Supplementary Online Content

Singh MK, Kelley RG, Howe ME, Reiss AL, Gotlib IH, Chang KD. Reward processing in healthy offspring of parents with bipolar disorder. *JAMA Psychiatry.* Published online August 20, 2014. doi:10.1001/jamapsychiatry.2014.1031.

eMethods

eFigure. Monetary Incentive Delay Paradigm Presented During Functional Magnetic Resonance Imaging.

eTable. Participant Demographic, Clinical, and Behavioral Variables

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

eMethods

Participants:

Families were recruited through local community advertisements and through clinics in an academic psychiatry department. An initial phone screen established English fluency and that children were age eligible and were unlikely to have past or current psychopathology, including substance use disorders. Other exclusion criteria for all subjects included a neurological condition (e.g. seizure disorder), IQ less than 80, or presence of metallic implants or braces.

Assessment of psychiatric health and family history:

All participants were evaluated by semi-structured clinical interviews using the Affective Modules of the Washington University in St. Louis Kiddie-Schedule for Affective Disorders and Schizophrenia (WASH-U KSADS)[1] and the Kiddie Schedule of Affective Disorders and Schizophrenia Present and Lifetime version (KSADS-PL)[2] by raters blind to family history status and with established symptom and diagnostic reliability (kappa>0.9). Masters level and higher trained interviewers with over 10 years of experience administered the interview separately to youth and their parents (about youth) in order to rule out current and lifetime psychopathology. Diagnostic decisions were made by board-certified child psychiatrists who were also blind to family history status (M.S. and K.D.C.). A different interviewer administered the Structured Clinical Interview for the DSM–IV (SCID)[3] to the parents, and the Family History Research Diagnostic Criteria assessed for psychopathology in first- or second-degree relatives.[4]

Monetary Incentive Delay (MID) Task:

All participants practiced and were tested for their comprehension of explicit cues presented in the MID task (eFigure 1).[5] Prior to entering the scanner, participants were shown prizes that they could win during the task if they earned enough money. The MID task was designed to probe neural responses to the anticipation and receipt of gain and loss outcomes, using a set of cues to indicate whether participants can win or avoid losing money if they respond quickly enough to a target (represented by a triangle) that follows a cue and anticipation period. On each trial participants were presented with a cue indicating that they had a chance to win or lose $0, $1, or $5. Circle cues indicated trials with the opportunity to win money, square cues indicated trials when money could be lost and lines within those shapes defined the number of dollars presented for that trial. Immediately after each trial participants were shown feedback (how much money they won or lost on that trial and a running total).

Each of these six trial types appeared 9 times for 6 seconds and was pseudo-randomly distributed, for a total of 54 trials per run (approximately 6 minutes x 2 runs). The two runs of the MID task were counterbalanced to control for practice effects. Cues were displayed for 250 ms, followed by a jittered anticipatory period (2000-2500 ms). The target was displayed for a varying duration (250-350 ms), determined from reaction times collected during a practice session before scanning and set such that participants would succeed on approximately 66% of their target responses. A jittered delay period separated the offset of the target stimulus from the onset of the feedback stimulus, so that the length of the entire trial was exactly 6 seconds. After the scan, participants were tested once again on their comprehension of the cues and made subjective ratings of emotional valence and arousal towards each cue.

MRI Data Collection and Pre-processing:

After being trained on the fMRI tasks and desensitized to the scanning environment by an MRI simulator, imaging-related procedures were performed using a 3T GE Discovery MR750 scanner (General Electric, Milwaukee) with a standard whole head coil (General Electric, Milwaukee). Functional images were collected with a T2-weighted spiral in/out pulse sequence: TR 2000 ms; echo time 30 ms; flip angle 80 degrees; field of view 220 mm, voxel-size 3.43 mm x 3.43 mm x 4 mm with 1 mm skip, 30 slices collected in ascending order, anterior and posterior commissure alignment, 192 temporal frames. An automated high-order shimming method was used before acquiring fMRI data to reduce field inhomogeneities. Structural images were collected to aid in localization of the functional data, three-dimensional high-resolution T1-weighted anatomical images were acquired using a spoiled gradient recall pulse sequence: TR=8.5 ms, TE= 3.4 ms, flip angle 15 degrees, field of view 220 mm, voxel-size 0.86 x 0.86 x 1.5mm, 1-NEX (number of excitation) scans, 124 coronal slices. Six participants (6 high-risk and 1 low-risk) originally recruited were excluded from analysis due to motion artifacts or poor behavioral performance, resulting in a sample size of 20 high-risk and 25 low-risk participants.

