Supplemental Data

Inclusion/exclusion criteria for major depressive disorder group and healthy control group

Additional inclusion criteria for the major depressive disorder group were: age of onset of first episode of major depressive disorder < 30 years, a Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR) score ≥ 14, and no failed antidepressant trials of adequate dose and duration, as defined by the Massachusetts General Hospital Antidepressant Treatment History Questionnaire (MGH-ATRQ), in the current episode. For the HC group an additional requirement was a QIDS-SR score < 8.

Exclusion criteria for all participants were: MRI contraindications such as metal in body, pregnancy or breastfeeding, epilepsy or other conditions requiring an anticonvulsant medication, a general medical condition that might require hospitalization or deemed terminal, a positive urine drug screen at the evaluation visit and receiving or have received, during the index episode, vagus nerve stimulation, Electroconvulsive Therapy (ECT), or Repetitive Transcranial Magnetic Stimulation (rTMS), or other somatic antidepressant treatments.

Additional exclusion criteria for the major depressive disorder group were: lifetime history of psychotic depressive, schizophrenic, bipolar (I, II, or not otherwise specified; NOS), schizoaffective, or other Axis I psychotic disorders; meeting DSM-IV criteria for substance dependence in the last 6 months (except for nicotine); requiring immediate hospitalization for psychiatric disorder; currently taking antipsychotic medications, anticonvulsant medications, mood stabilizers or central nervous system stimulants, daily use of benzodiazepines or hypnotics, or antidepressant medication used for the treatment of depression or other purposes such as smoking cessation; using agents that are potential augmenting agents; and receiving therapy that is depression-specific, such as Cognitive Behavioral Therapy (CBT) or Interpersonal

Psychotherapy of Depression (IPT). Exclusion criteria for the HC group were: current or lifetime history of major depressive disorder, psychotic depression, bipolar (I, II, or NOS) disorder, schizoaffective disorder, schizophrenia, or other Axis I psychotic disorders, current Axis I or Axis II diagnoses; substance dependence in the last 6 months (except for nicotine, or substance abuse in the last 2 months); currently taking any of the following exclusionary medications: antipsychotic medications, anticonvulsant medications, mood stabilizers, central nervous system stimulants, daily use of benzodiazepines or hypnotics, antidepressant medications, or any other psychotropic medication; and having received psychotherapy in the last 6 months.

Individuals in the major depressive disorder group were unmedicated for at least three months prior to participation in the study.

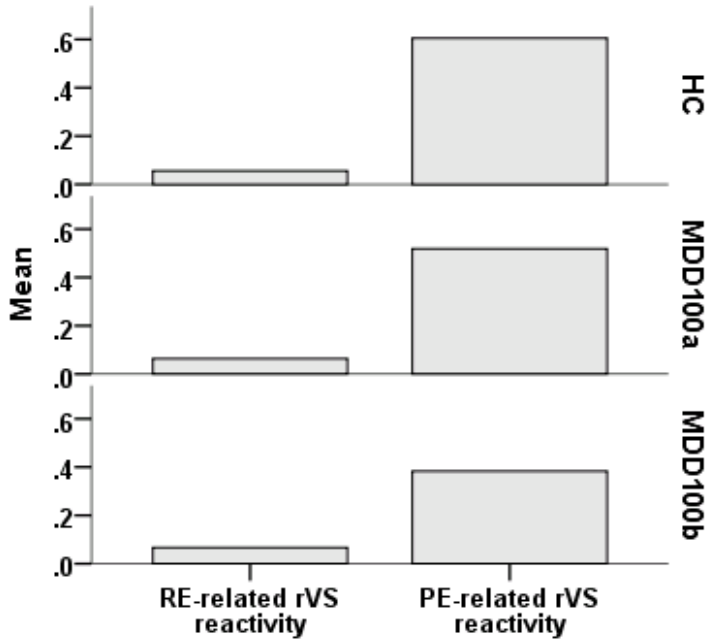
Table S1. Information regarding depression and lifetime comorbidity for the first-recruited cohort (MDD_{100a}; n=78), second-recruited cohort (MDD_{100b}; n=70), and total sample of depressed individuals (MDD_{200}; n=148).

