Supplementary Information

Supplementary Methods

Inclusion/exclusion criteria

Inclusion criteria for the depressed group were a current diagnosis of major depressive disorder, confirmed using the Structured Clinical Interview for DSM-IV (First *et al.*, 2002); a score of 17 to 28 on the 17-item Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960); and <2 weeks of lifetime psychiatric medication (and no medication in the past 3 months). Exclusion criteria for the depressed group were lifetime psychotic, bipolar, attention deficit, or substance use disorders (including nicotine). Inclusion criteria for the age-, gender- and race/ethnicity-matched healthy control group were an absence of lifetime psychiatric disorders or major medical illnesses. Exclusion criteria were tobacco or illicit substance use in the past 3 months; a family history of schizophrenia; pregnancy; breastfeeding; use of hormonal contraceptives.

Additional measures of hedonic function

The primary measure of anhedonia was the Snaith-Hamilton Pleasure Scale (SHAPS) (Snaith *et al.*, 1995), which is one of the most widely used assessments of anhedonia in depressed samples. This scale consists of 14 items that inquire about the level of pleasure experienced in response to pleasant stimuli and situations. It is scored on a scale from 1 (*Definitely Agree*) to 4 (*Definitely Disagree*) with scores ranging from 14 to 56. Higher scores are indicative or more severe anhedonia. This scoring method preserves the continuous structure of the data and is modified from the original scoring using by Snaith and colleagues (Snaith *et al.*, 1995), which recoded the four response categories into dichotomous categories (0=*Agree*, 1=*Disagree*) for the purposes of categorizing individuals as anhedonic or non-anhedonic. The modified scoring method, which has been used across numerous studies, has

been found to produce good to excellent internal consistency across both clinical and non-clinical populations (Franken *et al.*, 2007). Additional self-report measures of hedonic function were administered at baseline and post-treatment: the Temporal Experience of Pleasure Scale (TEPS) (Gard *et al.*, 2006), the anhedonic depression subscale of the Mood and Anxiety Symptom Questionnaire MASQ) (Watson *et al.*, 1995), and the Apathy Evaluation Scale (AES) (Marin *et al.*, 1991),

PRT quality control criteria

In order for response bias to be accurately interpreted, quality control criteria were applied to confirm that participants performed at a level that was above chance, and therefore high enough for them to be exposed to the asymmetrical reinforcement ratio. First, trials where the reaction time (RT) was < 150ms or > 2500ms were excluded, as were remaining trials with RT failing ±3SD from the mean. Cases where there were less than 80 valid trials per block, greater than 10 outlier trials per block, less 55% accuracy per block, or where the rich to lean reward ratio was lower than 2.5:1, were excluded from analyses. Next, response bias and discriminability scores were computed using these formulae:

Response bias: $$\log b = \frac{1}{2}\log\left(\frac{Rich_{correct} * Lean_{incorrect}}{Rich_{incorrect} * Lean_{correct}}\right)$$

Discriminability: $$\log d = \frac{1}{2}\log\left(\frac{Rich_{correct} * Lean_{correct}}{Rich_{incorrect} * Lean_{incorrect}}\right)$$

To compute response bias and discriminability for cases that had a zero in the formula, 0.5 was added to every cell in the formula matrix (Hautus, 1995). For regression analyses examining PRT performance as predictors of symptom improvement, the primary variable of interest was reward learning (block 3 response bias – block 1 response bias),

which was chosen in light of prior studies that have linked this variable to individual differences in striatal dopamine clearance (Kaiser *et al.*, 2018).

Computational modelling of the Probabilistic Reward Task (PRT)

To separate the influence of reward sensitivity (which operationalizes reduction in consummatory pleasure) and learning rate (which operationalizes participants' ability to learn from reward feedback) on PRT performance, we fitted a series of reinforcement learning models to the PRT choice data. In a prior, independent study, worse anhedonia has been linked to blunted reward sensitivity (Huys *et al.*, 2013). Learning rate was also of interest given that this separate study showed that a single low dose of pramipexole altered learning rate in healthy individuals (Huys *et al.*, 2013) (however, no study to date has examined the influence of pramipexole on these parameters in individuals with depression). These models tested whether participants associated rewards with stimulus-action pairs ('Stimulus-Action' model), with actions ('Action' model), or with a mixture of the two stimulus-action associations weighted by an uncertainty factor ('Belief' model). They also tested whether subjects treated zero outcomes as losses ('Punishment' model). The models were fitted using an empirical Bayesian random-effects approach and were compared using integrated group-level Bayesian Information Criterion factors following previously established procedures (Huys *et al.*, 2013). Individual subject parameter inference was constrained by an empirical prior distribution and no further assumptions were made. We found that the 'Belief' model gave the most parsimonious account of the data (group-level log Bayes factor compared to the second-most parsimonious model = 23, which is >20 and represents very strong evidence in favor of the better fitting model). This model assumes uncertainty within subjects about the presented stimulus. As such, they might assign rewards to both stimuli with only a certain preference for the actual presented stimulus. Five parameters were derived: (i) *reward sensitivity* assessed the immediate behavioral impact of rewards; (ii) *learning rate*

