the temporal pole), left cerebellum, and thalamus.

***Meta-regression analyses***

For both the anticipation and outcome, linear regression analysis revealed that there was no significant relationship between brain response differences in MDD patients and the clinical variables (the percentage of females, mean age, number of past depressive episodes and depression severity). Due to the limited datasets included in this study, we failed to conduct the meta-regression analysis for illness duration, onset of age, and degree of anhedonia.

**Supplementary Discussion**

***The relationship between distinct reward processes and subjective anhedonia***

Considering the clinical significance of anhedonic symptoms, it is important to investigate the brain-symptom associations between self-reported anhedonia and different components of reward processing in depressed individuals. Unfortunately, only a few studies included in our meta-analysis reported subjective measures of anhedonia, meaning that a meta-regression or subgroup analysis with the severity of anhedonia was not feasible. We cannot definitively state whether our findings of hyper-responsivity in the cortical prefrontal regions during the anticipation phase and hypo-responsivity of the mesocortical-limbic circuit across both the anticipation and outcome phases are closely related to self-rated anhedonia. According to previous studies, anticipatory and motivational aspects of reward processing may be more dysfunctional and may be closely linked to anhedonic symptoms, whereas the aspects of reward processing that relate to reward receipt may be relatively spared (Argyropoulos & Nutt, 2013; Dillon et al., 2014; Segarra et al., 2016). As with the anticipation of reward, hypo-responsivity in the ventral striatum (VS) during anticipation was inversely associated with the BDI anhedonia subscale (Meline Stoy et al., 2012). Another study reported that increased responses in the orbitofrontal cortex and nucleus accumbens (NAcc) during reward anticipation were associated with hedonic capacity as measured by the SHAPS (Ubl et al., 2015). As recently shown in a resting fMRI study, the elevated altered spontaneous neuronal activity of the ACC was correlated with anticipatory anhedonia (Liu, Li, Li, Ren, & Ma, 2021). As with the consumption of reward, there is previous evidence for the reduced cortical thickness of the ACC and OFC and diminished NAcc activity to be correlated with consummatory anhedonia in MDD (Liu et al., 2021; Redlich et al., 2015). No significant correlation between brain activation during reward outcome and anhedonic symptoms emerged. For example, hypoactivation in medial prefrontal areas and the ACC is not directly associated with SHAPS during receipt of reward (Segarra et al., 2016).

The heterogeneity of neural correlates of anhedonia observed in past studies may be partly due to the inconsistent conceptualization of anhedonia. While anhedonia has traditionally been viewed as failure to experience pleasure, more recent evidence has revealed a multifaceted reconceptualization that emphasizes different facets of hedonic function, including desire, effort/motivation, anticipation and consummatory pleasure (Rizvi, Pizzagalli, Sproule, & Kennedy, 2016). Other conceptual assessments of the anhedonia construct have emphasized incentive-reward motivation, or the subjective evaluation of the rewarding value of cues predicting reward occurrence (Berridge, Robinson, & Aldridge, 2009; Coccurello, 2019). The different measure or recode of anhedonia may also contribute to the variability of the results in the existing literature. Anhedonia measurement in MDD can utilize direct symptom scales or experimental tasks. Different measures and different task paradigms thus tap into the different facets of anhedonia. The precise relationship between distinct reward processes and subjective anhedonia needs to be carefully investigated in future research.

***The effect of anxiety comorbidity***

Anxiety symptoms frequently co-occur with depression. Comorbid anxiety and depressive disorder, also known as anxious depression, have distinct clinical characteristics such as poor treatment response and lower remission rates, from non-anxious depression (Fava et al., 2008; Goes et al., 2012). The diagnosis of anxious depression depends on a diagnosis of MDD plus at least two of five anxiety symptoms (Choi, Kim, & Jeon, 2020). It uses “with anxious distress specifier” to define anxious depression in DSM-5 criteria (American Psychiatric Association (APA), 2013). The identification of depression-specific effects might be confounded by high levels of anxiety comorbidity across studies.

