Supplementary Online Content

Eckstrand KL, Forbes EE, Bertocci MA, et al. Anhedonia reduction and the association between left ventral striatal reward response and 6-month improvement in life satisfaction in young adults. *JAMA Psychiatry.* Published online May 8, 2019. doi:10.1001/jamapsychiatry.2019.0864

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix 1. Methods

Participant Exclusion Criteria
Exclusion criteria included any history of serious medical/physical conditions: neurological disorder (past stroke, seizures, dementia), history of brain tumor/brain surgery, progressive endocrine disorder (Cushing's, Lupus), heart disorder (past history of heart attacks, arteriosclerosis) or other major systemic medical conditions (kidney disease, multiple sclerosis, cerebral palsy, blindness, serious physical disability) or chronic/acute condition including any managed by medication (chronic back problem, recent surgery); taking medication for an excluded medical condition; a visual disturbance (<20/40 Snellen visual acuity) when corrected by glasses; presence of metallic foreign objects in body, such as aneurysm clips or pacemakers, or a questionable history of metallic fragments; positive pregnancy test for female individuals, or self-reporting of pregnancy; claustrophobia; a Mini-Mental State Examination score <24; a premorbid IQ estimate <85 (as determined by the National Adult Reading Test); presence of an alcohol, tobacco, or substance use disorder in the prior 3 months; current treatment with psychotropic medication for >2 weeks; previous psychotropic medication treatment in the past 6 months. For typically-developing individuals, personal history of any psychiatric disorder or psychotropic medication use were also exclusion criteria. Twelve individuals were excluded due to incomplete data, two individuals were excluded due to excessive motion (>5mm), one participant was excluded due to excessive task performance errors (20, other participants <12), and six participants were excluded due to excessive signal loss (>30%).

Psychotropic Medication Load
The psychotropic medication load quantifies the number and dose of psychotropic medications for each participant, where greater numbers and doses of medications correspond to a greater medication load[1,2]. Antidepressants and mood-stabilizers were converted into low- or high-dose groupings. Low-dose were coded as levels 1 and 2, and high-dose as 3 and 4 based on previous criteria[3] Those not taking medication were scored as 0, for no medication dosage. Antipsychotics were converted to chlorpromazine dose equivalents with low- and high-dose, 1 and 2 respectively, representing chlorpromazine equivalents dose equal or below, or above, mean effective daily dose (ED_{50}) of chlorpromazine[4]. Benzodiazepine dose was coded as 0, 1 or 2, with reference to the midpoint of the *Physician's Desk Reference*-recommended daily dose range for each medication. A composite measure of psychotropic medication load was calculated by summing the individual medication codes for each medication category for each individual participant. The change in psychotropic load between baseline and 6-month follow-up was calculated as the mean difference in psychotropic load between timepoints.

Monetary Reward Paradigm
Win trials comprised expectation of a win followed by a win outcome or no change; loss trials comprised expectation of a loss followed by a loss or no change; mixed trials comprised expectation of either win or loss, followed by win or loss; and neutral trials had no expectation of either win or loss, followed by no change. Each trial comprised a visually presented card, and participants guessed via button press whether the card's value was higher or lower than the number "5" (4 seconds). Participants then were presented with a jittered 2-6s expectancy cue where they waited for feedback as to whether their guess was accurate and if money was awarded. An outcome cue was presented for 1 second followed by an intertrial interval of 0.5-1.5 seconds. Participants completed two 8-minute blocks of 48 trials (12 per trial type) randomized with predetermined outcomes. Participants were informed that their performance would result in a monetary reward after the scan: $1 per win and $0.75 deduction per loss, with the total possible reward equaling $6. While participants believed monetary outcome was due to performance, a fixed amount was given to all participants[5]. All participants were debriefed regarding the fixed amount outcome at the end of the visit on the day of the neuroimaging assessment.

Reward prediction error (RPE), reward expectancy (RE), and outcome expectancy (OE) were derived from the monetary values associated with each trial type. RPE was calculated as the difference between the expected and outcome reward values for each trial type: +$0.50 for a win and –$0.50 for no win in the possible win condition; +$0.375 for a no loss and –$0.375 for a loss in the possible loss condition; +$0.875 for a win and –$0.875 for a loss in the mixed condition and zero in the neutral condition. Reward expectancy (RE) and outcome expectancy (OE) were calculated during the reward anticipation period in each trial. RE was defined as the expected value of the arrow: +$0.50 for the possible win condition (50% chance of winning $1), –$0.375 for the possible loss condition (50% chance of losing $0.75), +$0.125 for the mixed condition (50% chance of winning $1; 50% chance of losing $0.75), and zero for the neutral condition. In contrast, OE represented the range of unsigned values of possible

outcomes where the greatest value was for the mixed trials ($1−$0.75 = 1.75) and lowest for neutral trials (zero). Possible win ($1−$0 = 1) and possible loss (0−$0.75 = 0.75) trial values were in between.