represented subjects' ability to accumulate rewards over time and learn from the rewards; (iii) *belief* indicated subjects' uncertainty about which stimulus was actually presented; (iv) *instruction sensitivity* measured subjects' ability to follow the instructions; (v) *initial bias* indicated subjects' initial bias towards one response or the other. This study focused on the reward sensitivity and learning rate parameters, which were analyzed in the transformed space in order to prevent issues associated with non-Gaussianity. In the current study, reward sensitivity and learning rate parameters were negatively correlated at trend level in both the healthy control (r= -0.41, p=0.07) and depressed groups (r= -0.40, p=0.06).

fMRI preprocessing and analysis

Functional images were preprocesses with SPM8 and analyzed with NeuroElf software (http://neuroelf.net/). Images were slice-time corrected and realigned to the first image in each run, warped to the Montreal Neurological Institute template, and smoothed (6mm Gaussian kernel). Next, first-level analyses were conducted using a general linear model (GLM) that included six stick function regressors convolved with a hemodynamic response for choice, feedback, and outcome, each with trial-specific parametric regressors (choice value, feedback prediction error, and monetary outcome prediction error). A high-pass temporal filter (Fourier transform, 200sec) and motion parameters were included in the model as nuisance regressors. A second-level model was developed that included regressors for choice, feedback prediction error, and outcome prediction error, each separated by a jittered interval. Prediction error regressors for use with the fMRI GLM were generated using a Q-learning model as has been established for this task in prior work (for details, see Reinen *et al.*, 2014). Gain and loss condition learning signals were analyzed using separate regressors in the same model.

Analyses focused on activation in a ventral striatal region of interest (See Supplementary Fig. 2). This region was defined using the automated meta-analysis Neurosynth. We used "ventral striatum" as the Neurosynth search term, identified the peak coordinates, and extracted activation for each participant in voxels within a 6mm sphere (radius) surrounding the region and its bilateral counterpart. There are currently 14,371 studies in the Neurosynth database and the term "ventral striatum" yielded 415 studies and 12,989 activations.

PET imaging

First, a 7sec computed tomography (CT) scan was conducted, followed by a 120-minute baseline scan. Next, 0.5 mg/kg of amphetamine was administered orally. Three hours later, another CT scan was conducted, followed by the second 120-minute scan. PET scanning was performed on a Biograph multispectral PET-CT (Siemens Healthineers, Knoxville, TN).

Aspects of trial design

Participants were recruited from the New York State Psychiatric Institute Division of Translational Imaging (healthy controls) and the New York State Psychiatric Institute Division of Clinical Therapeutics Anxiety Disorders Clinic and Depression Evaluation Service, and the Depression and Anxiety Center of Mount Sinai Icahn School of Medicine (MDD participants). Participants were initially screened via telephone and those who appeared eligible were invited to take part in a psychiatric and medical history evaluation (by a MD or PhD/PsyD), as well as a full SCID interview to confirm diagnosis of MDD. For those deemed eligible following the SCID interview, a physical examination was performed by a physician. This included a blood test for hematology, liver, thyroid and kidney function assessments, as well as a pregnancy test in women of child-bearing potential. Participant's

height and weight were obtains, an EKG was performed and participants were screened for metal and other MR contraindications. Ineligible subjects with MDD or other disorders were referred for clinical treatment.

Participants who were deemed eligible based on the initial clinical and medical screen were scheduled to return to complete self-report measures of anhedonia, mood and anxiety symptoms, the PRT, MRI and PET scans. These procedures were scheduled for 2 separate days less than 1 week apart. Following these baseline assessments the MDD participants received 6 weeks of open-label treatment with pramipexole, during which time they returned for weekly visits with a psychiatrist to monitor treatment. Weekly independent evaluator assessments of symptom severity and side effects were also obtained. Following the six weeks of treatment, a second counterbalanced version of the PRT was administered behaviorally. Full details of the trial protocol can be found at https://clinicaltrials.gov/ct2/show/NCT02033369.