Analyses comparing MDD subjects with or without comorbid anxiety disorders may help to rule out this confounding effect. In all 12 of the datasets enrolled in the anticipation meta-analysis, 4 datasets recruited MDD without comorbid with anxiety (MDD without anxiety), 6 datasets included patients comorbid with anxiety disorder (MDD with anxiety), and 2 datasets were not included because of missing information. Similarly, for the outcome meta-analysis, 3 datasets recruited patients without comorbid anxiety disorders, and 6 datasets included patients with comorbid anxiety disorder. It considerably reduced the sample size when we limited the selection of studies for the meta-analysis with respect to the presence or absence of comorbid anxiety. In regard to reward anticipation, the exploratory subgroup analyses revealed that individuals with anxious depression exhibited increased brain activity in the bilateral mPFC, ACC, MCC, and right MFG, and decreased activity in the left stratum and right cerebellum. In contrast to the anticipation, MDD with anxiety subgroup analysis during the outcome stage is more replicable. We further tested the influence of anxiety comorbidity by computing the association between brain activity and the percentage of patients with a co-occurring anxiety disorder using meta-regression analysis. We did not detect any significant associations between anxiety comorbidity and brain response during anticipation or outcome. There is evidence that, relative to individuals with MDD without anxiety, MDD with anxiety showed stronger activation in the prefrontal cortex, hippocampus, insula and caudate (Andreescu et al., 2009; Crane et al., 2016; Gorka, Nelson, Phan, & Shankman, 2014) and showed greater grey matter changes in the frontal and temporal cortex (Inkster et al., 2011; Wehry et al., 2015). MDD individuals with anxiety often have more severe depressive symptoms, which may help to explain this effect (Norton, Temple, & Pettit, 2008). Previous findings are also mixed; however, several studies have found that having anxiety comorbidity attenuates the typical response of depression (Espinoza Oyarce, Shaw, Alateeq, & Cherbuin, 2020; Etkin & Schatzberg, 2011). Future research will be needed to reveal more consistent and sophisticated monetary related functional neuroimaging biomarkers to differentiate the anxious depression subtype from the non-anxious subtype.

***The effect of medication***

Converging evidence suggests that antidepressant treatment, even on an acute time scale, can significantly impact brain structure and function (Enneking, Leehr, Dannlowski, & Redlich, 2020; M. Stoy et al., 2012; Takamura et al., 2017). To observe the potential effect of medication on MID-related brain changes, it is better to compare treated patients directly to treatment-naïve individuals, compare pre-treatment and post-treatment results, or compare treatment and placebo conditions. In fact, most treatment studies of neuroimaging markers in MDD have not examined reward paradigms, but rather focused on affective stimulus processing using emotion-related paradigms or included resting state (Brandt et al., 2021; Wang et al., 2014). To address these issues, we conducted subgroup analyses of MDD patients who underwent a wash-out period before MRI scanning. Most of the results of the wash-out subgroup analyses were consistent with the pooled analysis, except for the blunted response to reward in the right VS and IFG during the anticipation stage. This may suggest that pharmacological manipulation slightly changes dopamine signalling and normalizes reward processing in depression followed by the transient wash-out period. Our finding is in line with evidence from imaging studies indicating that antidepressant treatment can influence grey matter volume (Dai et al., 2020; Enneking et al., 2020) and neural activity (Meline Stoy et al., 2012; Takamura et al., 2017) in depression. Previous functional MRI studies have indicated improved frontostriatal function and functional connectivity in depression using an emotion regulation paradigm after antidepressant treatment (Reed et al., 2018, 2019) The IFG might be related to the neurobiological mechanism of depressive symptoms, which influences emotion detection, regulation, and cognitive control (Urgesi, Mattiassi, Buiatti, & Marini, 2016). Antidepressants can normalize the structural changes of IFG in patients with depression (Dai et al., 2020), and impact functional connectivity with IFG in executive control network (Ichikawa et al., 2020). Our finding of subgroup analysis is also consistent with the reported hypoactivity of the VS during the anticipation of monetary incentives in unmedicated MDD patients relative to controls before, but not after six weeks of escitalopram treatment (Meline Stoy et al., 2012). This is probably due to the delayed onset of drug action and maintenance (Chen & Skolnick, 2007). Together, it cannot be fully ruled out the effect of antidepressant medications that may cause some of the observed alterations and complicated other side effects of medication in our findings.

**Supplementary references**

American Psychiatric Association (APA). (2013). *Diagnostic and statistical manual of mental disorders: DSM-5* (5th ed.). Washington, DC: APA.

