Methods

Participants

Inclusion criteria

All participants were right-handed (as assessed by the Edinburgh scale; 1). Exclusion criteria included a lifetime history of severe neurological illnesses, schizophrenia, and a history of alcohol or drug abuse or dependence within the past 6 months, use of painkillers within the last month, pregnancy and presence of counter-indications for MRI scanning (mainly metal in the body and claustrophobia).

Questionnaires

BSL-23

The Borderline Symptom List short form (BSL-23), French version (2), is a 23-item self-rated scale which quantitatively assesses symptoms of BPD, based on the DSM-IV 3. This is a unidimensional scale and items are rated on a 5-point Likert scale from 0 (not at all) to 4 (very much).

CTQ

Childhood Trauma Questionnaire (CTQ; 4) French version, is a 28-item self-rated scale which quantifies degree of childhood trauma in the home. It consists of 5 subscales: emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect. Responses are measured on a 5-point Likert scale (1 = never true, 2 = rarely true, 3 = sometimes true, 4 = often true, 5 = very often true). Each subscale is represented by five questions with a score range from 5 to 25.

BDI-II short version

The Beck Depression Inventory (BDI; 5) used contains 13 self-rated items on a scale of 0–3 to give score of 0–39.

MADRS

The Montgomery and Asberg Depression Rating Scale (MADRS; 6) contains 10 items rated on a scale of 0–6 with anchors at two-point intervals to give a score of 0–60. It is based on observation of the patient as well as an interview.

MRI data acquisition and analysis

ART repair

To account for residual movement artefacts after realignment, Artefact Detection Toolbox (ART; http://web.mit.edu/swg/software.htm) was used. Specifically, an image was defined as an outlier (artefact) image if the head displacement was greater than 0.2 mm in the x, y, or z direction, if the rotational displacement was greater than 0.02 radians, from the previous image, or if the global mean intensity in the image was greater than 9 standard deviations from the mean image intensity for the entire scan. Any image that was identified as an outlier was entered into the SPM model as a regressor of no interest. No participant had more than 5% of total outlier scans.

Medication load

We computed an index of medication load for each BPD participant based on the summation of the different dosages of each medication. To do so, we first coded the dosage as absent (0), low (1) or high (2) for each medication separately. For antidepressants, we used a previously employed approach (7) that differentiates between 4 levels of dosages, which we then converted into low-dose (levels 1 and 2) and high-dose (levels 3 and 4). For antipsychotic treatments, we converted the doses into chlorpromazine dose equivalents, and coded as 0, 1 or 2, for no medication, up to mean effective daily dose, or above the daily dose as defined by Davis and Chen (2004). Anxiolytic (lorazepam and alprazolam) psychostimulant (methylphenidate) doses were similarly coded as 0, 1 or 2, with reference to the midpoint of the Physician's Desk Reference-recommended daily dose range. Finally, we generated a composite measure of total medication load, reflecting dose and variety of different medications taken, by summing all individual medication codes for each medication category for each individual BPD participant.

To test the effects of Medication load on our significantly activated brain regions from Model 1 and 2 (i.e. full-factorial analysis for the cues and feedbacks), we conducted a series of repeated measures ANCOVAs using the beta estimates extracted from each region individually. These ANCOVAs included the covariate "Medication Load" and the within-subjects factor 'Social Condition' (social, non-social) for the cues, and 'Social Condition' (social, non-social) x 'Reward Outcome' (win, lose) for the feedbacks. We specifically checked for an effect in the relevant interactions (i.e. Social Condition x Medication Load for the cues, and Social Condition x Reward Outcome x Medication Load for the feedbacks). Additionally, to test the effects of medication on Model 3 (i.e. an independent samples t-test), we correlated the extracted beta estimates with medication load.