	MDD_{100a}	MDD_{100b}	MDD_{200}
	Mean (SD)	**Mean (SD)**	**Mean (SD)**
Age of onset	15.68 (5.87); n=78	16.63 (5.76); n=70	16.13 (5.82); n=148
Illness duration (years)	22.79 (14.19); n=78	18.97 (13.07); n=70	20.99 (13.76); n=148
Duration of current episode (months)	44.3 (67.8); n=78	32.73 (57.05); n=69	38.87 (63.04); n=147
Total number of episodes	9.39 (12.65); n=72	9.12 (17.52); n=64	9.26 (15.08); n=136
Lifetime Comorbid Anxiety Disorders (yes/no)	43/35	39/30	82/65
Lifetime Comorbid Eating Disorders (yes/no)	2/76	2/68	4/144
Lifetime Comorbid Substance Use Disorders (yes/no)	16/62	16/53	32/115

Relationship between reward expectancy and prediction error-related ventral striatal reactivity in the first-recruited cohort (MDD_{100a}), second-recruited cohort (MDD_{100b}), and total sample of depressed individuals (MDD_{200}) using additional covariates.

We examined the relationship between reward expectancy and prediction error-related right ventral striatal reactivity in individuals with major depressive disorder when also controlling for illness duration and history of substance abuse, given the potential impact of these factors on ventral striatal activity. The reward expectancy and prediction error relationship remained non-significant (MDD_{100a}: $r(69)=0.1$, $p=0.62$; MDD_{100b}: $r(59)=-0.16$, $p=0.22$; MDD_{200}: $r(137)=-0.03$, $p=0.77$).

Figure S1. Comparison of reward expectancy (RE) and prediction error (PE)-related right ventral striatal (rVS) reactivity in healthy controls (HC; n=31), the first-recruited cohort (MDD_{100b}; n=78) and the second-recruited cohort (MDD_{100b};n=70) of depressed individuals.



To further assess the reliability of reward expectancy and prediction error-related reactivity patterns across the different cohorts, we conducted tests of the strength of support for a hypothesis of no difference between the cohorts on the basis of reward expectancy- and prediction error-related right ventral striatal reactivity. Bayes factors revealed relatively strong evidence in favor of the null hypothesis between the first-recruited cohort (MDD_{100a}) and second-recruited cohort (MDD_{100b}) of depressed individuals and healthy individuals on both measures (7.45-12.17), and also between the total sample of depressed individuals (MDD_{200}) and healthy individuals (9.60-13.94).

Moderation analyses (robust regression)

To mitigate against possible effects of outliers in anhedonia scores, we repeated our moderation analyses using robust regression, employing a Huber weighting function (Matlab, MathWorks). A similar pattern of findings was observed, with the MASQ-AD×RE interaction term providing strongest prediction of variation in PE-related reactivity.

Effects of sex and site

Males and females showed similar patterns of reward expectancy and prediction error-related ventral striatal reactivity (i.e., lower reward expectancy than prediction error-related reactivity). However, across all depressed and healthy individuals, males showed higher prediction error-related right ventral striatal reactivity ($t_{(177)=}$ 2.36; p=0.02) and a trend for higher reward expectancy-related right ventral striatal reactivity ($t_{(177)}$= 1.84; p=0.07).

Patterns of reward expectancy and prediction error-related ventral striatal reactivity were also similar across sites. However, there were significant differences in levels of reactivity for

prediction error ($f_{(4,174)}$=2.83; p=.032) and marginally significant differences in levels of reactivity for reward expectancy ($f_{(4,174)}$=2.35; p=.056) across sites.

Whole-brain analyses (reward expectancy and prediction error)

We conducted whole-brain analyses for reward expectancy and prediction error accounting for age, sex, site and slice signal-to-noise ratio (sSNR) in the first-recruited cohort (MDD_{100a}) and healthy individuals, in the second-recruited cohort (MDD_{100b}) and healthy individuals, and across all study participants with a family-wise error (FWE) cluster threshold of p<0.05. We also examined relationships between symptom severity and reward expectancy and prediction error-related reactivity using scores for the Mood and Anxiety Symptom Questionnaire Anhedonic Depression Scale (MASQ-AD), the Mood and Anxiety Symptom Questionnaire Anxious Arousal Scale (MASQ-AA), the Hamilton Rating Scale for Depression (HAM-D) and the Spielberger State Anxiety Inventory (STAI-S) as regressors, with covariates as above, in a second-level whole-brain multiple regression-model.

MDD_{100a} and healthy individuals

To reward expectancy, across individuals, there was a small significant cluster in the right occipital cortex (with a threshold of p<0.001 uncorrected there was also activation in the caudate nucleus extending to ventral striatum and the left occipital cortex). To prediction error, across individuals, there was activation in multiple regions implicated in reward and emotion processing including ventral striatum, amygdala, cingulate cortex, superior temporal gyrus and medial frontal cortex (mPFC).