Andreescu, C., Butters, M., Lenze, E. J., Venkatraman, V. K., Nable, M., Reynolds, C. F., 3rd, & Aizenstein, H. J. (2009). fMRI activation in late-life anxious depression: a potential biomarker. *International Journal of Geriatric Psychiatry, 24*(8), 820-828. doi:10.1002/gps.2327

Argyropoulos, S. V., & Nutt, D. J. (2013). Anhedonia revisited: Is there a role for dopamine-targeting drugs for depression? *Journal of Psychopharmacology, 27*(10), 869-877. doi:Doi 10.1177/0269881113494104

Berridge, K. C., Robinson, T. E., & Aldridge, J. W. (2009). Dissecting components of reward: 'liking', 'wanting', and learning. *Current Opinion in Pharmacology, 9*(1), 65-73. doi:10.1016/j.coph.2008.12.014

Brandt, I. M., Kohler-Forsberg, K., Ganz, M., Ozenne, B., Jorgensen, M. B., Poulsen, A., . . . Fisher, P. M. (2021). Reward processing in major depressive disorder and prediction of treatment response - Neuropharm study. *European Neuripsychopharmacology, 44*, 23-33. doi:10.1016/j.euroneuro.2020.12.010

Chen, Z., & Skolnick, P. (2007). Triple uptake inhibitors: therapeutic potential in depression and beyond. *Expert Opinion on Investigational Drugs, 16*(9), 1365-1377. doi:10.1517/13543784.16.9.1365

Choi, K. W., Kim, Y. K., & Jeon, H. J. (2020). Comorbid Anxiety and Depression: Clinical and Conceptual Consideration and Transdiagnostic Treatment. *Adv Exp Med Biol, 1191*, 219-235. doi:10.1007/978-981-32-9705-0\_14

Coccurello, R. (2019). Anhedonia in depression symptomatology: Appetite dysregulation and defective brain reward processing. *Behavioural Brain Research, 372*, 112041. doi:10.1016/j.bbr.2019.112041

Crane, N. A., Jenkins, L. M., Dion, C., Meyers, K. K., Weldon, A. L., Gabriel, L. B., . . . Langenecker, S. A. (2016). Comorbid anxiety increases cognitive control activation in Major Depressive Disorder. *Depression and Anxiety, 33*(10), 967-977. doi:10.1002/da.22541

Dai, D., Lacadie, C. M., Holmes, S. E., Cool, R., Anticevic, A., Averill, C., . . . Esterlis, I. (2020). Ketamine Normalizes the Structural Alterations of Inferior Frontal Gyrus in Depression. *Chronic Stress (Thousand Oaks), 4*, 2470547020980681. doi:10.1177/2470547020980681

Dillon, D. G., Rosso, I. M., Pechtel, P., Killgore, W. D. S., Rauch, S. L., & Pizzagalli, D. A. (2014). Peril and Pleasure: An Rdoc-Inspired Examination of Threat Responses and Reward Processing in Anxiety and Depression. *Depression and Anxiety, 31*(3), 233-249. doi:10.1002/da.22202

Enneking, V., Leehr, E. J., Dannlowski, U., & Redlich, R. (2020). Brain structural effects of treatments for depression and biomarkers of response: a systematic review of neuroimaging studies. *Psychological Medicine, 50*(2), 187-209. doi:10.1017/S0033291719003660

Espinoza Oyarce, D. A., Shaw, M. E., Alateeq, K., & Cherbuin, N. (2020). Volumetric brain differences in clinical depression in association with anxiety: a systematic review with meta-analysis. *Journal of Psychiatry and Neuroscience, 45*(6), 406-429. doi:10.1503/jpn.190156

Etkin, A., & Schatzberg, A. F. (2011). Common abnormalities and disorder-specific compensation during implicit regulation of emotional processing in generalized anxiety and major depressive disorders. *American Journal of Psychiatry, 168*(9), 968-978. doi:10.1176/appi.ajp.2011.10091290

Fan, J., Liu, W., Xia, J., Li, S., Gao, F., Zhu, J., . . . Zhu, X. (2021). Childhood trauma is associated with elevated anhedonia and altered core reward circuitry in major depression patients and controls. *Human Brain Mapping, 42*(2), 286-297. doi:10.1002/hbm.25222

Fava, M., Rush, A. J., Alpert, J. E., Balasubramani, G. K., Wisniewski, S. R., Carmin, C. N., . . . Trivedi, M. H. (2008). Difference in treatment outcome in outpatients with anxious versus nonanxious depression: a STAR\*D report. *American Journal of Psychiatry, 165*(3), 342-351. doi:10.1176/appi.ajp.2007.06111868