Functional images were processed with SPM8 (Wellcome Department of Cognitive Neurology, London, UK), including realignment, slice time correction, coregistration, normalization into MNI space with 2 mm voxel resampling, and spatial smoothing. Images were repaired by interpolation from the nearest unaffected volumes, using the *ArtRepair* software toolbox for SPM (http://cibsr.stanford.edu/tools/methods/artrepair-software.html) if motion exceeded a 0.5 mm/TR threshold or if global signal was greater than 3% from the mean global signal of all

images. Subjects were excluded from the analysis if the number of repaired images exceeds 20% of the task. Data were coregistered and spatially normalized normalization to a subject-based custom Montreal Neurological Institute space template created with template-o-matic[6] using segmented structural grey matter images. Normalized images were then smoothed with a 4 mm FWHM Gaussian filter.[7]

Statistical Analyses:

We conducted two-way (group [high-risk, low-risk] by valence [reward, loss]) analyses of variance (ANOVAs) on reaction times and accuracy. Group t-tests were used to compare total money gained. A group by valence by incentive level [$5, $1, $0] ANOVA indicated that reaction times did not differ as a function of incentive level. Therefore, trials presenting anticipation of reward cues (i.e., $1 and $5) were combined to increase statistical power, as were trials presenting anticipation of loss cues.

Using a fixed effects model in SPM8, we computed statistical contrasts for anticipation and feedback phases of reward and loss. For anticipation, we compared trials with reward or loss cues to corresponding non-reward and non-loss trials. For feedback, we compared trials in which participants gained money to non-reward feedback trials, and we compared trials in which participants avoided losing money to non-loss trials. We applied a high-pass filter of 120 seconds and included 6 motion regressor nuisance covariates in the model. We excluded seven participants (6 high-risk and 1 low-risk) originally recruited from analyses due to motion artifacts or poor behavioral performance (total correct hits <30%), resulting in an analysis sample of 20 high-risk and 25 low-risk youth. There were no significant group differences in the means of the six motion parameters ($p>.05$).

To examine group differences in brain activation during reward processing, we conducted a two-way (group [high-risk, low-risk] by valence [reward, loss]) voxel-wise analysis of covariance (ANCOVA) in SPM8 as our primary analysis for both anticipation and feedback contrasts after adjusting for YMRS, CDRS, and MASC scores. Voxel-wise analyses were constrained to an inclusive mask (26653 voxels) covering the following *a priori* bilateral reward-related regions defined by the automated anatomical labeling atlas (AAL)[8]; anterior cingulate, amygdala, hippocampus, insula, caudate, putamen, globus pallidus, middle frontal gyrus, inferior orbitofrontal gyrus, and ventrolateral prefrontal cortices. Significant activations ($p<0.05$ family-wise error corrected (FWE)) associated with the main effect of group, main effect of valence, and the interaction of group and valence were identified for the comparison of anticipated and received rewards versus non-rewards, and anticipated and avoided losses versus non-losses. Activation foci were superimposed on high-resolution, T1-weighted images in MNI space, and their locations were interpreted using the Talairach atlas and known neuroanatomical landmarks. Significant activation clusters were identified at $p<.01$ signal height $p<.05$ FWE cluster extent (k=138), that was calculated using standard methods by AlphaSim Monte Carlo simulations, based on parameters for matrix size of 91x109x91, voxel dimensions of $2mm^3$, 9 mm FWHM image smoothness calculated by 3dFWHMx (AFNI), 10,000 simulations and the ROI mask defined above.[9]

