Trauma Impacts Prospective Relationships Between Reward-Related Ventral Striatal and Amygdala Activation and 1-Year Future Hypo/Mania Trajectories

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Supplemental Methods

Participant Inclusion and Exclusion Criteria

Participants were eligible for inclusion in this longitudinal study if the following criteria were met: ages 18-25 years of age; right handed; actively seeing treatment for psychological distress; are clearly experiencing psychological distress as evidenced by ratings on clinician-rated symptoms scales (HAMA, HRSD or SCID-5-RV); and are not currently on psychotropic medication, have been off psychotropic medication for ≥3 months, or have only been on psychotropic medication for ≤2 weeks. Individuals with psychotic disorders were excluded, as were those with alcohol or substance use disorder or illicit substance use over the last three months, excepting cannabis. Participants were not excluded on the basis of other psychiatric diagnoses.

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 any psychotropic medication for >2 weeks; previous psychotropic medication treatment in the past 3 months. Participants with incomplete imaging data (N=2), excessive task motion (>5mm; N=1), excessive task performance errors or missing post-scan performance data (N=4), and excessive signal loss (>30%; N=4) were excluded from analyses.

Trauma History

The trauma history questionnaire (THQ) is the gold standard assessment for examining lifetime trauma exposure (1). Over 24 items, it measures lifetime trauma exposure in the categories of crime-related events (e.g. robbery), general disasters (e.g. serious car accident, illness, deaths in family), and unwanted physical/sexual experiences (i.e., assaults), with the total score being the sum of traumatic events endorsed. Lifetime trauma exposure for the manuscript analyses was operationalized as the number of traumatic events endorsed during the baseline visit. At subsequent visits, participants repeated the THQ, re-assessing lifetime trauma. To determine interval trauma exposure, we examined the difference in traumatic events reported between baseline and follow-up visits. Participants reporting greater lifetime trauma at either follow-up visit was reported as having trauma exposure during the study period. Trauma exposure during the study period was operationalized as a dichotomous (Yes/No) variable.

Affective Symptoms

Clinician-rated affective symptoms, measured using the HAMA(2), HRSD(3), and YMRS(4) were traditionally scored by a trained clinician with 30 years' experience in clinical research. The HAMA is a 14-item scale measuring the severity of anxiety symptoms. Each item is scored on a scale of 0 (symptom absent) to 4 (severe symptoms), with total HAMA scores ranging from 0 to 56 where higher scores indicate higher anxiety. The HRSD is a 17-item scale measuring the severity of depression symptoms. Nine items are scored on a scale of 0 (absent) to 4 (severe) while eight items are scored on a scale of 0 (absent) to 2 (severe), with total HRSD scores ranging from 0-52 with higher scores indicating higher depression. The YMRS is an 11-item scale measuring the severity of mania symptoms. Four of the items are scored on a 0 (absent) to 8 (severe) scale while the remaining seven items are scored on a 0 (absent) to 4 (severe), with total YMRS scores ranging from 0 to 60, with higher scores indicating higher levels of hypomania/mania.

Self-report affective symptoms were measured using the MASQ-AD(5), MASQ-AA(5), and SHAPS(6). The MASQ is a 90-item instrument with multiple subscales used to assess depression and anxiety symptoms. The MASQ-AD subscale is a 22-item measure (total score 22-110) assessing depression symptoms and the MASQ-AA is a 17-item measure (total score 17-85) assessing anxiety symptoms. Per traditional scoring, subscales are converted to a mean 1-5 metric to account for variability in score range and number of items, with higher scores representing more severe symptoms. The SHAPS is a 14-item subscale measuring severity of anhedonia. The items are scored on a scale of 1 (strongly disagree) to 4 (strongly agree), with items reversed-scored prior to sum (total range 14-56) such that higher scores indicate higher levels of anhedonia.

For clinician-rated measures, 43 individuals completed all three visits;16 completed baseline and 1-year visits. For self-report measures, 42 individuals completed all three visits;12 completed baseline and 1-year visits.

Reliability measures on baseline symptom scales in the larger sample of n=269, which included participants on whom 6-and 12-month follow data were not collected and thus were not included in the present paper, demonstrated excellent reliability for self-report measures (Cronbach's α: MASQ-AD = 0.949; MASQ-AA = 0.929; SHAPS = 0.938). The reliability of the HAMA and HRSD were good (Cronbach's α: HAMA = 0.880; HRSD = 0.904) while the reliability of the YMRS was acceptable (Cronbach's α: YMRS = 0.610), similar to other reports(7, 8).

Medication and Psychotropic Medication Load

Two participants began psychotropic medication in the two weeks prior to initial visit but previously had not been on psychotropic medication for over 3 months, consistent with inclusion criteria. Twelve participants were started on daily psychotropic medications between initial and 12 month follow-up visit; one participant's dosage of an antidepressant increased. Eleven 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.

Participants could pursue psychotropic medication between visits, which was quantified per individual by computing psychotropic medication load(9). 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(9, 10). 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(11). 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(12). 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 at each timepoint was calculated by summing the individual medication codes for each medication category for each individual participant.

The change in psychotropic load between baseline, 6- and 12-month follow-up was calculated as the mean difference in psychotropic load between baseline and follow-up timepoints.

Outpatient Mental Health Treatment

To assess for mental health usage during the study period, participants were asked "Have you ever (since we last saw you) had outpatient treatment from a mental health professional?" as part of a general information supplement. This supplement does not distinguish the profession of the mental health provider nor identify psychotherapeutic modalities. A dichotomous variable (Yes/No) was determined based on participants' affirmative response to the question at either the 6 month or 1 year follow up visits.