There were no significant differences in activation between MDD_{100a} and healthy individuals to either reward expectancy or prediction error. Also, there were no significant

relationships between any of the symptom measures and reward expectancy and prediction error-related wholebrain reactivity.

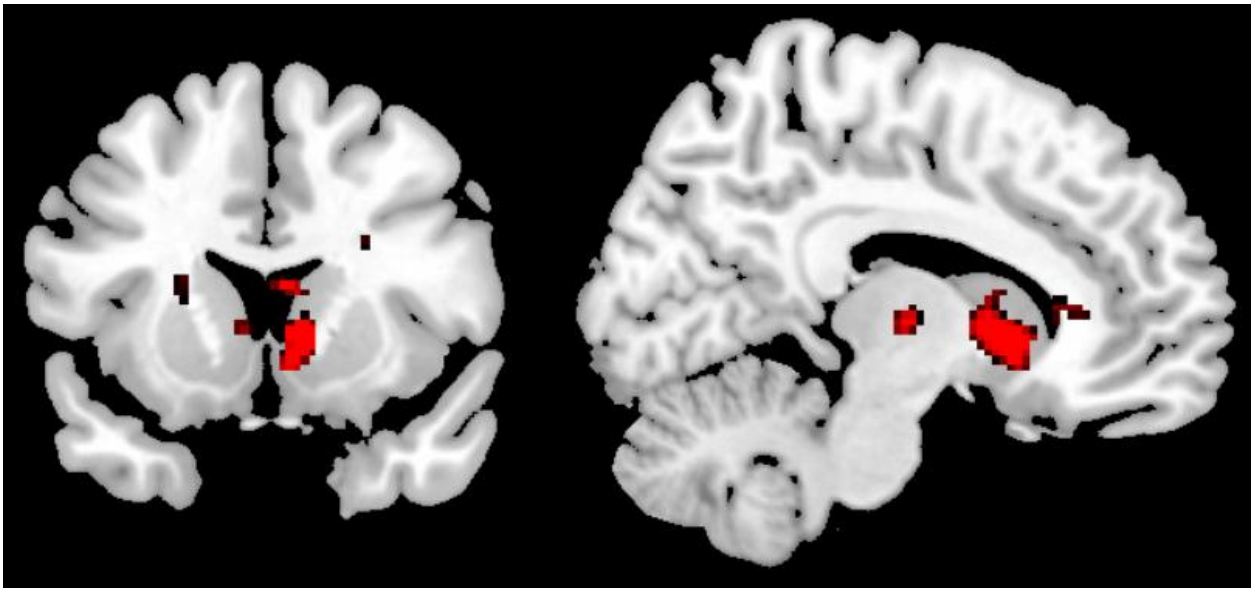
MDD_{100b} and healthy individuals

Results for all analyses were comparable to those reported above for MDD_{100a} and healthy individuals.

Whole-brain analysis for the moderation of anhedonia on the relationship between reward expectancy and prediction error-related reactivity: First-recruited cohort of depressed individuals and healthy controls

A wholebrain moderation analysis in the first-recruited cohort (MDD_{100a}) and healthy individuals, accounting for age, sex, site and sSNR using a threshold of t= 3.4 showed a moderation effect of MASQ-AD anhedonia on the relationship between reward expectancy and prediction error-related reactivity in the right caudate nucleus (peak voxel: t=5.00; x=10 y=12 z=2; 304 voxels), left middle cingulate cortex (peak voxel: t=4.09; x=0 y=-30 z=472; 185 voxels), right thalamus (peak voxel: t=4.04; x=10 y=-14, z=4; 51 voxels), right supramarginal gyrus (peak voxel: t=4.71; x=64 y=-28, z=34; 50 voxels), left putamen (peak voxel: t=4.06; x=-22 y=16, z=8; 39 voxels), and right angular gyrus (peak voxel: t=4.34; x=56 y=-58, z=34; 22 voxels).

