Supplemental Information

Supplemental Methods

Reward Task

Participants were scanned while performing a number guessing reward task[1] that reliably activates fronto-striatal reward circuitry, and has been used previously in neuroimaging studies of adults and youth with mood disorders.[1,2] The task required participants to guess whether the upcoming number is smaller or greater than 5. Participants were told that they would receive $1 if they were correct and lose $0.50 if they were incorrect, and that they could win up to $10 in the game. If a participant correctly guessed the number, a green upward arrow appears (Figure 1). If an incorrect guess was made, a red downward arrow appeared. There were fifteen 7-sec Win trials, fifteen 7-sec Loss trials, and eighteen 6-sec Control trials. Control trials did not involve any guessing (and, consequently, no winning or losing) and required pressing a button when an asterisk appeared on the screen. Each Win and Loss trial comprised a 3-sec guessing period when participants decided whether the upcoming number was greater/lower than 5. The actual number was then presented for 500 ms, followed by a 500 ms green upward arrow (for positive feedback) or 500 ms red downward arrow (for negative feedback), and then a 3,000 ms inter-stimulus interval fixation cross. Outcome was fixed for all participants so that each participant won $10. Previous studies using this task showed that participants were unaware of the fixed outcome of the task and believed that their performance was due to chance.[1]

fMRI data acquisition and analysis

fMRI data were acquired using a Siemens MAGNETOM TrioTim 3T MR system. A high-resolution structural image (1x1x1 mm) was acquired using MPRAGE (TR = 2300 msec, TE = 3.93 msec, FOV =256 , FA = 9°, 192 slices). Functional data were collected using a gradient-echo, echo-planar sequence (voxel size: 3.2x3.2x3.1mm, TR=2000 msec, TE=28 msec, FOV=205, FA=90°, 38 slices). These data comprised 178 volumes (TRs). Field maps were collected at the 4x4x4 mm

resolution using a gradient echo sequence (TR=488 msec, TE1=4.92ms, TE2=7.38ms, FOV=256, FA=60°, 32 slices). Data preprocessing and co-registration to the MNI152_T1_2mm template was done to using FSL5.0.2 (www.fmrib.ox.ac.uk/fsl).

The images were preprocessed and analyzed using FSL 5.0.2 (www.fmrib.ox.ac.uk/fsl). Preprocessing included motion correction with MCFLIRT,[3] non-brain removal using BET,[4] fieldmap-based EPI unwarping using PRELUDE+FUGUE,[5] spatial smoothing with a Gaussian kernel of FWHM 6mm; grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor; high-pass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma=100.0s). A field map image used in the fMRI data analysis was prepared using the fsl_prepare_fieldmap script. No slice-timing correction was applied. The high-resolution structural images were segmented using the fsl_anat script to separate white matter, grey matter and cerebrospinal fluid (CSF), and to also segment subcortical structures. The white matter and CSF masks were then coregistered with functional images, and their timecourses were extracted from the preprocessed functional data for further analyses. Motion outliers (time points where the fMRI signal was corrupted due to subject motion) were identified using the fsl_motion_outliers script (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLMotionOutliers). A confound matrix from this analysis was then combined with the white matter and CSF time courses and used as a confound variable of no interest in the first-level analyses.

Co-registration was carried out using FLIRT (FMRIB's Linear Image Registration Tool[3,6] and FNIRT (FMRIB's Non-linear Image Registration Tool.[7] BOLD images were registered to the high-resolution structural (MPRAGE) images using FLIRT, the high-resolution images were registered to the MNI152_T1_2mm template using FNIRT, and the two resulting transformations were concatenated and applied to the original BOLD image (http://www.fmrib.ox.ac.uk/fsl/flirt/gui.html) to transform it to MNI space. The registration quality was checked for each subject. In rare cases FNIRT was substituted with FLIRT to obtain a better quality registration.