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(13). All participants were debriefed regarding the fixed amount outcome at the end of the visit on the day of the neuroimaging assessment.

Reward expectancy (RE), the expected value of a potential reward, and outcome expectancy (OE), the anticipated outcome of a trial, 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(14). 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

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.

While meta-analyses have been used to create task-based activation masks (e.g. Neurosynth(15)), the present a priori mask was based on reward regions delineated in animal and translational research defining the reward circuit. The a priori mask utilized, comprised of bilateral VS, amygdala, ACC, OFC, and vlPFC, is a larger mask compared to meta-analytic masks for monetary reward (see Figure S2B). While a larger mask has the potential to decrease power, we chose the a priori mask in order to thoroughly examine regions in the reward circuit.

To determine whether the observed interactions were present at 6 months, the multivariate linear models were repeated using the change in self-report and clinician-rated symptoms between baseline and 6 months. The change in symptom scores between initial and 6-month visits was used instead of the growth curve, as growth curves cannot be calculated between only two data points. 43 individuals had complete data from clinician-rated symptoms scales and 42 individuals had complete data from self-report symptom scales.

Sequential goodness of fit (SGOF+) testing was used to control for multiple comparisons in multiple linear regression models. SGOF+ testing uses exact binomial tests at a specified power level ($\alpha<0.05$) comparing the observed distribution of *p*-values against the uniform distribution of *p*-values using a maximum likelihood discriminant rule to determine the number of significant tests that could be explained by chance. Observed p-values are determined to be accepted or rejected as significant. As such, SGOF+ testing does not alter the *p*-value and instead simply accepts or rejects it as being significant within the family of tests performed (for details on SGOF+ testing, see (16, 17)).

Supplemental Results

Participants

40 of the 59 participants met criteria for one or more DSM diagnoses at initial visit (see Table S1). Of those 40 participants, 18 met criteria for one diagnosis, 14 met criteria for two diagnoses, 6 met criteria for three diagnoses, and 2 met criteria for four or more diagnoses.

50 (84%) individuals had experienced one or more lifetime traumatic events with a range from 0 to 7 events (see Table S2). Of those experiencing traumatic events, 18 (36%) had experienced crime-related events, 43 (86%) had experienced general disasters, and 22 (44%) had experienced physical/sexual assaults. Over the course of the study period 19 individuals had an increase in their THQ score between baseline and 6- or 12-month follow-up visit, indicating a trauma exposure during the study period. 40 individuals did not have an increase in their trauma exposure, including 13 individuals no change in traumatic events between baseline and follow-up visits and 27 individuals also reported a lower THQ score over the course of follow-up compared to their baseline visit.

Severity of self-report and clinician rated affective and anxiety symptoms at each visit are presented in Table S3.

Effect of Scanner Type

Thirty-two participants were scanned on the 3.0 Tesla Siemens Trio 2 MRI scanner and twenty-seven were scanned on the 3.0 Tesla Siemens Prisma MRI scanner. Within the reward mask at a statistical threshold of $p_{FWE}<0.05$, bilateral VS activation to RPE was detected by both scanners (see Table S4). Right ACC activation to RPE was also significant in the 3.0 Tesla Siemens Trio 2 MRI scanner. Right amygdala activation to RPE was not detected when examining significant activation to RPE in each group separately.

Relationships Within Predictor and Outcome Variables

Neural activation to RPE in the four non- homologous neural regions were as follows: left VS – R amygdala: r=0.445, $p<0.001$; left VS – right ACC: r=0.282, $p=0.033$; right amygdala – right ACC: r= 0.397, $p=0.002$; right amygdala – right VS: r=0.626, $p=<0.001$; right ACC – right VS: r=0.418, $p=0.001$.

1-year clinician-rated anxiety and depressive symptom trajectories correlated with each other and with self-report measures whereas self-report anxiety and depressive symptoms were not correlated (see Table S5). Clinician-rated mania symptom trajectory did not correlate with either clinician-rated or self-report anxiety and depression symptoms.

Effect of Trauma Exposure

Trauma exposure was not related to neural activation to RPE at the initial visit (see Table S6). Number of traumatic events was not associated with affective and anxiety symptom trajectories (see Table S7); however, after controlling for baseline symptoms, trauma exposure was positively associated with greater mania symptoms at 1 year ($F[1,56]=6.023$, $p=0.017$; see Table S8). Trauma exposure was not associated with other self-report or clinician-rated symptoms at 1 year after controlling for baseline symptoms.

Effect of Neural Activation to RPE only

Without accounting for trauma exposure in predictive models, neural activation to RPE in VS, amygdala, and ACC did not predict worsening clinician-rated or self-report symptoms over one year.

Effect of Diagnosis

After adding DSM diagnosis to the second level imaging model for RPE, all regions remained significantly activated (Left VS: $k_E = 120$, $T = 8.31$, $p_{FWE} = 0.001$; Right VS: $k_E = 259$, $T = 8.46$, $p_{FWE} = <0.001$; Right rostral-dorsal ACC: $k_E = 44$, $T = 4.80$, $p_{FWE} = 0.006$; Right amygdala: $k_E = 19$, $T = 5.48$, $p_{FWE} =0.014$). After extracting activation from these regions and repeated the multiple linear regression with clinician-rated affective symptoms and trauma exposure, worsening future mania symptoms was still predicted by greater activation to RPE in the left VS in individuals with lower trauma ($F[1,46]=5.082$, $p=0.029$) and right amygdala in individuals with greater trauma exposure ($F[1,46]=4.184$, $p=0.047$).