Supplementary Results

Associations among PRT performance, fMRI and PET variables and baseline symptom severity

There were no correlations among the PRT variables (i.e., reward learning, reward sensitivity, learning rate), the fMRI-based ventral striatal prediction errors, and the PET-based BP_{ND} or ΔBP_{ND} across the entire sample. When examining the groups separately, among controls there were trend-level correlations between ΔBP_{ND} and gain feedback prediction error in both the left (r=-0.40, p=0.08) and right (r=-0.44, p=0.053) ventral striatum, such that greater ventrostriatal dopamine release was associated with a stronger ventrostriatal response to unexpected correct feedback (note that negative values of ΔBP_{ND} indicate greater ventrostriatal dopamine release). There was also a trend-level correlation

between lower ΔBP_{ND} and greater gain outcome prediction error in the left ventral striatum (r=0.40, p=0.09). No significant associations emerged within the depressed group (all ps>0.05).

In terms of correlations between measures of reward processing, ventrostriatal dopamine function and symptoms in the depressed group, lower reward sensitivity (derived from the computational model) was associated with worse anhedonia on the SHAPS (r=-0.46, p=0.03), replicating prior work (Huys *et al.*, 2013). In contrast, neither ventrostriatal prediction errors, BP_{ND} nor ΔBP_{ND} correlated with baseline symptom severity (all ps>0.05).

Baseline PRT reward learning and reward sensitivity as predictors of post-treatment anhedonia, controlling for changes in non-anhedonic symptoms and depressive episodes

Highlighting specificity, both PRT reward learning and the reward sensitivity parameter remained significant predictors at an uncorrected threshold (p<0.02 for both predictors) of post-treatment SHAPS scores when controlling for changes in non-anhedonic depressive symptoms (MASQ GDD subscale scores) and anxiety (MASQ AA subscale scores). Furthermore, we confirmed that neither baseline reward learning nor baseline reward sensitivity predicted post-treatment MASQ GDD scores or MASQ AA scores, after controlling for baseline MASQ GDD and MASQ AA scores, respectively (all ps>0.30). In addition, baseline reward learning and baseline reward sensitivity remained significant predictors of post-treatment SHAPS scores when controlling for the number of lifetime major depressive episodes (p<0.01 for both predictors), indicating that the results were not driven by individual differences in baseline depressive illness severity.

Given that baseline reward learning and reward sensitivity predicted post-treatment SHAPS scores, we also examined whether changes in PRT performance from pre- to post-treatment predicted change in SHAPS scores. To do this we ran stepwise multiple regression

analyses that included baseline SHAPS scores and baseline PRT performance in the first step, post-treatment PRT performance in the second step, and post-treatment SHAPS scores as the dependent variable. Results showed that neither post-treatment reward learning (β=0.17, *p*=0.37) nor post-treatment reward sensitivity (β=0.10, *p*=0.63) emerged as significant predictors of post-treatment SHAPS scores when entered into the second step of the model. Furthermore, in both models, baseline reward learning (β=-0.71, *p*=0.002) and baseline reward sensitivity (β=-0.61, *p*=0.008) remained significant at the second step, confirming that baseline reward learning and sensitivity, rather than change in reward learning and sensitivity, predicted post-treatment anhedonia severity.

Supplementary Discussion

Additional limitations and future directions

Lack of association between reward learning and measures of ventrostriatal dopamine function

Given that reward learning has been hypothesized to be driven by phasic firing of dopamine in the striatum, we had expected that fMRI-based measures of ventrostriatal prediction error signaling and PET-based measures of ventrostriatal dopamine release and receptor availability would correlate with individual differences in behavioral reward learning. However, neither ventrostriatal prediction error signaling nor measures of dopamine release or receptor availability correlated with behavioral performance on the PRT (i.e., as indexed by response bias or the two computational parameters) (see Supplementary Results). There are several possible reasons for this. First, the sample size was relatively small, which may have reduced our power to observe significant associations between measures of ventrostriatal dopamine function and behavior. Second, although the PRT has been widely used to study reward learning and its relationship to frontostriatal function (e.g., Vrieze *et al.*,

2013; Kaiser *et al.*, 2018), it is a relatively simple task that only involves learning actions in response to a single stimulus dimension that is associated with gains. Accordingly, the relationship between ventrostriatal dopamine release and ventrostriatal prediction error signaling with other aspects of learning (e.g., learning stimulus-outcome associations using more complex, multidimensional stimuli) was not examined. Future studies may benefit from using additional measures of reward learning in order to clarify the lack of association observed in the current study.