Figure S2. Whole brain anhedonia moderation in the first-recruited cohort of depressed individuals and healthy controls

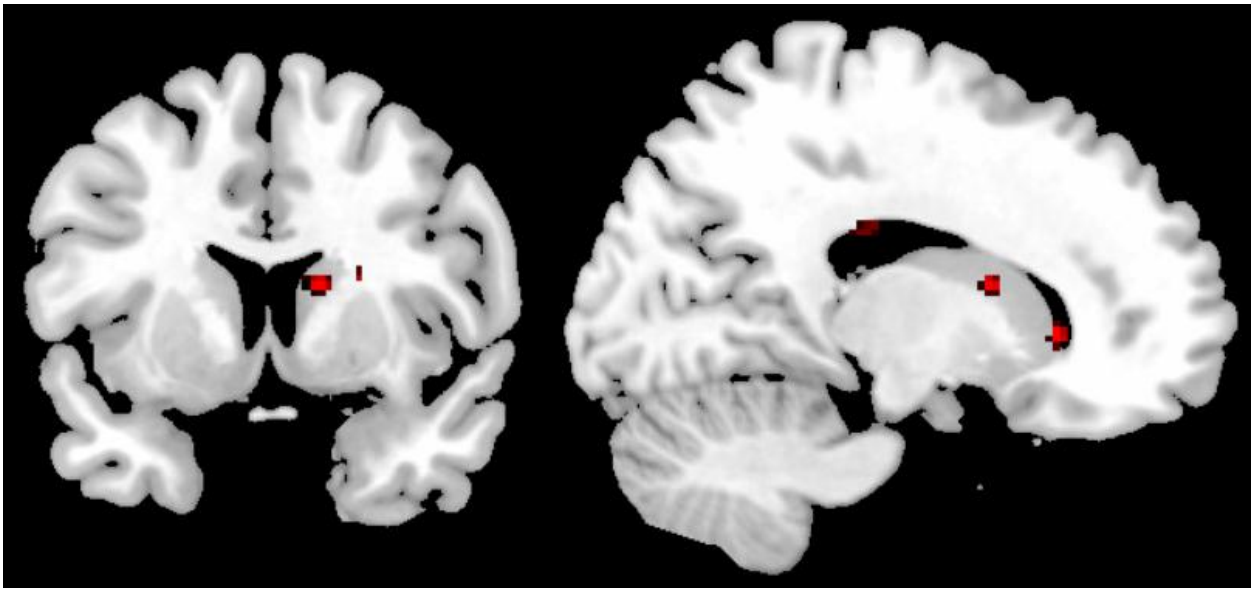


Threshold: *t*=3.4

Whole-brain analysis for the moderation of anhedonia on the relationship between reward expectancy and prediction error-related reactivity: Second-recruited cohort of depressed individuals and healthy controls

A wholebrain moderation analysis in the second-recruited cohort (MDD_{100a}) and healthy individuals, accounting for age, sex, site and sSNR using a threshold of *t*= 3.4 showed a moderation effect of MASQ-AD anhedonia on the relationship between reward expectancy and prediction error-related reactivity in the right anterior caudate (peak voxel: *t*=4.4; x=16 y=26 z=0; 26 voxels), right middle occipital gyrus (peak voxel: *t*=4.42; x=46 y=-80 z=20; 23 voxels) and right caudate nucleus (peak voxel: *t*=4.09; x=12 y=10, z=14; 21 voxels).

Figure S3. Whole brain anhedonia moderation in the second-recruited cohort of depressed individuals and healthy controls



Threshold: *t*=3.4

Comparison of correlation coefficients between reward expectancy and prediction error-related right caudate reactivity for anhedonia range equivalent subgroups in the first and second-recruited cohorts of depressed individuals.

We extracted mean parameter estimates, reflecting reward expectancy and prediction error reactivity, from the right anterior caudate using a 6 mm sphere centered at x=16 y=26 z=0 (based on the wholebrain moderation analysis in all participants). A comparison of reward expectancy-prediction error correlation coefficients for low, moderate and high anhedonia subgroups using range equivalent MASQ-AD scores showed comparable patterns in the two cohorts (low anhedonia: MDD_{100a}:$r(17)$ =-.28, MDD_{100b}:$r(17)$=-0.36; moderate anhedonia: MDD_{100a}:$r(39)$=0.16; MDD_{100b}:$r(27)$=0.41; high anhedonia: MDD_{100a}:$r(15)$=0.5; MDD_{100b}:$r(19)$=0.16.