Effect of Medication

Two participants had recently started on psychotropic medication in the two weeks prior to initial scan. Twelve participants were started on daily psychotropic medications between initial and 12 month follow-up visit; one participant's dosage of an antidepressant increased. Eleven 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. There was no difference in medication usage based on a history of trauma exposure (t[1,57]=0.373, p=0.711).

In a multivariate ANOVA with affective and anxiety symptom trajectories as dependent variables and psychotropic medication change as the independent variable, medication usage between baseline and follow-up did not influence improvements in self-report anhedonic depression (MASQ-AD: F[1,57]= 0.781, p=0.381), anxious arousal (MASQ-AA: F[1,57]=0.875, p=0.353*),* or anhedonia (SHAPS: F[1,57]=2.296, p=0.471). In a separate repeated measures ANOVA, medication usage between baseline and follow-up similarly did not influence clinician-rated depression (HRSD: F[1,57]=3.087, p=0.084), anxiety (HAMA: F[1,57]=0.624, p=0.433), or mania (YMRS: F[1,57]=0.022, p=0.882) symptoms.

Changes in psychotropic medication did not moderate the interaction between trauma exposure and activation to RPE in the left VS (β=0.5922, p=0.340) and right amygdala (β=0.303, p=0.508) in predicting mania symptom trajectory. After excluding the two individuals who were started on medication prior to baseline imaging, the significance of key findings from the multivariate linear models were unchanged. There was a still significant effect of predictor variables on 1-year clinician-rated hypo/mania trajectory (F[9,43]=2.653, η^2=0.357, p=0.015), but not clinician-rated depression or anxiety trajectory. This effect was specifically predicted by greater left VS activation to RPE (F[1,43]=8.769, η^2=0.169, p=0.005) and lower right amygdala activation to RPE(F[1,43]=4.965, η^2=0.104, p=0.031), as well as the interaction between these regions and trauma exposure. Specifically, trauma exposure interacted with regions with significant RPE neural activation in the left VS(F[1,43]=6.912, η^2=0.138, p=0.012) and right amygdala(F[1,43]=4.080, η^2=0.087, p=0.050) to predict 1-year change in clinician-rated hypo/mania severity.

Effect of Trauma Exposure During the Study Period

To ensure that the main effects were not impacted by trauma exposure during the study period, we repeated the multiple linear regression model examining the relationship between baseline lifetime trauma exposure, neural activation to RPE and future clinician-rated affective and anxiety symptom trajectories and included trauma exposure during the study period as a covariate. After including trauma exposure during the study period, the worsening mania symptoms were still predicted by left VS activation to RPE (F[1,44]=7.479,p=0.009) and right amygdala activation to RPE (F[1,44]=8.687,p=0.005). Given the known biases of self-report measures over time, these results should be interpreted with caution.

Effect of Outpatient Mental Health Treatment

30 participants reported receiving outpatient mental health treatment during the study period. In a multivariate ANOVA with affective and anxiety symptom trajectories as dependent variables and outpatient mental health treatment during the study period as the independent variable, outpatient mental health treatment did not influence trajectories of self-report affective and anxiety symptoms: MASQ-AD ($F[1,57]=2.592$,$p=0.113$); MASQ-AA ($F[1,57]=0.541$,$p=0.465$); SHAPS ($F[1,57]=0.036$,$p=0.849$). Outpatient mental health treatment similarly did not influence clinician-rated affective and anxiety symptom trajectories: HAMA ($F[1,57]=0.344$, $p=0.561$); HRSD ($F[1,57]=0.903$,$p=0.346$); YMRS ($F[1,57]=0.005$,$p=0.944$).

Outpatient mental health treatment during the study period did not moderate the interaction between trauma exposure and activation to RPE in the left VS ($\beta=-0.255$, $p=0.605$) and right amygdala ($\beta=0.076$,$p=0.837$) in predicting mania symptom trajectory.

Relationship Between Neural Activation to RPE and 6-month Symptom Trajectories

To replicate our previous findings(18), we examined the relationship between regions with neural activation to RPE and change in self-report symptoms between baseline and 6 months. Consistent with previous findings, greater left VS activation to RPE was associated with a reduction in SHAPS over 6 months ($F[1,40]=4.428$, $p=0.042$; see Table S9).

Effect of Outliers

After including the three outliers that were >3SD from the mean, the increase in 1-year hypo/mania severity was still predicted by greater left VS activation to RPE($F[1,48]=5.211$, $\eta^2=0.109$,, $p=0.019$) and lower right amygdala activation to RPE($F[1,48]=4.168$, $\eta^2=0.089$, $p=0.035$) and not neural activation to RPE in the right VS or right rostral-dorsal ACC (see Table S12).

Figure S1. Standardized monetary reward task.