Preprocessed data were submitted to a first-level GLM analysis implemented using FEAT (FMRI Expert Analysis Tool, v6.0). The model included four regressors (Win, Loss, and Control trials, and Instructions). The magnitude of activation was examined for each of these conditions and to the Win-Control, Loss-Control, and Win-Loss contrasts. All group-level analyses were conducted using FLAME1 (FMRIB's Local Analysis of Mixed Effects). Whenever possible, gender, age, IQ, and presence/absence of psychopathology were used as covariates in the group-level analyses in order to factor out the effects of these variables. Significant clusters of activation were determined by thresholding Z-statistic images in the reward circuitry mask using voxel-wise $p<0.001$ ($z>3.09$) and a corrected cluster significance threshold of $p<0.05$.[8]

Supplemental Results

Post-hoc comparison of activation and connectivity measures in participants without psychopathology and unmedicated participants

RFP activation was significantly greater in BO than in HC (participants without psychopathology: $t(39)=4.3$, $p<0.001$; unmedicated participants: $t(45)=3.4$, $p=0.001$) and was also significantly greater in NBO than in HC (participants without psychopathology: $t(37)=2.9$, $p=0.006$; unmedicated participants: $t(45)=2.5$, $p=0.01$). Bilateral VS-right vlPFC functional connectivity was significantly more negative in BO than in NBO (participants without medications: $t(46)=-3.3$, $p=0.002$; the comparison just missed significance in BO and NBO without psychopathology: $t(32)=-2.6$, $p=0.02$); and in BO vs. HC (participants without psychopathology: $t(39)=-5.8$, $p<0.001$; unmedicated participants: $t(45)=-6.0$, $p<0.001$).

Supplemental Tables

Table S1

Demographic and clinical variables for participants without current psychiatric diagnoses and participants untreated with psychotropic medications.

	BO	NBO	HC	Statistics	p-value
Youth without psychiatric diagnoses					
Number of youth without psychiatric diagnoses	18 (62%)	16 (57%)	23 (100%)	BO vs. NBO $\chi2(2)<1$	ns
Age at scan	13.84(2.60)	13.82(2.08)	13.74(1.80)	$F(2,54)<1$	ns
Gender (female)	6	7	11	$\chi2(2)<1$	ns
Handedness (right hand)	16	21	21	Yates' $\chi2(2)<1$	ns
IQ (WASI)	106.67(13.63)	100.50(13.03)	105.78(13.79)	$F(2,54)<1$	ns
SES based on parental education	5.44(0.92)	5.38(1.02)	5.30(1.02)	$F(2,54)<1$	ns
SCARED Parent Total	7.56(6.45)	6.33(6.97)	4.17(4.32)	$F(2,53)=1.8$	ns
SCARED Child Total	8.89(8.56)	7.50(9.56)	9.33(11.42)	$F(2,54)<1$	ns
MFQ Parent	4.44(5.85)	6.71(12.05)	1.57(2.09)	$F(2,52)=2.4$	ns
MFQ Child	5.83(8.05)	8.38(9.26)	5.09(10.57)	$F(2,54)<1$	ns
CALS Parent Total	6.22(8.59)	5.60(9.74)	1.78(2.59)	$F(2,53)=2.3$	ns
CALS Child Total	6.56(8.51)	7.19(9.00)	5.96(13.39)	$F(2,54)<1$	ns
Youth untreated with psychotropic medications					
Number of youth untreated with psychotropic medications	24(83%)	24(86%)	23(100%)	BO vs. NBO $\chi2(2)<1$	ns
Age at scan	14.00(2.43)	13.75(2.41)	13.74(1.80)	$F(2,68)<1$	ns

Gender (female)	11	11	11	$\chi 2(2)<1$	ns
Handedness (right hand)	22	23	21	Yates' $\chi 2(2)<1$	ns
IQ (WASI)	104.46(14.39)	102.46(13.15)	105.78(13.79)	F(2,68)<1	ns
SES based on parental education	5.50(0.93)	5.42(0.93)	5.30(1.02)	F(2,68)<1	ns
SCARED Parent Total	9.29(6.30)	9.65(9.89)	4.17(4.32)	F(2,67)=4.2	0.02
SCARED Child Total	11.79(9.13)	10.29(14.31)	9.33(11.42)	F(2,68)<1	ns
MFQ Parent	4.88(6.19)	5.95(9.75)	1.57(2.09)	F(2,66)=2.6	ns
MFQ Child	8.67(8.90)	9.54(10.97)	5.09(10.57)	F(2,68)=1.3	ns
CALS Parent Total	6.54(9.30)	5.43(8.22)	1.78(2.59)	F(2,67)=2.7	ns
CALS Child Total	9.17(8.85)	9.04(12.09)	5.96(13.39)	F(2,68)<1	ns