fMRI Acquisition Parameters

Functional neuroimaging data were collected at the University of Pittsburgh using a 3.0 Tesla Siemens Trio 2 MRI scanner or a 3.0 Tesla Siemens Prisma MRI scanner using the same acquisition parameters. Blood-oxygenation-level-dependent (BOLD) images were acquired with a multi-band gradient echo EPI sequence (18 slices, three-factor multiband; 2.3 mm isotropic voxels; TR=1500ms, TE=30ms; field of view=220 × 220 mm; matrix 96 × 96; flip angle 55°, bandwidth 1860 Hz Px–1). Structural 3D axial MPRAGE images (TR=1500ms, TE=3.19ms; flip angle 8° FOV=256 × 256 mm; 1 mm isotropic voxels; 176 continuous slices) and fieldmaps (2.3 mm isotropic voxels; TR=500 ms, TE1=4.92 ms, TE2=7.38 ms; FOV=220 × 220 mm; flip angle 45°, bandwidth 1302 Hz Px–1) were acquired in the same session. Fieldmaps were not available for 11 participants (6 healthy, 5 distressed).

fMRI Preprocessing

Imaging data were processed using SPM, FSL, and AFNI using Nipype[6]. For each participant, BOLD images were realigned to the first volume in the time series and co-registered with the participant's structural image. Field maps were used to correct for image distortion using FSL FUGUE. Structural images were normalized using a non-linear transformation to the standard MNI/ICBM 152 template and segmented into gray matter, white matter, and cerebrospinal fluid (CSF). Using DARTEL, BOLD images were transformed into the same space using the structural image and resampled at $2mm^3$ isotropic voxel size. Activation spikes in the BOLD images were corrected using AFNI 3dDespike. BOLD images were then normalized for intensity and spatially smoothed (FWHM 6mm) using an adaptive smoothing method implemented in FSL SUSAN.

Data Analyses

For first level analyses, RE was a parametric modulator coupled to the anticipation phase reflecting the expected value of the arrow; OE was a regressor coupled anticipation phase reflecting the unsigned value of possible future outcomes; RPE was coupled to the outcome and defined as the difference between the outcome and expected value. Another regressor modeled any omission errors. Gram-Schmidt orthogonalization was applied to GLM regressors. The GLM was fit to the two task blocks separately and parameter estimates were combined across each. Physiologic fluctuations with the mean signal in CSF, white matter, and high deviation voxels were determined with CompCor[7,8] and entered as a covariate to reduce noise. Motion parameters during scanning were entered as covariates to control for head movement. A 60s high-pass filter and autoregressive modelling were implemented during fitting.

The BOLD signal in seed regions was deconvolved to estimate neural activation to each regressor. This estimated activation was then multiplied by each column in the GLM, including each regressor (RPE, RE, OE), and convolved with a hemodynamic response function. These three PPI interaction regressors were then included in the GLM alongside the three task regressors, motion parameters, and mean time course in the seed regions. Whole-brain PPI contrast images were generated by regressing the BOLD signal across all whole-brain regions onto (1) the task main effect, (2) the BOLD signal from the seed region, and (3) each of the three convolved PPI interaction regressors. Functional connectivity was determined by the difference between the β coefficients of the seed and whole-brain regions to each PPI regressor.

eAppendix 2. Results

Baseline DSM Diagnoses
39 of the 52 recruited participants met criteria for one or more DSM diagnoses (see Table 1). Of the 39 meeting criteria, 18 met criteria for a single diagnosis: depressive disorder (n=4), anxiety disorder (n=10), externalizing disorder (n=1), sleep disorder (n=1), adjustment disorder (n=2). 21 participants met criteria for two or more psychiatric diagnoses.

Improvement in Affective Symptoms over Six Months
In the 6 months following the initial visit, participants experienced decreased self-reported anhedonic depression (MASQ-AD; $p<0.001$), anxious arousal (MASQ-AA; $p=0.001$), and anhedonia severity (SHAPS; $p=<0.001$). They also experienced decreased clinician rated anxiety (HAMA; $p<0.001$) and depression (HRSD; $p<0.001$), but not mania (YMRS; $p=0.233$; Supplementary Table 1). These improvements were not influenced by psychotropic medication.

Relationship Between Predictor Variables
Relationships among the five non hemisphere homologous neural regions were all $r<0.4$, $p>0.003$ (left VS – left ACC: r=0.342, $p=0.013$; left VS – right ACC: r=0.321, $p=0.020$; left VS – left amygdala: r=0.399, $p=0.003$; right VS – right ACC: r=0.356, $p=0.010$; right VS – left amygdala: r=0.400, $p=0.003$; right VS – left ACC: r=0.292, $p=0.035$; left Amygdala – left ACC: r=0.356, $p=0.010$; left Amygdala – right ACC: r=0.382, $p=0.005$), and thus were included as independent variables in each of the two multivariate linear regression models testing relationships among RPE-related neural activity and baseline-6 month symptom changes.