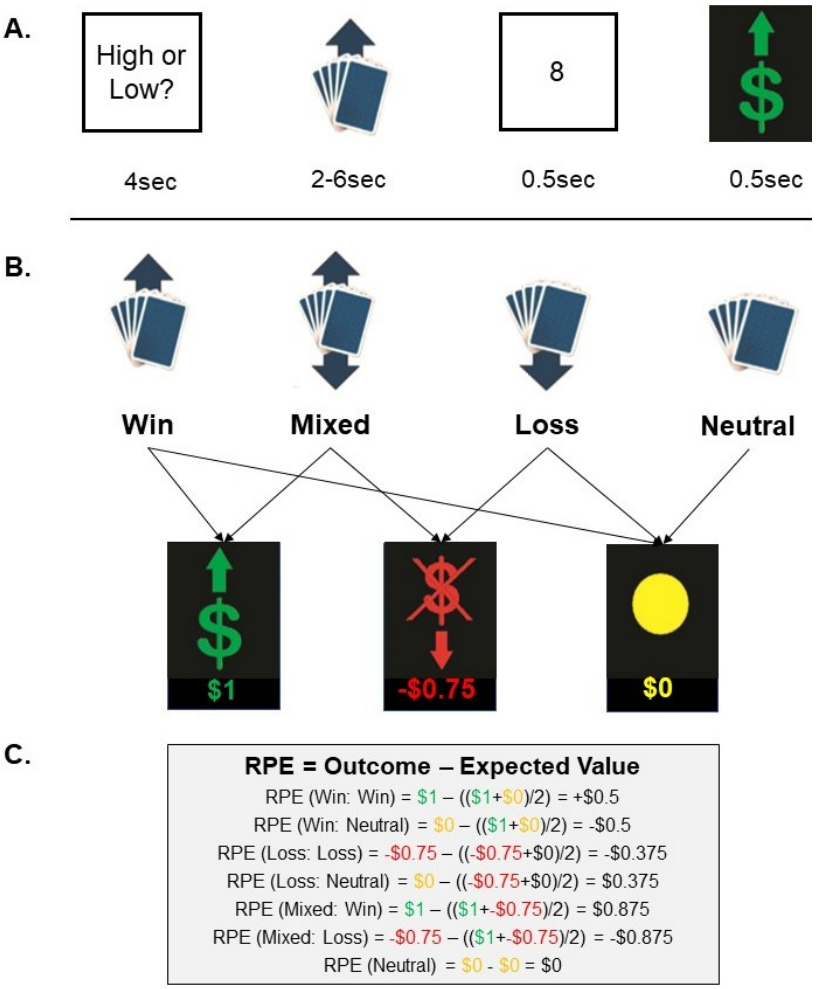

Figure S2. A. Reward mask for voxelwise analyses composed of bilateral anterior cingulate cortex (ACC; Brodmann Area [BA] 32; green), ventrolateral prefrontal cortex (vlPFC; BA47; dark blue), orbitofrontal cortex (OFC; BA11; red), ventral striatum (VS; yellow), and amygdala (light blue). **B.** Overlap of a priori reward mask (red) with Neurosynth meta-analytic mask for "monetary reward" (green), demonstrating mask overlap primarily in VS and rostral-dorsal ACC.

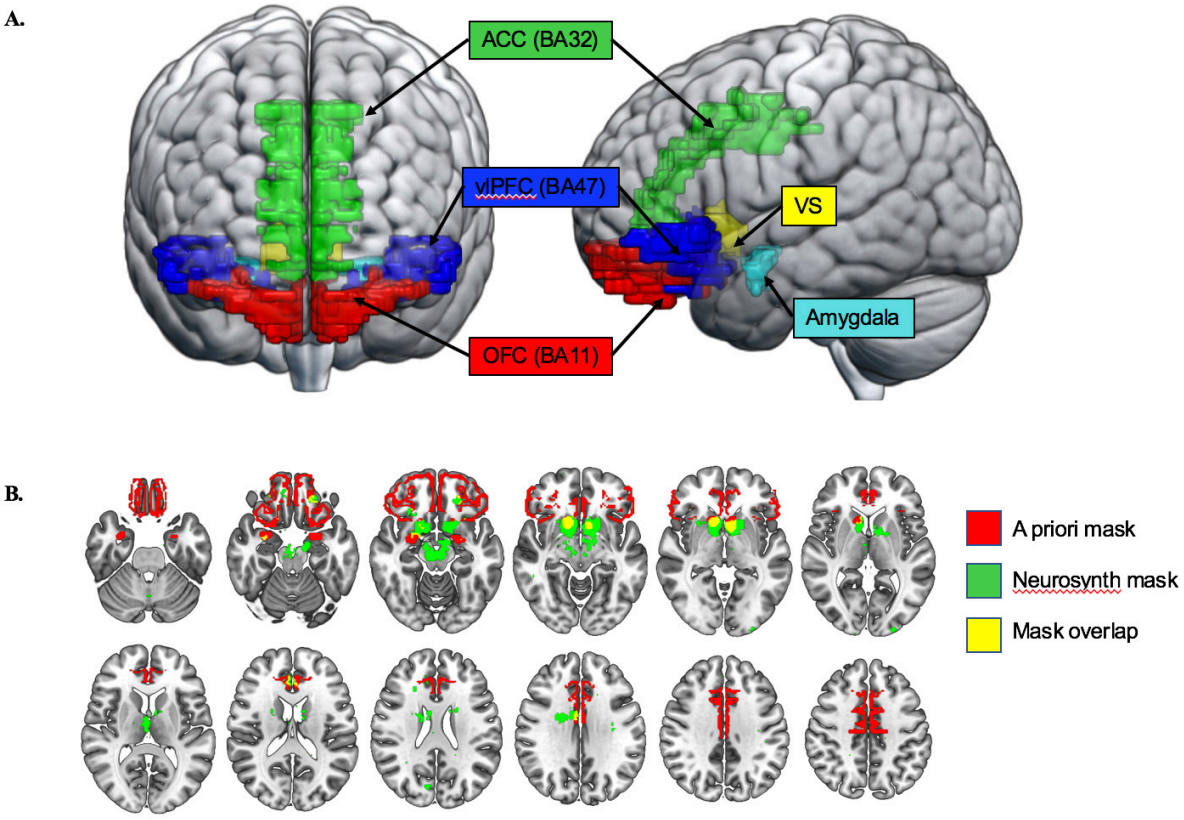

Figure S3. The interaction of trauma exposure and neural activity to RPE predicts the development of depressive and hypo/mania symptoms in the A. right amygdala and B. left ventral striatum, respectively