Possible reasons for the lack of changes in reward learning from pre- to post-treatment

Given evidence that a single low dose of pramipexole has been previously found to reduce reward learning in healthy humans (Pizzagalli *et al.*, 2008) and rats (Der-Avakian *et al.*, 2013; Lamontagne *et al.*, 2018) as well as reduce phasic dopamine firing in rodents (Tokunaga *et al.*, 2012), the lack of effects of pramipexole on reward learning was surprising. One possibility is that pramipexole improves symptoms via alterations in other facets of reinforcement learning. For example, Argyelan and colleagues (Argyelan *et al.*, 2018) found that in Parkinson's Disease, dopamine agonists (levodopa or pramipexole) modulated punishment learning and attenuated striatal responses to punishment, leaving reward learning and reward-related striatal activation unaltered. Although this resulted in a higher ratio of striatal activation to reward versus punishment, this effect was driven by dopaminergic attenuation of punishment-related neural activation. Future studies assessing changes in both punishment and reward learning pre- and post-pramipexole could provide further insights into pramipexole's effects on other aspects of learning.

Potential for negative effects of long-term pramipexole treatment on reward function

One important consideration that warrants further investigation is whether treatment with pramipexole may lead to a worsening of depression and anhedonia when used over the long term, in a similar manner to that observed in individuals who abuse recreational substances that have dopaminergic effects, such as cocaine. Specifically, although these recreational drugs have pro-hedonic effects over the short term, with continuous long-term exposure their use leads to compensatory changes in the reward system via the process of allostasis, which can lead to the emergence of depression (Koob & Le Moal, 2001). Although we only examined the effects of a relatively short course of pramipexole treatment (i.e., 6 weeks) some studies suggest that longer-term treatment (e.g., 16 weeks) may be relatively safe and effective in the management of treatment-resistant depression. For example, Lattanzi *et al*. (2002) reported a 68% response rate to pramipexole augmentation in a sample of individuals with treatment-resistant depression who were treated with pramipexole for up to 16 weeks. In a follow-up to this study that tracked rates of sustained remission in patients who received treatment with pramipexole for up to 1 year, Cassano and colleagues (2004) found that 60.9% of patients experienced sustained remission of their major depressive episode during the follow-up period. Similar findings have been observed in individuals with bipolar depression, where pramipexole given as an adjunct to a mood stabilizer for an average of 6.7 ± 9.0 months was found to improve depressive symptoms significantly within four weeks and this improvement was maintained for over 9 months (El-Mallakh *et al*., 2010). This suggests that unlike drugs of abuse, pramipexole does not appear to cause a worsening of depressive or anhedonic symptoms over the long term. However, future studies are needed to fully understand the potential adverse effects of long-term treatment with pramipexole, particularly since long-term treatment with the drug or other dopamine agonists

has been associated with the emergence of impulse control disorders in subsets of individuals with Parkinson's disease undergoing dopamine replacement therapy (Weintraub *et al.*, 2010; Garcia-Ruiz *et al.*, 2014).

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Supplementary Table 1. Changes in reward learning and symptoms from pre- to post-treatment in the depressed (MDD) group

Measure, M (SD)	MDD baseline	MDD week 6	*P* Value	Cohen's *d*
HDRS 17-item total	20.0 (2.6)	8.1 (5.4)	<0.001	2.16
SHAPS	31.6 (6.6)	25.3 (6.9)	0.003	0.75
CGI	3.0 (0.9)[1]	1.8 (0.8)	<0.001	1.00
MASQ Anhedonic Depression subscale	82.9 (10.7)	59.6 (18.5)	<0.001	1.14
MASQ General Distress Depression subscale	40.2 (11.8)	23.9 (12.9)	<0.001	1.38
MASQ General Distress Anxiety subscale	23.6 (7.1)	18.0 (5.4)	0.001	0.84
MASQ Anxious Arousal subscale	25.3 (7.5)	21.7 (6.0)	0.03	0.51
Apathy Evaluation Scale	41.0 (9.2)	31.7 (9.5)	0.001	0.85
TEPS subscale				
Anticipatory	36.9 (8.4)	43.2 (7.9)	0.02	0.58
Consummatory	30.4 (7.7)	35.6 (6.5)	0.007	0.65
PRT variables				
Reward learning (block 3 – block 1 response bias)	0.1 (0.2)	0.1 (0.2)	0.83	0.00
Reward sensitivity (model parameter)	1.2 (0.3)	1.2 (0.3)	0.95	0.00
Learning rate (model parameter)	-3.5 (1.8)	-4.4 (1.3)	0.10	1.10
Discriminability	0.5 (0.2)	0.4 (0.2)	0.06	0.99