Furukawa, T. A., Reijnders, M., Kishimoto, S., Sakata, M., DeRubeis, R. J., Dimidjian, S., . . . Cuijpers, P. (2019). Translating the BDI and BDI-II into the HAMD and vice versa with equipercentile linking. *Epidemiology and Psychiatric Sciences, 29*, e24. doi:10.1017/S2045796019000088

Goes, F. S., McCusker, M. G., Bienvenu, O. J., Mackinnon, D. F., Mondimore, F. M., Schweizer, B., . . . Potash, J. B. (2012). Co-morbid anxiety disorders in bipolar disorder and major depression: familial aggregation and clinical characteristics of co-morbid panic disorder, social phobia, specific phobia and obsessive-compulsive disorder. *Psychological Medicine, 42*(7), 1449-1459. doi:10.1017/S0033291711002637

Gorka, S. M., Nelson, B. D., Phan, K. L., & Shankman, S. A. (2014). Insula response to unpredictable and predictable aversiveness in individuals with panic disorder and comorbid depression. *Biol Mood Anxiety Disord, 4*, 9. doi:10.1186/2045-5380-4-9

Ichikawa, N., Lisi, G., Yahata, N., Okada, G., Takamura, M., Hashimoto, R. I., . . . Okamoto, Y. (2020). Primary functional brain connections associated with melancholic major depressive disorder and modulation by antidepressants. *Scientific Reports, 10*(1), 3542. doi:10.1038/s41598-020-60527-z

Inkster, B., Rao, A. W., Ridler, K., Nichols, T. E., Saemann, P. G., Auer, D. P., . . . Matthews, P. M. (2011). Structural brain changes in patients with recurrent major depressive disorder presenting with anxiety symptoms. *Journal of Neuroimaging, 21*(4), 375-382. doi:10.1111/j.1552-6569.2010.00515.x

Liu, X., Li, L., Li, M., Ren, Z., & Ma, P. (2021). Characterizing the subtype of anhedonia in major depressive disorder: A symptom-specific multimodal MRI study. *Psychiatry Research Neuroimaging, 308*, 111239. doi:10.1016/j.pscychresns.2020.111239

Norton, P. J., Temple, S. R., & Pettit, J. W. (2008). Suicidal ideation and anxiety disorders: elevated risk or artifact of comorbid depression? *Journal of Behavior Therapy and Experimental Psychiatry, 39*(4), 515-525. doi:10.1016/j.jbtep.2007.10.010

Radua, J., Borgwardt, S., Crescini, A., Mataix-Cols, D., Meyer-Lindenberg, A., McGuire, P. K., & Fusar-Poli, P. (2012a). Multimodal meta-analysis of structural and functional brain changes in first episode psychosis and the effects of antipsychotic medication. *Neuroscience and Biobehavioral Reviews, 36*(10), 2325-2333. doi:10.1016/j.neubiorev.2012.07.012

Radua, J., & Mataix-Cols, D. (2009). Voxel-wise meta-analysis of grey matter changes in obsessive-compulsive disorder. *British Journal of Psychiatry, 195*(5), 393-402. doi:10.1192/bjp.bp.108.055046

Radua, J., & Mataix-Cols, D. (2012). Meta-analytic methods for neuroimaging data explained. *Biol Mood Anxiety Disord, 2*, 6. doi:10.1186/2045-5380-2-6

Radua, J., Mataix-Cols, D., Phillips, M. L., El-Hage, W., Kronhaus, D. M., Cardoner, N., & Surguladze, S. (2012b). A new meta-analytic method for neuroimaging studies that combines reported peak coordinates and statistical parametric maps. *European Psychiatry, 27*(8), 605-611. doi:10.1016/j.eurpsy.2011.04.001

Radua, J., Rubia, K., Canales-Rodriguez, E. J., Pomarol-Clotet, E., Fusar-Poli, P., & Mataix-Cols, D. (2014). Anisotropic kernels for coordinate-based meta-analyses of neuroimaging studies. *Frontiers in Psychiatry, 5*, 13. doi:10.3389/fpsyt.2014.00013

Redlich, R., Dohm, K., Grotegerd, D., Opel, N., Zwitserlood, P., Heindel, W., . . . Dannlowski, U. (2015). Reward Processing in Unipolar and Bipolar Depression: A Functional MRI Study. *Neuropsychopharmacology, 40*(11), 2623-2631. doi:10.1038/npp.2015.110