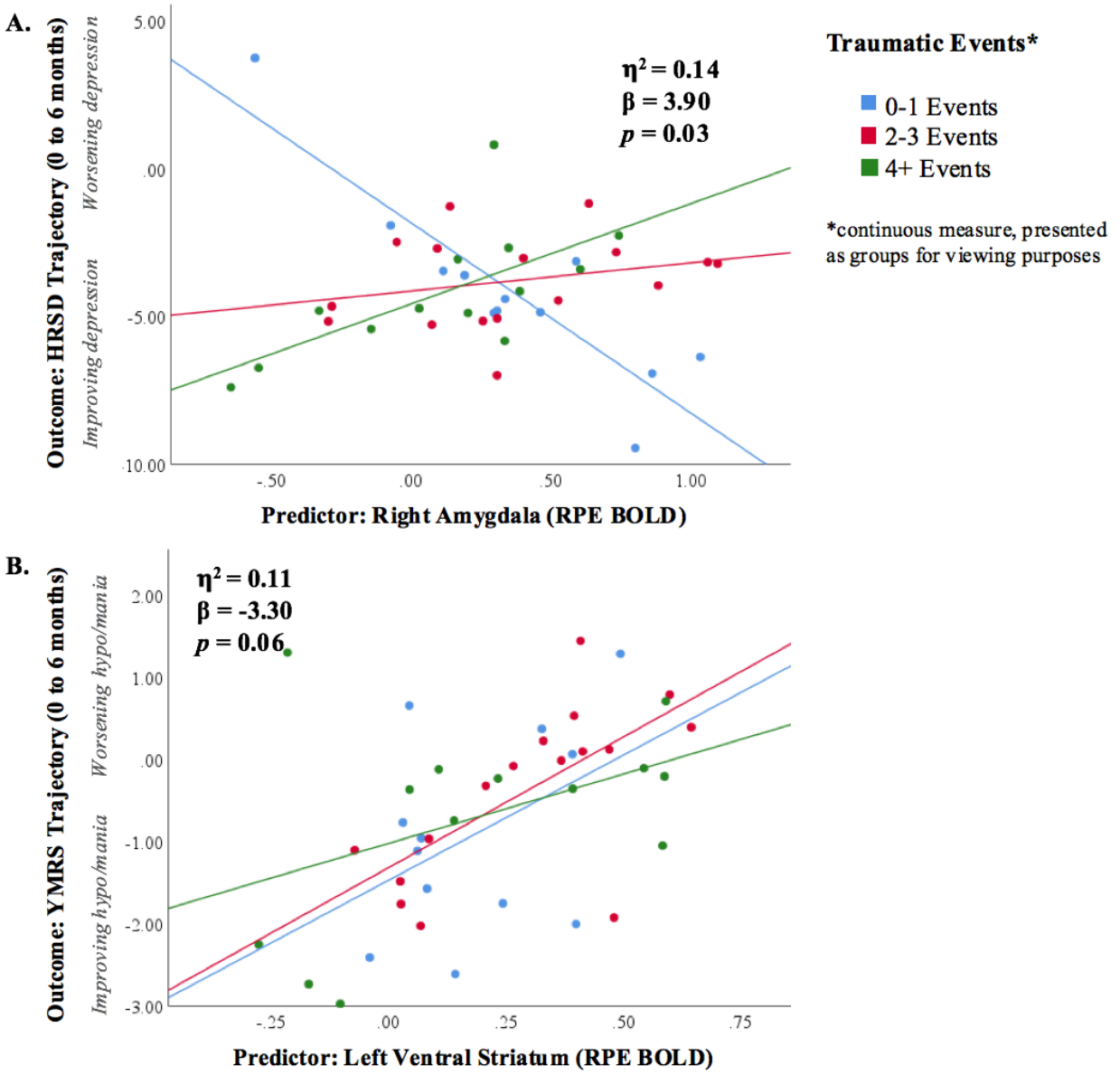

Table S1. Diagnoses* at initial visit

	N
Current Bipolar Disorder	1
Current Unipolar Depressive Disorder	14
Current Anxiety Disorder	30
Current Eating Disorder	3
Current Externalizing Disorder	7
Current Trauma-Related Disorder	3
Current only Sleep Disorder	11
Current only Somatoform Disorder	3
Current only Adjustment Disorder	2

*some participants have more than one diagnosis (N=22)

Table S2. Lifetime trauma exposure at initial visit

Number of Lifetime Traumatic Events	**N**
0 events	9
1 event	9
2 events	13
3 events	13
4 events	9
5+ events	6

Table S3. Descriptive characteristics of affective and anxiety symptoms

	0 months		6 months		12 months		1-Year Slope
	Range	Mean ± SD	Range	Mean ± SD	Range	Mean ± SD	Mean ± SD
HAMA	0 - 27	11.76 ± 6.86	0 – 24	8.93 ± 6.22	0 – 23	7.53 ± 5.75	-2.14 ± 1.29
HRSD	2 – 30	14.20 ± 6.74	0 – 24	11.23 ± 4.93	0 – 26	10.32 ± 6.27	-1.98 ± 0.55
YMRS	0 – 9	3.03 ± 2.16	0 – 9	2.42 ± 2.49	0 – 10	2.58 ± 2.88	-0.22 ± 1.01
MASQ-AD	1.73 – 4.68	3.40 ± 0.65	1.64 – 4.91	3.00 ± 0.76	1.09 – 4.59	2.87 ± 0.81	-0.27 ± 0.02
MASQ-AA	1 – 4.18	1.67 ± 0.72	1 – 4.12	1.52 ± 0.64	1 – 2.64	1.46 ± 0.51	-0.10 ± 0.08
SHAPS	14 - 43	26.76 ± 6.98	14 - 52	23.36 ± 7.41	14 - 41	23.02 ± 7.31	-2.00 ± 2.20