Supplemental Discussion

One possible alternative explanation for group differences in reward expectancy-prediction error correlations was that individuals with major depressive disorder did show the same relationship as healthy individuals but had a reduced range of reward expectancy and prediction error-related ventral striatal reactivity, caused by smaller between-subjects variability in learning rate (e.g. clustered around zero). If this were true, the reward expectancy predictor in the full (major depressive disorder and healthy controls) model would have captured all of the variability in the prediction error predictor, even if it were unable to do so in the major depressive disorder group alone. This was not the case, however, given that anhedonia was a significant moderator of the relationship between reward expectancy and prediction error-related ventral striatal reactivity in the full model, and thereby indicated a range of learning rates associated with anhedonia severity across individuals with major depressive disorder and healthy individuals. Another possibility is that severely anhedonic individuals showed reduced reward expectancy and/or prediction error-related reactivity per se, that resulted in an absence of the above relationship between reward expectancy and prediction error-related ventral striatal reactivity. There was no evidence for this effect: in fact, correlations between anhedonia severity and reward expectancy/prediction error activation were close to zero. Moreover, inspection of the distribution of data revealed no obvious presence of an altered distribution of reward expectancy and prediction error-related ventral striatal reactivity in the major depressive disorder group. Other non-specific accounts, such as the presence of generally noisier data in the major depressive disorder group are also rendered less probable by the model, which took into account site and signal-to-noise ratio. Furthermore, the two groups were well-matched on measures of within-scanner motion and signal to noise ratio.

Table S2. Imaging parameters for the four clinical sites: Columbia University (CU), Massachusetts General Hospital (MGH), the University of Michigan (UM) and the University of Texas Southwestern Medical Center (UTSW).

	CU	MGH	UM	UTSW
Scanner	General Electric 3T*	Siemens 3T	Phillips 3T	Phillips 3T
Structural	FSPGR TR = 6.0 ms TE = 2.4 ms TI = 900 ms Flip Angle = 9° FOV= 256×256 mm Slice Thickness = 1 mm Matrix = 256×256 178 continuous slices (4 discarded)	MPRAGE TR = 2300 ms TE = 2.54 ms TI = 900 ms Flip Angle = 9° FOV= 256×256 mm Slice Thickness = 1 mm Matrix = 256×256 176 continuous slices	Turbo Field Echo (TFE) TR = 8.2 ms TE = 3.7 ms TI = 1100 ms Flip Angle = 12° FOV= 256×256 mm Slice Thickness = 1mm Matrix = 256×256 178 continuous slices	MPRAGE TR = 2100 ms TE = 3.7 ms TI = 1100 ms Flip Angle = 12° FOV= 256×256 mm Slice Thickness = 1mm Matrix = 256×256 178 continuous slices
Functional	TR/TE=2000/28msec Flip Angle 90° FOV=205×205 mm Slice thickness: 3.1 mm Matrix 64×64	TR/TE=2000/28msec Flip Angle 90° FOV=205×205 mm Slice thickness: 3.1 mm Matrix 64×64	TR/TE=2000/28msec Flip Angle 90° FOV=205×205 mm Slice thickness: 3.1 mm Matrix 64×64	TR/TE=2000/28msec Flip Angle 90° FOV=205×205 mm Slice thickness: 3.1 mm Matrix 64×64

* Scanner has been upgraded in 2013 (all parameters for structural/functional scans remained the same). We accounted for this in all analyses by adding another dummy code for site.

Table S3. A comparison of motion and signal-to-noise ratio (SNR) measures in the first-recruited cohort (MDD_{100a}) and second-recruited cohort (MDD_{100b}) of depressed individuals and healthy controls (HC).

	MDD_{100a}		MDD_{100b}		HC		Statistics (MDD_{100a} vs HC; MDD_{100b} vs HC)
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	
Mean Motion (mm)	0.57 (.37)		0.48 (0.29)		0.47 (0.37)		$t_{(107)}$= 1.27, p=0.21; $t_{(98)}$=0.16, p=0.87
Max Motion (mm)	1.19 (.72)		1.05 (0.65)		1 (.85)		$t_{(107)}$=1.13, p=0.26; $t_{(98)}$=0.304, p=0.76
Macro Motions	1.35 (2.98)		.94 (2.11)		0.84 (2.52)		$t_{(107)}$=0.835, p=0.41; $t_{(98)}$=0.213, p=0.83
Slice SNR	249.3 (86.52)		234.25 (65.76)		247.22 (99.65)		$t_{(107)}$=0.108, p=0.91; $t_{(42.2)}$= -0.663, p=0.51[1]
Voxel SNR	56.52 (15.4)		55.47 (12.04)		57.29 (16.63)		$t_{(107)}$=-0.229, p=0.82; $t_{(44.7)}$=-0.548, p=0.59[1]

[1]=equal variance not assumed