Reed, J. L., Nugent, A. C., Furey, M. L., Szczepanik, J. E., Evans, J. W., & Zarate, C. A., Jr. (2018). Ketamine normalizes brain activity during emotionally valenced attentional processing in depression. *NeuroImage-Clinical, 20*, 92-101. doi:10.1016/j.nicl.2018.07.006

Reed, J. L., Nugent, A. C., Furey, M. L., Szczepanik, J. E., Evans, J. W., & Zarate, C. A., Jr. (2019). Effects of Ketamine on Brain Activity During Emotional Processing: Differential Findings in Depressed Versus Healthy Control Participants. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, 4*(7), 610-618. doi:10.1016/j.bpsc.2019.01.005

Rizvi, S. J., Pizzagalli, D. A., Sproule, B. A., & Kennedy, S. H. (2016). Assessing anhedonia in depression: Potentials and pitfalls. *Neuroscience and Biobehavioral Reviews, 65*, 21-35. doi:10.1016/j.neubiorev.2016.03.004

Segarra, N., Metastasio, A., Ziauddeen, H., Spencer, J., Reinders, N. R., Dudas, R. B., . . . Murray, G. K. (2016). Abnormal Frontostriatal Activity During Unexpected Reward Receipt in Depression and Schizophrenia: Relationship to Anhedonia. *Neuropsychopharmacology, 41*(8), 2001-2010. doi:10.1038/npp.2015.370

Stoy, M., Schlagenhauf, F., Sterzer, P., Bermpohl, F., Hagele, C., Suchotzki, K., . . . Strohle, A. (2012). Hyporeactivity of ventral striatum towards incentive stimuli in unmedicated depressed patients normalizes after treatment with escitalopram. *Journal of Psychopharmacology, 26*(5), 677-688. doi:10.1177/0269881111416686

Stoy, M., Schlagenhauf, F., Sterzer, P., Bermpohl, F., Hägele, C., Suchotzki, K., . . . Ströhle, A. (2012). Hyporeactivity of ventral striatum towards incentive stimuli in unmedicated depressed patients normalizes after treatment with escitalopram. *Journal of Psychopharmacology, 26*(5), 677-688. doi:10.1177/0269881111416686

Takamura, M., Okamoto, Y., Okada, G., Toki, S., Yamamoto, T., Ichikawa, N., . . . Yamawaki, S. (2017). Patients with major depressive disorder exhibit reduced reward size coding in the striatum. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 79*(Pt B), 317-323. doi:10.1016/j.pnpbp.2017.07.006

Ubl, B., Kuehner, C., Kirsch, P., Ruttorf, M., Diener, C., & Flor, H. (2015). Altered neural reward and loss processing and prediction error signalling in depression. *Social Cognitive and Affective Neuroscience, 10*(8), 1102-1112. doi:10.1093/scan/nsu158

Urgesi, C., Mattiassi, A. D., Buiatti, T., & Marini, A. (2016). Tell it to a child! A brain stimulation study of the role of left inferior frontal gyrus in emotion regulation during storytelling. *Neuroimage, 136*, 26-36. doi:10.1016/j.neuroimage.2016.05.039

Wang, L., Li, K., Zhang, Q., Zeng, Y., Dai, W., Su, Y., . . . Si, T. (2014). Short-term effects of escitalopram on regional brain function in first-episode drug-naive patients with major depressive disorder assessed by resting-state functional magnetic resonance imaging. *Psychological Medicine, 44*(7), 1417-1426. doi:10.1017/S0033291713002031

Wehry, A. M., McNamara, R. K., Adler, C. M., Eliassen, J. C., Croarkin, P., Cerullo, M. A., . . . Strawn, J. R. (2015). Neurostructural impact of co-occurring anxiety in pediatric patients with major depressive disorder: a voxel-based morphometry study. *Journal of Affective Disorders, 171*, 54-59. doi:10.1016/j.jad.2014.09.004



**Fig. S1.** Flowchart of the article selection process.

Of 611 articles initially identified, 11 studies were finally enrolled in this meta-analysis during the reward anticipation phase, and 8 studies were finally enrolled during the reward outcome phase.