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

Table S4. Differences in neural activation to reward prediction error (RPE) between scanner types thresholded at p_{FWE}<0.05, kE > 20 voxels

Region	Hemisphere	Voxels	T-score	x	y	z
3.0 Tesla Siemens Trio 2 MRI						
Ventral Striatum	R	226	6.47	12	8	-6
	L	71	6.31	-12	12	-8
Anterior Cingulate Cortex	R	99	5.23	6	44	2
3.0 Tesla Siemens Prisma MRI						
Ventral Striatum	R	84	5.91	8	16	-8
	L	22	5.03	-10	14	-8

Table S5. Correlations between 1-year symptom trajectories

1-Year Symptom Trajectory		HAMA	HRSD	YMRS	MASQ-AD	MASQ-AA	SHAPS
HAMA	r	-	0.869	0.056	0.406	0.688	0.495
	p	-	<0.001	0.672	0.001	<0.001	<0.001
HRSD	r	-	-	-0.009	0.530	0.576	0.407
	p	-	-	0.957	<0.001	<0.001	0.001
YMRS	r	-	-	-	-0.050	-0.137	0.144
	p	-	-	-	0.705	0.302	0.278
MASQ-AD	r	-	-	-	-	0.188	0.020
	p	-	-	-	-	0.154	0.883
MASQ-AA	r	-	-	-	-	-	0.425
	p	-	-	-	-	-	0.001
SHAPS	r	-	-	-	-	-	-
	p	-	-	-	-	-	-

Table S6. Association of trauma to reward activation during RPE†

		β	Partial η^2	*p*-value	95% CI LL	95% CI UL
Trauma Exposure	Left Ventral Striatum	-0.021	0.016	0.350	-0.066	0.024
	Right Amygdala	-0.036	0.014	0.386	-0.117	0.046
	Right ACC	-0.001	<0.001	0.977	-0.079	0.077
	Right Ventral Striatum	0.011	0.003	0.672	-0.041	0.063

†intercept included in each model

Table S7. Association of trauma to affective symptoms trajectory between 0 and 12 months

		β	Partial η^2	*p*-value	95% CI LL	95% CI UL
Clinician Rated Symptoms						
Trauma Exposure	HAMA	-0.018	<0.001	0.870	-0.234	0.198
	HRSD	-0.01	0.001	0.825	-0.103	0.082
	YMRS	0.064	0.010	0.449	-0.104	0.232
Self-Report Symptoms						
Trauma Exposure	MASQ-AD	0.002	0.026	0.231	-0.002	0.007
	MASQ-AA	0.001	0.001	0.843	-0.012	0.014
	SHAPS	-0.322	0.055	0.077	-0.681	0.036

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

Table S8. Association of trauma to affective symptoms at 12 months†

	β	Partial η^2	*p*-value	95% CI LL	95% CI UL
Clinician Rated Symptoms at 12 Months					
HAMA	-0.138	0.006	0.757	-1.030	0.753
HDRS	-0.027	0.006	0.957	-1.011	0.958
YMRS	**0.489**	**0.118**	**0.017**	**0.090**	**0.889**
Self-Report Symptoms at 12 Months					
MASQ-AD	-0.064	0.019	0.327	-0.192	0.065
MASQ-AA	-0.028	0.011	0.376	-0.091	0.035
SHAPS	-0.818	0.027	0.179	-2.025	0.389

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

†Baseline affective and anxiety symptoms were controlled for in each model

Table S9. 1-year Self-Report Multivariate Linear Model showing association of neural activation during RPE with self report affective symptoms between 0 and 12 months