Effect of Diagnosis
After adding DSM diagnosis to the second level imaging model for RPE, all regions remained significantly activated (Left VS: $k_E = 42$, T = 6.23, $p_{FWE} = <0.001$; Right VS: $k_E = 128$, T = 6.90, $p_{FWE} = <0.001$; Left rostral-dorsal ACC: $k_E = 88$, T = 4.72, $p_{FWE} = 0.009$; Right rostral-dorsal ACC: $k_E = 156$, T = 4.46, $p_{FWE} = 0.018$; Left amygdala: $k_E = 24$, T = 4.19, $p_{FWE} = 0.038$). After extracting activation from these regions and repeated the multiple linear regression with self-reported affective symptoms, left VS activation predicted a reduction in anhedonia over 6 months. The reduction in anhedonia mediated the relationship between left VS activation to RPE and improved psychosocial function (*c-path*: β=0.522; p=0.010; *ab path*: 95%CI:0.028,0.532; *c' path:* β=0.315; $p=0.147$).

Effect of Medication
Ten participants were started on psychotropic medication between baseline and follow-up visits; one participant's dosage of an antidepressant increased. Eight participants were started on antidepressants, two were started on atypical antipsychotics, one was started on a mood stabilizer and one was started on a stimulant. The average length of treatment between baseline and follow-up was 2.90±3.27 months.

In a repeated measures ANOVA including psychotropic medication change as a covariate, medication usage between baseline and follow-up did not influence improvements in self-reported anhedonic depression (MASQ-AD: F[3,47] = 0.715, $p=0.548$), anxious arousal (MASQ-AA: F[3,47] = 1.734, $p=0.173$), or anhedonia (SHAPS: F[3,47] = 0.361, $p=0.782$). In a separate repeated measures ANOVA, medication usage between baseline and follow-up similarly did not influence clinician-rated depression (HRSD: F[3,47] = 0.313, $p=0.816$), anxiety (HAMA: F[3,47] = 2.01, $p=0.125$), or mania (YMRS: F[3.47] = 0.482, $p=0.696$) symptoms.

Changes in psychotropic medication did not moderate the association between left ventral striatum activation to RPE and the change in SHAPS between baseline and follow-up visits (β=-0.028, $p=0.979$), nor did it moderate the association between the change in anhedonia symptoms and improvement in LIFE-RIFT satisfaction (β=-0.14, $p=0.805$). After removing individuals who were started on psychotropic medication, the mediation model was still significant (*c-path*: β=0.490; p=0.023; *ab path*: 95%CI:0.033,0.558; *c' path:* β=0.274; $p=0.224$).

eReferences
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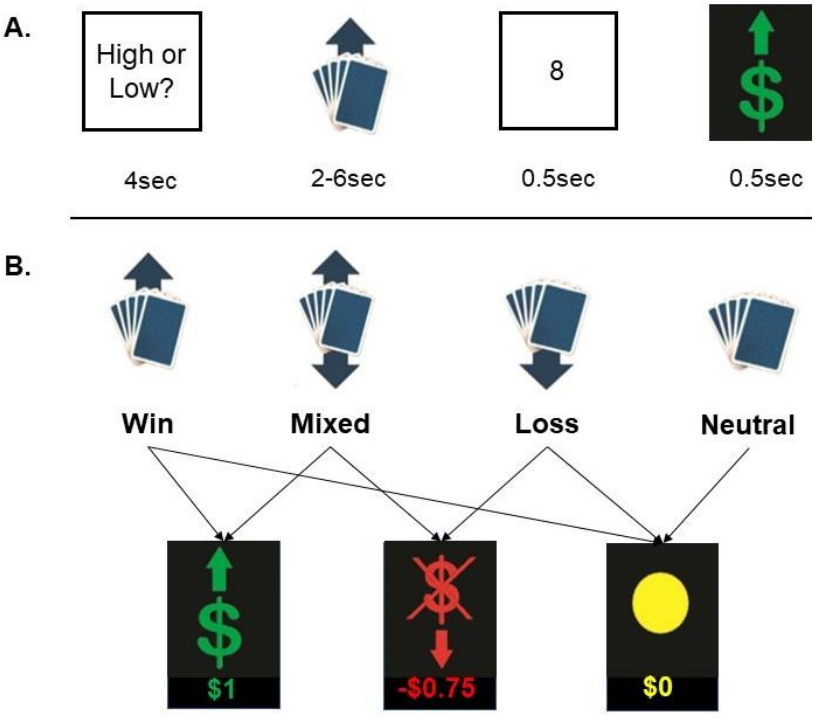
eFigure. Standardized Monetary Reward Task