Table S2

Main Effect of Condition on Activation in the reward mask

	Region	nvox	z-score	X	Y	Z
			Main effect of Condition: Win-Control>Loss-Control			
L	LIFG	1641	4.9	-48	8	20
L	ACC/Paracingulate	437	4.35	-8	24	40
L	MFG/SFG	423	4.48	-28	-4	60
R	MFG/IFG	237	3.86	46	8	38
L	L Caudate (dorsal)	200	3.83	-10	16	4
R	R Thalamus	121	4.15	12	-12	10
			Main effect of Condition: Win-Control<Loss-Control			
	none					

Note: L – left, R – right, B – bilateral, g.- gyrus, LIF – left inferior frontal gyrus, ACC – anterior cingulate cortex, MFG – middle frontal gyrus, SFG – superior frontal gyrus,

Supplemental Figures

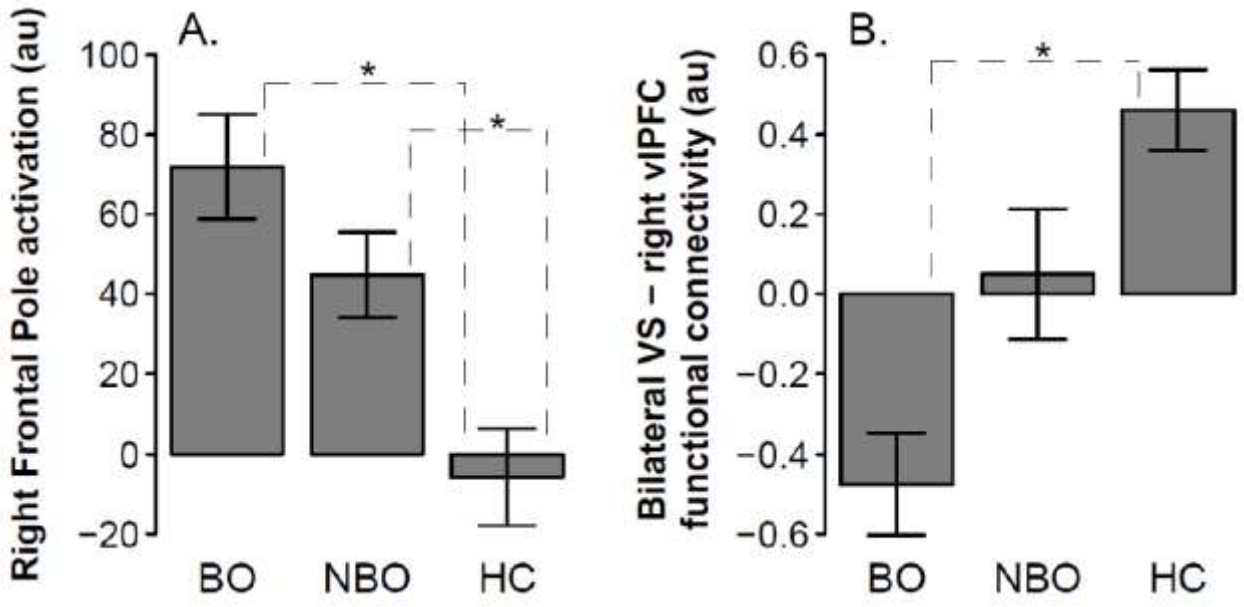

Figure S1. RFP activation and bilateral VS-right vlPFC functional connectivity in participants without current psychopathology for decision-making trials (i.e., Win and Loss trials) vs. non-decision-making trials (i.e., Control trials).