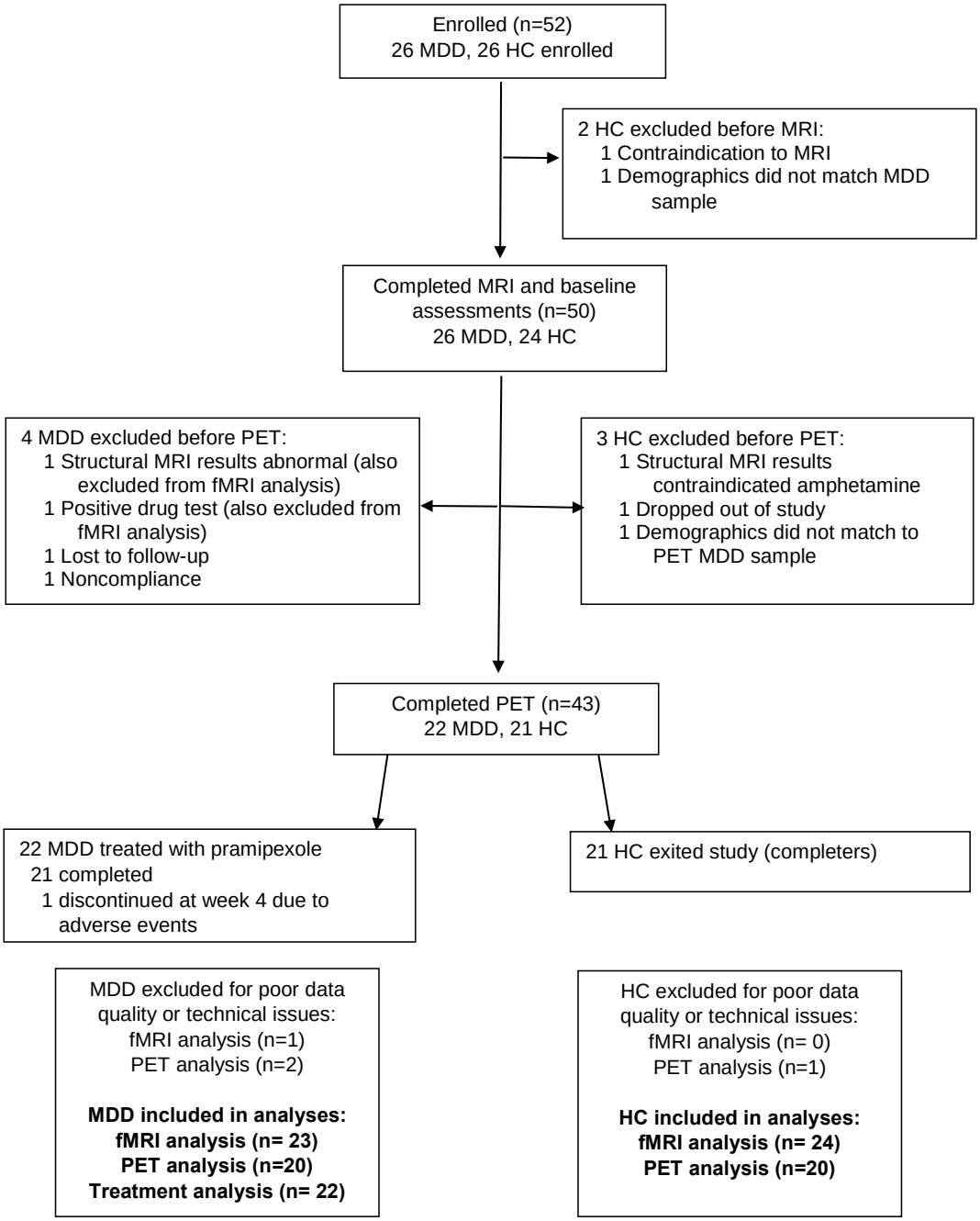
Note. MDD=major depressive disorder; HDRS=Hamilton Depression Rating Scale; CGI=Clinical Global Impression-Change Scale; MASQ=Mood & Anxiety Symptom Questionnaire; TEPS=Temporal Experience of Pleasure Scale; PRT=Probabilitic Reward Task. Descriptive statistics for symptom scores are based on the 21 MDD subjects who completed treatment. Statistics for PRT variables are based on the 17 MDD subjects who completed treatment and had valid PRT data at both baseline and week 6.
[1]Since the CGI change scale captures change in clinical impairment from one time point to the next, the "baseline" mean and SD for this measure reflects ratings given at week 1 (which capture changes in clinical impairment from baseline to week 1).