Comorbid disorders

To test the effects of comorbid disorders (i.e. patients suffering from current depression and ADHD) on our significantly activated brain regions from Model 1 and 2 (i.e. full-factorial analysis for the cues and feedbacks), we conducted a series of repeated measures ANOVAs using the beta estimates extracted from each region individually. These ANOVAs included the between subjects factors "Comorbidity" (yes, no) and the within-subjects factor 'Social Condition' (social, non-social) for the cues, and 'Social Condition' (social, non-social) x 'Reward Outcome' (win, lose) for the feedbacks. We specifically checked for an effect in the relevant interactions (i.e. Social Condition x Comorbidity for the cues, and Social Condition x Reward Outcome x Comorbidity for the feedbacks) as well as the main effects of Comorbidity. To understand the effects of comorbidity on the pgACC activity (Figure 4 in the main paper), we conducted independent samples t-tests between BPD patients with and without each disorder on the extracted beta weights.

Results

Medication Load Results

All ANCOVAs/correlations yielded non-significant results in all relevant main effects and interactions (all p>.06; Supplemental Table S4). Taken together, we can suggest that medication did not have a large effect on the neural activations reported here. It should also be noted, that 3 participants were prescribed benzodiazepines. To ensure there was not a large confound from these patients, we also re-ran the neuroimaging analyses listen in the main text. Across all 4 models, there was a very limited difference when removing the patients (e.g. a reduction of 5-6 voxels).

Comorbid Disorders Results

All ANOVAs/t-tests yielded non-significant results in all relevant main effects and interactions (Supplemental Table S5).

Model 4- Independent Samples T-Test Regression Analysis: Social Win > Non-social Win Amygdala Regression

As mentioned in the main text, we conducted an additional analysis to understand the effects of the social win>non-social win amygdala betas on the processing of the cues. Specifically, we entered these beta estimates from the bilateral amygdala ROI as a covariate in an independent samples t-test for social>non-social cues, for each group separately (Figure S1). This analysis did not reveal any significantly activated voxels when contrasting the regressor for either group independently (i.e. BPD: social cue>non-social cue, HC: social cue>non-social cue), nor for the comparison between the two (i.e. BPD>HC; social cue>non-social cue, HC>BPD; social cue>non-social cue).

References

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8. Davis JM, Chen N (2004): Dose response and dose equivalence of antipsychotics. *J Clin Psychopharmacol*. 24: 192–208.

Figures and Tables

Table S1: Relevant whole brain t-contrast results (p>.001, k>88) for model 1 (i.e. social>non-social cues)					
Contrast	Anatomic Region	Cluster size	Peak MNI coordinates		
			x	y	z
Positive Main Effect of Group (i.e. BPD>HC)	No Significantly Activated Voxels				
Negative Main Effect of Group (i.e. HC>BPD)	No Significantly Activated Voxels				
Positive Interaction Group x Cue (i.e. BPD>HC; social>non-social Cue)	R. STS	95	60	-37	-14
Negative Interaction Group x Cue (i.e. HC>BPD; social>non-social cue)	No Significantly Activated Voxels				

Table S2: Relevant whole brain t-contrast results (p>.001, k>88) for model 2 (i.e. social>non-social feedbacks)					
Contrast	Anatomic Region	Cluster size	Peak MNI coordinates		
			x	y	z
All Group Main Effects and Interactions	No significantly activated voxels				

Table S3. Relevant whole brain t-contrast results (p>.001, k>88) for model 3 (i.e. social>non-social cue amygdala regression)					
Contrast	Anatomic Region	Cluster size	Peak MNI coordinates		
			x	y	z
Positive BPD regression	No significantly activated voxels				
Negative BPD regression	pgACC/R. Middle Frontal gyrus	195	9	38	10
			3	7	13
	L. Putamen/L. Caudate	103	-24	-4	4
	L. Middle Frontal Gyrus	92	-27	47	13
BPD>HC	No significantly activated voxels				
HC>BPD	pgACC	93	9	41	10