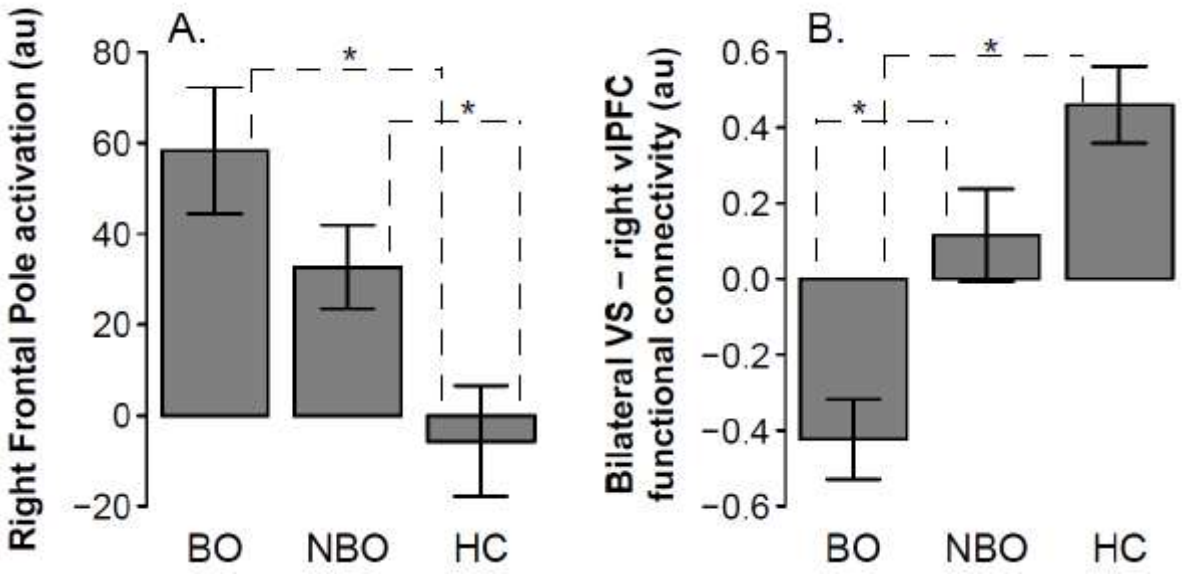

Figure S2. RFP activation and bilateral VS-right vlPFC functional connectivity in unmedicated participants for decision-making trials (i.e., Win and Loss trials) vs. non-decision-making trials (i.e., Control trials).

References

1. Forbes EE, Brown SM, Kimak M, Ferrell RE, Manuck SB, Hariri AR. Genetic variation in components of dopamine neurotransmission impacts ventral striatal reactivity associated with impulsivity. *Mol Psychiatry.* 2009;14(1):60–70.

2. Bebko G, Bertocci MA, Fournier JC, et al. Parsing Dimensional vs Diagnostic Category-Related Patterns of Reward Circuitry Function in Behaviorally and Emotionally Dysregulated Youth in the Longitudinal Assessment of Manic Symptoms Study. *JAMA Psychiatry.* 2014;71(1):71-80.

3. Jenkinson M, Bannister P, Brady M, Smith S. Improved optimization for the robust and accurate linear registration and motion correction of brain images. *Neuroimage*. 2002;17(2):825–841.

4. Smith SM. Fast robust automated brain extraction. *Hum Brain Mapp.* 2002;17(3):143-155.

5. Jenkinson M. Fast, automated, N-dimensional phase-unwrapping algorithm. *Magn Reson Med.* 2003;49(1):193-197.

6. Jenkinson M, Smith S. A global optimisation method for robust affine registration of brain images.

Med Image Anal. 2001;5(2):143-156.

7. Andersson JLR, Jenkinson M, Smith S. Non-linear registration aka spatial normalisation. Oxford: FMRIB Centre; Technical Report FMRIB Technical Report TR07JA2. 2007.

8. Worsley KJ. Statistical analysis of activation images. Ch 14, in: Jezzard P, Matthews PM, Smith SM, eds. Functional MRI: An Introduction to Methods. OUP; 2001.