	Univariate Tests[a]		*Predictor-Outcome Relationships*						
	Adjusted R^2	*p*-value		F	β	Partial η^2	*p*-value	95% CI LL	95% CI UL
Anhedonic Depression (MASQ-AD)	-0.038	0.636	Intercept	701.045	-0.289	0.940	<0.001	-0.311	-0.267
			Trauma Exposure	1.108	0.004	0.024	0.298	-0.003	0.010
			Left Ventral Striatum	0.231	-0.018	0.005	0.633	-0.094	0.058
			Right Amygdala	0.001	0.001	<0.001	0.979	-0.039	0.040
			Right ACC	0.275	0.011	0.006	0.603	-0.030	0.051
			Right Ventral Striatum	0.557	0.034	0.012	0.459	-0.057	0.124
			Left Ventral Striatum * Trauma	0.246	0.007	0.005	0.622	-0.022	0.036
			Right Amygdala * Trauma	0.048	0.002	0.001	0.827	-0.013	0.016
			Right ACC * Trauma	1.06	-0.008	0.023	0.309	-0.024	0.008
			Right Ventral Striatum * Trauma	0.065	-0.005	0.001	0.800	-0.041	0.032
Anxious Arousal (MASQ-AA)	-0.091	0.865	Intercept	11.185	-0.120	0.199	0.002	-0.192	-0.048
			Trauma Exposure	0.993	0.011	0.022	0.324	-0.011	0.033
			Left Ventral Striatum	0.097	-0.039	0.002	0.757	-0.289	0.212
			Right Amygdala	0.139	0.024	0.003	0.711	-0.106	0.154
			Right ACC	0.113	-0.022	0.003	0.738	-0.157	0.112
			Right Ventral Striatum	0.669	0.121	0.015	0.418	-0.177	0.418
			Left Ventral Striatum * Trauma	0.001	0.001	<0.001	0.980	-0.094	0.096
			Right Amygdala * Trauma	0.002	-0.001	<0.001	0.963	-0.049	0.047
			Right ACC * Trauma	0.002	0.004	0.001	0.873	-0.048	0.056
			Right Ventral Striatum * Trauma	0.821	-0.053	0.018	0.370	-0.172	0.065
Anhedonia (SHAPS)	-0.109	0.924	Intercept	3.432	-1.939	0.071	0.070	-4.047	0.169
			Trauma Exposure	0.025	-0.050	0.001	0.876	-0.696	0.595
			Left Ventral Striatum	0.019	0.505	<0.001	0.890	-6.797	7.808
			Right Amygdala	0.001	0.064	<0.001	0.973	-3.719	3.846
			Right ACC	0.047	0.421	0.001	0.829	-3.494	4.336
			Right Ventral Striatum	0.144	1.632	0.003	0.706	-7.039	10.303
			Left Ventral Striatum * Trauma	0.006	0.103	<0.001	0.941	-2.672	2.879
			Right Amygdala * Trauma	0.003	-0.036	<0.001	0.959	-1.439	1.367
			Right ACC * Trauma	0.198	-0.334	0.004	0.658	-1.845	1.177
			Right Ventral Striatum * Trauma	0.181	-0.730	0.004	0.673	-4.190	2.729

[a]These statistics refer to the effect size and significance of the univariate tests nested in the multivariate linear model

MASQ-AA, Mood and Anxiety Symptom Questionnaire – Anxious Arousal; MASQ-AD, Mood and Anxiety Symptom Questionnaire – Anhedonic Depression; SHAPS, Snaith Hamilton Pleasure Scale

Table S10. 6 month Clinician Rated Multivariate Linear Model showing association of neural activation during RPE with clinician rated affective symptoms between 0 and 6 months

	Univariate Tests[a]		*Predictor-Outcome Relationships*						
	Adjusted R^2	*p*-value		F	β	Partial η^2	*p*-value	95% CI LL	95% CI UL
Anxiety (HAMA)	-0.104	0.801	Intercept	0.853	-2.803	0.027	0.363	-8.991	3.385
			Trauma Exposure	0.046	-0.190	0.001	0.831	-1.988	1.609
			Left Ventral Striatum	0.059	3.011	0.002	0.810	-22.316	28.338
			Right Amygdala	1.331	-6.235	0.041	0.257	-17.257	4.788
			Right ACC	0.574	-5.361	0.018	0.454	-19.795	9.073
			Right Ventral Striatum	0.292	6.730	0.009	0.593	-18.669	32.129
			Left Ventral Striatum * Trauma	0.698	-3.565	0.022	0.410	-12.269	5.139
			Right Amygdala * Trauma	2.102	2.867	0.063	0.157	-1.167	6.902
			Right ACC * Trauma	1.358	3.081	0.042	0.253	-2.310	8.472
			Right Ventral Striatum * Trauma	0.184	-2.115	0.006	0.671	-12.167	7.937
Depression (HRSD)	-0.055	0.644	Intercept	0.929	-2.545	0.029	0.343	-7.931	2.841
			Trauma Exposure	0.339	-0.447	0.011	0.565	-2.012	1.118
			Left Ventral Striatum	0.01	1.085	<0.001	0.921	-20.959	23.130
			Right Amygdala	4.712	-10.211	0.132	0.038	-19.805	-0.617
			Right ACC	0.367	3.732	0.012	0.549	-8.831	16.295
			Right Ventral Striatum	0.032	1.931	0.001	0.860	-20.176	24.038
			Left Ventral Striatum * Trauma	0.499	-2.623	0.016	0.485	-10.199	4.953
			Right Amygdala * Trauma	5.125	3.898	0.142	0.031	0.386	7.409
			Right ACC * Trauma	0.119	-0.794	0.004	0.732	-5.487	3.898
			Right Ventral Striatum * Trauma	0.018	0.580	0.001	0.893	-8.169	9.330
Mania (YMRS)	-0.009	0.491	Intercept	0.382	-0.755	0.012	0.541	-3.249	1.738
			Trauma Exposure	0.323	-0.202	0.010	0.574	-0.927	0.523
			Left Ventral Striatum	2.823	8.409	0.083	0.103	-1.798	18.615
			Right Amygdala	1.208	-2.394	0.038	0.280	-6.835	2.048
			Right ACC	0.857	-2.640	0.027	0.362	-8.457	3.177
			Right Ventral Striatum	0.019	-0.698	0.001	0.890	-10.933	9.538
			Left Ventral Striatum * Trauma	3.683	-3.301	0.106	0.064	-6.808	0.207
			Right Amygdala * Trauma	1.905	1.100	0.058	0.177	-0.525	2.726
			Right ACC * Trauma	1.122	1.128	0.035	0.298	-1.044	3.301
			Right Ventral Striatum * Trauma	0.268	1.027	0.009	0.609	-3.024	5.078

[a]These statistics refer to the effect size and significance of the univariate tests nested in the multivariate linear model
HAMA, Hamilton Anxiety Rating Scale; HRSD, Hamilton Rating Scale for Depression; YMRS, Young Mania Rating Scale