**Table S1.** Subgroup and jack-knife sensitivity analyses of brain activation differences between MDD patients and HC during the anticipation

|  |  |  |  |
| --- | --- | --- | --- |
| **Studies**  | **P > HC** |  | **P < HC** |
| **(Datasets)** | **L** | **R & L**  | **R & L** | **R** |  | **R** | **L** | **R** | **R** |
|  | **IFG & PoCG** | **mPFC (with extension to ACC)** | **MCC** | **MFG** |  | **cerebellum** | **Striatum, insula & amygdala** | **striatum** | **IFG** |
| **Subgroup analyses** |  |  |  |  |  |  |  |  |  |
| Studies including MDD patients with comorbid anxiety (n=6) | N | Y | Y | Y |  | Y | Y | N | N |
| Studies including MDD patients had at least 2 weeks washout periods before the scan (n=9) | Y | Y | Y | Y |  | Y | Y | N | N |
| Studies using 3.0 T MRI scanner (n=8) | N | Y | Y | Y |  | Y | N | Y | Y |
| **Sensitivity analyses** |  |  |  |  |  |  |  |  |  |
| Admon (2017) | Y | Y | Y | Y |  | Y | Y | Y | Y |
| Arrondo (2015) | Y | Y | Y | Y |  | Y | Y | Y | N |
| Carl (2016) | Y | Y | Y | Y |  | Y | Y | Y | Y |
| DelDonno (2019) | Y | Y | Y | Y |  | N | Y | Y | Y |
| Hagele (2015) | Y | Y | Y | Y |  | Y | Y | N | Y |
| Knutson (2008) | Y | Y | Y | Y |  | Y | N | Y | Y |
| Pizzagalli (2009) Dataset1 | Y | Y | Y | Y |  | Y | N | Y | Y |
| Pizzagalli (2009) Dataset2 | Y | N | N | Y |  | N | N | Y | Y |
| Schwarz (2020) | Y | Y | Y | Y |  | Y | Y | Y | Y |
| Stoy (2012) | Y | Y | Y | N |  | Y | Y | Y | Y |
| Ubl (2015) | Y | Y | Y | Y |  | Y | Y | Y | Y |
| Wakatsuki (2022) | Y | Y | Y | Y |   | Y | Y | Y | Y |

Abbreviations: MDD = major depressive disorder; P = MDD patients; HC = healthy controls; R = right; L = left; IFG = inferior frontal gyrus; PoCG = postcentral gyrus; mPFC = medial prefrontal cortex; ACC = anterior cingulate cortex; MCC = median cingulate cortex; MFG = middle frontal gyrus; Y= yes; N = no.

**Table S2.** Subgroup and jack-knife sensitivity analyses of brain activation differences between MDD patients and HC during the outcome phase

|  |  |  |  |
| --- | --- | --- | --- |
| **Studies** | **P > HC** |  | **P < HC** |
| **(Datasets)** | **L** |  | **R & L** | **R**  | **L** | **R** | **L** | **R** | **L** | **L** | **R** |
|  | **ITG** |  | **ACC & MCC** | **striatum** | **caudate** | **IFG** | **precentral gyrus** | **insula &****temporal pole** | **cerebellum** | **thalamus** | **MFG** |
| **Subgroup analyses** |  |  |  |  |  |  |  |  |  |  |  |
| Studies including MDD patients with comorbid anxiety (n=6) | N |  | Y | Y | Y | Y | Y | Y | Y | Y | N |
| Studies including MDD patients had at least 2 weeks washout periods before the scan (n=8) | Y |  | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Studies using 3.0 T MRI scanner (n=6) | N |  | Y | N | N | Y | Y | Y | Y | Y | N |
| **Sensitivity analyses** |  |  |  |  |  |  |  |  |  |  |  |
| Admon (2017) | Y |  | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Carl (2016) | Y |  | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Knutson (2008) Dataset1 | Y |  | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Knutson (2008) Dataset2 | Y |  | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Pizzagalli (2009) Dataset1 | N |  | Y | Y | Y | Y | N | Y | N | Y | Y |
| Pizzagalli (2009) Dataset2 | Y |  | Y | Y | Y | Y | N | Y | Y | N | N |
| Reinen (2021) | Y |  | Y | Y | Y | Y | Y | N | N | Y | Y |
| Schwarz (2020) | Y |  | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Ubl (2015) | Y |  | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Wakatsuki (2022) | Y |   | Y | Y | Y | Y | Y | Y | Y | Y | Y |

Abbreviations: MDD = major depressive disorder; P = MDD patients; HC = healthy controls; R = right; L =left; ITG = inferior temporal gyrus; ACC = anterior cingulate cortex; MCC = median cingulate cortex; IFG = inferior frontal gyrus; MFG = middle frontal gyrus; Y = yes; N = no.