Supplementary Table 2. Treatment Emergent Adverse Events[1]

	Rate of Treatment Emergent Adverse Event (N, %)
Headache	13 (15%)
Heartburn	7 (32%)
Nausea	18 (82%)
Vomiting	7 (32%)
Decreased Appetite	6 (27%)
Increased Appetite	6 (27%)
Dry Mouth	10 (46%)
Constipation	4 (18%)
Diarrhea	5 (23%)
Excessive Sweating	4 (18%)
Skin Problems	5 (23%)
Bruising Easily	2 (9%)
Restlessness	9 (41%)
Tremor	2 (9%)
Nervousness	6 (27%)
Impaired Coordination	4 (18%)
Insomnia	9 (41%)
Fatigue	2 (9%)
Somnolence	11 (50%)
Sleep Attacks	5 (23%)[2]
Decreased Libido	7 (32%)
Sexual Dysfunction	3 (14%)
Urinary Dysfunction	1 (5%)
Blurry Vision	6 (27%)
Lightheadedness	10 (45%)
Postural Dizziness	8 (36%)
Forgetfulness	7 (32%)
Impaired Concentration	2 (9%)
Swelling in Legs	1 (5%)
Compulsive Gambling or Shopping	3 (14%)[3]
Hallucinations or Illusions	1 (5%)[4]

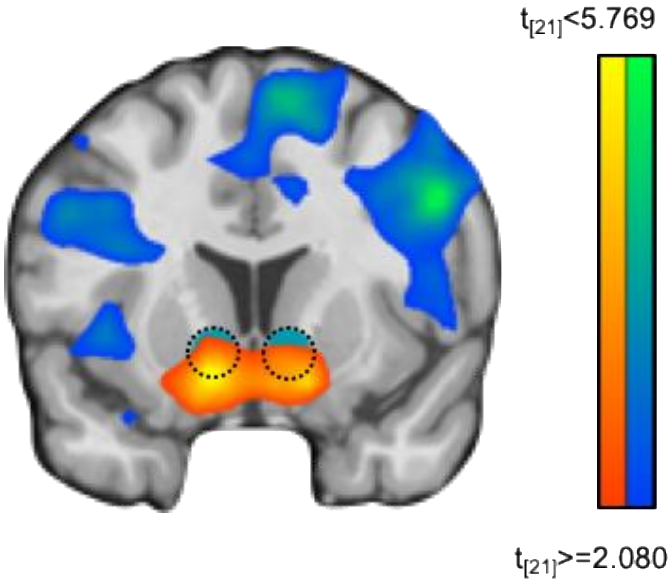
[1]At baseline and at each weekly visit during treatment, participants gave a rating for each symptom listed in the first column, ranging from 0 (Absent) to 3 (Severe). An adverse event was coded as present if, relative to baseline rating, severity was increased at any subsequent weekly rating.
[2]Sleep "attacks" were all mild. They involved a sudden urge to go to sleep but could always be resisted.
[3]Three patients reported one episode of excessive shopping, but none were clearly outside of their normal range of behavior.
[4]One patient thought she heard her name being called once

Supplementary Fig. 1. CONSORT diagram



Supplementary Fig. 1. Figure shows the flow of participants into the study, along with reasons for exclusion.

Supplementary Fig. 2. Ventral striatal region-of-interest



Supplementary Fig. 2. Figure shows the spherical regions-of-interest (ROI) in the left and right ventral striatum (black dashed outline) created based on the results of automated meta-analysis (Neurosynth). For the purposes of visualization, the ROIs are overlaid onto a map showing the prediction error in the healthy control group (p<0.05 uncorrected, y=10, feedback and outcome gain conditions). Results show good coverage of the prediction error by the ventral striatal ROIs.