Table S11. 6 month Self Report Multivariate Linear Model showing association of neural activation during RPE with self report affective symptoms between 0 and 6 months

	Univariate Tests[a]		*Predictor-Outcome Relationships*						
	Adjusted R^2	*p*-value		F	β	Partial η^2	*p*-value	95% CI LL	95% CI UL
Anhedonic Depression (MASQ-AD)	-0.064	0.808	Intercept	5.231	-0.407	0.203	0.028	-0.767	0.046
			Left Ventral Striatum	0.863	-0.665	0.018	0.359	-2.115	0.786
			Right Amygdala	0.642	-0.261	0.019	0.428	-0.923	0.400
			Right ACC	<0.001	0.000	<0.001	0.999	-0.589	0.590
			Right Ventral Striatum	0.942	0.673	0.035	0.338	-0.733	2.079
Anxious Arousal (MASQ-AA)	-0.022	0.544	Intercept	0.784	-0.116	0.043	0.382	-0.382	0.150
			Left Ventral Striatum	0.012	0.057	0.001	0.915	-1.013	1.126
			Right Amygdala	0.186	0.104	0.005	0.669	-0.384	0.591
			Right ACC	1.378	-0.251	0.034	0.248	-0.686	0.183
			Right Ventral Striatum	0.503	-0.363	0.011	0.483	-1.400	0.674
Anhedonia (SHAPS)	0.029	0.290	Intercept	1.548	-2.004	0.086	0.222	-5.270	1.263
			Left Ventral Striatum	4.428	-13.639	0.099	0.042	-26.784	-0.494
			Right Amygdala	0.474	2.035	0.012	0.496	-3.960	8.031
			Right ACC	0.187	-1.139	0.003	0.668	-6.477	4.199
			Right Ventral Striatum	0.757	5.467	0.029	0.390	-7.277	18.212

[a]These statistics refer to the effect size and significance of the univariate tests nested in the multivariate linear model
HAMA, Hamilton Anxiety Rating Scale; HRSD, Hamilton Rating Scale for Depression; YMRS, Young Mania Rating Scale

Table S12. Association of neural activation during RPE with clinician-rated affective symptom trajectory between 0 and 12 months including outliers

	Univariate Tests[a]		*Predictor-Outcome Relationships*						
	Adjusted R^2	*p*-value		F	β	Partial η^2	*p*-value	95% CI LL	95% CI UL
Anxiety (HAMA)	-0.135	0.998	Intercept	24.012	-2.188	0.312	<0.001	-3.130	-1.246
			Trauma Exposure	0.175	0.026	0.001	0.874	-0.299	0.351
			Left Ventral Striatum	0.053	0.089	<0.001	0.964	-3.885	4.063
			Right Amygdala	0.265	-0.969	0.017	0.371	-3.127	1.189
			Right ACC	0.030	0.194	0.002	0.767	-1.112	1.500
			Right Ventral Striatum	0.499	1.438	0.010	0.499	-2.806	5.683
			Left Ventral Striatum * Trauma	0.211	-0.017	<0.001	0.981	-1.415	1.381
			Right Amygdala * Trauma	0.988	0.565	0.041	0.158	-0.227	1.357
			Right ACC * Trauma	0.026	0.016	<0.001	0.954	-0.531	0.562
			Right Ventral Striatum * Trauma	0.910	-0.822	0.02	0.33	-2.504	0.859
Depression (HRSD)	-0.142	0.993	Intercept	105.928	-2.029	0.676	<0.001	-2.436	-1.621
			Trauma Exposure	0.049	0.008	<0.001	0.91	-0.133	0.149
			Left Ventral Striatum	0.111	-0.182	0.001	0.833	-1.902	1.538
			Right Amygdala	0.003	-0.104	0.001	0.823	-1.038	0.829
			Right ACC	<0.001	0.011	<0.001	0.968	-0.554	0.577
			Right Ventral Striatum	0.525	0.647	0.010	0.482	-1.190	2.484
			Left Ventral Striatum * Trauma	0.341	0.106	0.003	0.727	-0.499	0.711
			Right Amygdala * Trauma	0.121	0.090	0.006	0.6	-0.253	0.433
			Right ACC * Trauma	0.127	-0.031	0.001	0.796	-0.267	0.206
			Right Ventral Striatum * Trauma	0.497	-0.257	0.010	0.481	-0.985	0.471
Mania (YMRS)	0.115	0.085	Intercept	2.944	-0.480	0.044	0.143	-1.127	0.168
			Trauma Exposure	0.014	-0.047	0.004	0.673	-0.271	0.176
			Left Ventral Striatum	5.153	3.471	0.120	0.014	0.739	6.203
			Right Amygdala	4.226	-1.802	0.111	0.018	-3.285	-0.318
			Right ACC	4.043	0.969	0.089	0.035	0.071	1.867
			Right Ventral Striatum	1.511	-1.848	0.033	0.209	-4.766	1.071
			Left Ventral Striatum * Trauma	4.094	-1.157	0.109	0.019	-2.117	-0.196
			Right Amygdala * Trauma	2.824	0.586	0.089	0.035	0.042	1.131
			Right ACC * Trauma	3.071	-0.274	0.043	0.149	-0.649	0.102
			Right Ventral Striatum * Trauma	3.276	1.030	0.063	0.080	-0.126	2.186

[a]These statistics refer to the effect size and significance of the univariate tests nested in the multivariate linear model
HAMA, Hamilton Anxiety Rating Scale; HRSD, Hamilton Rating Scale for Depression; YMRS, Young Mania Rating Scale

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