eTable 1. Improvement in Baseline Affective Symptoms Between Baseline and 6-Month Follow-up				
		Baseline	**6 Months**	
Affective Symptoms		Mean ± SD	Mean ± SD	*P* Value[a]
Clinician-Rated	Anxiety (HAMA)	12.86 ± 6.64	8.53 ± 5.87	**<.001**
	Depression (HRSD)	15.76 ± 6.75	11.12 ± 5.58	**<.001**
	Mania (YMRS)	2.80 ± 1.94	2.27 ± 2.16	.233
Self-Reported	Anhedonic Depression (MASQ-AD)	3.46 ± 0.68	2.99 ± 0.78	**<.001**
	Anxious Arousal (MASQ-AA)	1.75 ± 0.69	1.51 ± 0.64	**.003**
	Anhedonia (SHAPS)	27.51 ± 7.33	23.14 ± 7.73	**<.001**

[a] Repeated measures ANOVA
HAMA, Hamilton Anxiety Rating Scale; HRSD, Hamilton Rating Scale for Depression; MASQ-AA, Mood and Anxiety Symptom Questionnaire – Anxious Arousal; MASQ-AD, Mood and Anxiety Symptom Questionnaire – Anhedonic Depression; SHAPS, Snaith Hamilton Pleasure Scale; YMRS, Young Mania Rating Scale

eTable 2. Whole Brain Neural Activation							
Region	**Hemisphere**	**Voxel p_{FWE}**	**Voxels**	**T-score**	**x**	**y**	**z**
Outcome Expectancy							
Cuneus	L	0.013	244	5.44	-6	-92	4
Lingual Gyrus	L	0.022	271	5.23	-20	-86	-10
Reward Expectancy							
Occipital Lobe	R	<0.001	3313	10.91	42	-78	-8
	L	<0.001	2643	9.43	-38	-84	-4
Reward Prediction Error							
Ventral Striatum/Amygdala	R	<0.001	518	7.43	20	12	-14
	L	0.001	357	6.27	-10	14	-4
Anterior Cingulate Cortex	R	0.018	1332	5.35	2	56	-6
Inferior Parietal Lobule	R	0.025	185	5.23	32	-34	32
Middle Cingulate Cortex	R	0.041	432	5.05	10	-44	26

eTable 3. Association of Neural Activation to RPE With Change in Clinician-Rated Affective Symptoms Between Baseline and 6 Months

Affective Symptom		β	*p*-value	95% CI	
				LL	UL
Anxiety (HAMA)	Left Ventral Striatum	-1.924	0.420	-6.681	2.833
	Left Amygdala	0.496	0.763	-2.795	3.788
	Left ACC	0.004	0.999	-4.372	4.380
	Right Ventral Striatum	0.161	0.940	-4.114	4.436
	Right ACC	1.160	0.648	-3.920	6.241
Depression (HRSD)	Left Ventral Striatum	-2.529	0.288	-7.260	2.202
	Left Amygdala	-1.099	0.503	-4.372	2.175
	Left ACC	-1.711	0.433	-6.063	2.641
	Right Ventral Striatum	0.900	0.672	-3.352	5.151
	Right ACC	3.562	0.163	-1.490	8.614
Mania (YMRS)	Left Ventral Striatum	0.741	0.421	-1.097	2.579
	Left Amygdala	-0.339	0.594	-1.611	0.932
	Left ACC	0.577	0.496	-1.114	2.268
	Right Ventral Striatum	0.780	0.347	-0.872	2.431
	Right ACC	-0.683	0.487	-2.646	1.280

HAMA, Hamilton Anxiety Rating Scale; HRSD, Hamilton Rating Scale for Depression; YMRS, Young Mania Rating Scale

eTable 4. Six-Month Change in Anhedonia Symptoms Mediates the Association Between Left VS Activation and Improved Life Satisfaction Including Psychotropic Medication Use as a Covariate

LIFE-RIFT	Mediation Model [β(*p*)]		Bootstrapping bias-corrected 95% CI			
	Direct (c')	Total (c)	Effect (P_M)	SE	Lower Level CI	Upper Level CI
Total	-0.013 (0.651)	0.016 (0.617)	1.794	0.018	0.005	0.084
Work	-0.020 (0.789)	0.012 (0.880)	2.600	0.040	-0.027	0.116
Interpersonal Relationships	-0.028 (0.763)	0.083 (0.389)	1.337	0.058	0.028	0.266
Satisfaction	**0.134 (0.161)**	**0.239 (0.012)**	**0.437**	**0.056**	**0.024**	**0.253**
Recreation	-0.095 (0.151)	-0.109 (0.134)	0.136	0.035	-0.100	0.043

Coefficients in boldface denote significant mediation. CI = Confidence interval.