Table S4. The effects of Medication load on significantly activated brain regions in the BPD group (N=21)			
Model 1: Cues			
	Region: Right STS		
		F	p
	Main effect of Medication Load	0.387	0.541
	Social Condition x Medication Load	0.298	0.592
Model 2: Feedbacks			
	Region: Bilateral Amygdala		
		F	p
	Main effect of Medication Load	0.113	0.740
	Social Condition x Medication Load	0.017	0.898
	Reward Outcome x Medication Load	1.982	0.175
	Social Condition x Reward Outcome x Medication Load	0.697	0.414
Model 3: Cue regression analysis			
	Region: pgACC		
		r	p
	Correlation with Medication Load	-0.384	0.086

Table S5. The effects of comorbidity (depression and ADHD) on significantly activated brain regions in the BPD group (N=21)					
Model 1: Cues					
	Region: Right STS				
		Depression		ADHD	
		F	p	F	p
	Social Condition x Comorbidity	0.76	0.39	1.95	0.18
	Main effect of Comorbidity	0.50	0.49	0.30	0.59
Model 2: Feedbacks					
	Region: Bilateral Amygdala				
		Depression		ADHD	
		F	p	F	p
	Social Condition x Comorbidity	1.08	0.31	0.32	0.58
	Reward Outcome x Comorbidity	0.53	0.48	0.55	0.47
	Social Condition x Reward Outcome x Comorbidity	0.20	0.66	0.81	0.38
	Main effect of Comorbidity	0.11	0.75	1.47	0.24
Model 3: Cue analysis					
	Region: pgACC				
		Depression		ADHD	
		t (df)	p	t (df)	p
	Independent samples t-test	0.86 (19)	0.40	-0.02 (19)	0.98

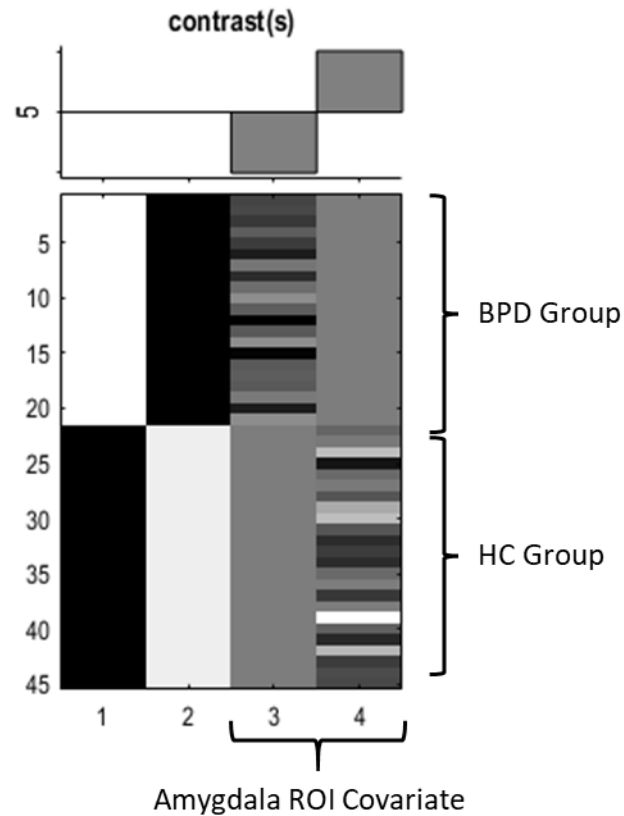| Table S6. CTQ Amygdala Correlations							
		CTQ total	emotional abuse	physical abuse	sexual abuse	emotional neglect	physical neglect
Bilateral amygdala social loss>non-social loss beta estimates	rho	-0.35	-0.25	-.46	0.02	-0.35	-0.32
	p	0.12	0.27	0.04	0.93	0.12	0.16
	N	21	21	21	21	21	21

Figure S1: SPM design matrix from Model 3 showing the group covariate contrast that produced the pgACC activation. The beta estimates from the amygdala ROI during the social loss (vs non-social loss) feedback were entered as a covariate into an independent samples t-test for the contrast social cue>non-social cue contrast. The example shows here the group (HC>BPD) contrast which produced the pgACC activation explained in in the main paper (i.e. Figure 4).