We used a psychophysiological interaction (PPI) analysis in SPM8 to evaluate functional connectivity between reward-related ROIs from our voxel-wise analysis and the rest of the brain.[10] The deconvolved activation time courses from the seed ROIs were multiplied by a block vector representing the contrast of interest. The individual model contained regressors for the interaction, the seed region time course, the original conditions, and motion regressors. The regressors were convolved with the canonical hemodynamic response function. The generated contrast images were then compared between high- and low-risk groups at a second-level random effects analysis adjusted for YMRS, CDRS and MASC. We used two-sample t-tests to identify significant group differences of activation connectivity with the seed region. A significant PPI effect had a cluster-level threshold FWE corrected for multiple comparisons ($p<.05$) with a height threshold of $p<.01$ uncorrected and represents significantly higher connectivity between the seed regions and corresponding target regions during one condition (anticipation and feedback) than another condition (control).[11]

To explore the roles of trait impulsivity and novelty-seeking in reward processing, within-group correlations were computed between impulsivity and novelty-seeking scores and bilateral amygdala, insula, and NAcc ROIs across all conditions. Amygdala and insula ROIs were defined by the AAL atlas.[8] NAcc was defined by 5mm spheres localized to the following coordinates: (MNI x, y, z; ±10,10,-2).[12] Mean Z-scores were extracted using ROI extraction (http://gablab.mit.edu/downloads/rex.pdf) and imported into SPSS19 (http://www.spss.com/) for analysis.

References

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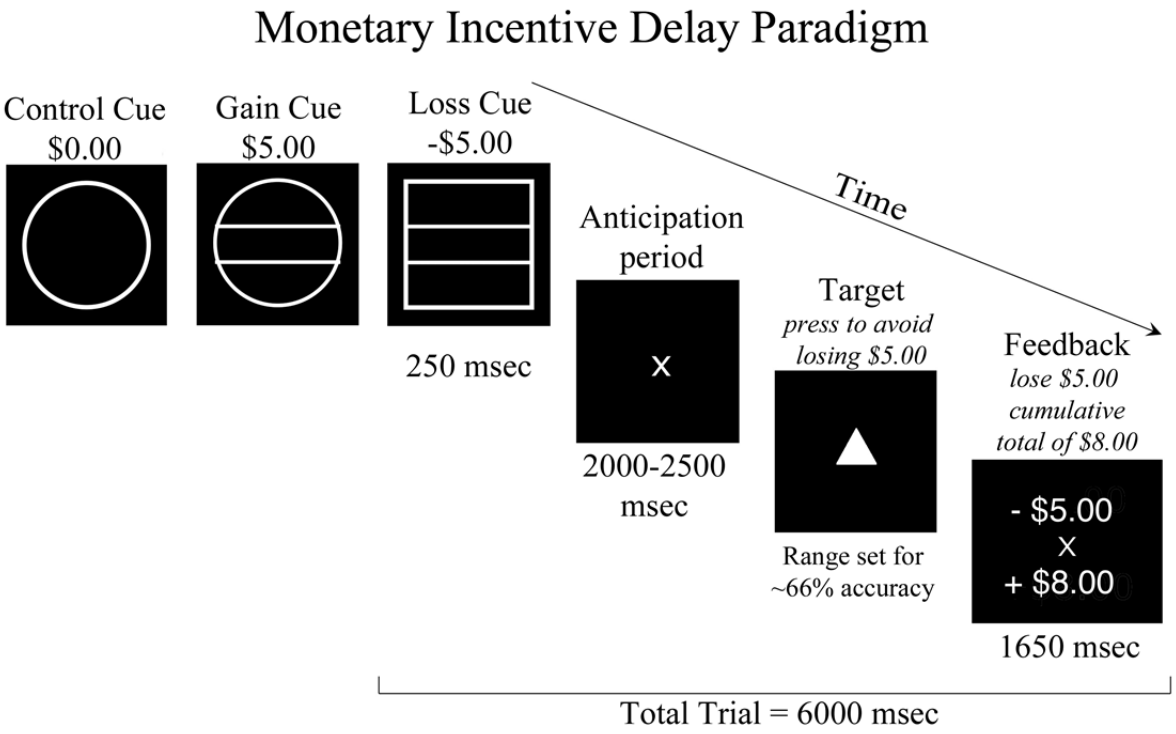
eFigure. Monetary Incentive Delay Paradigm Presented During Functional Magnetic Resonance Imaging.



eTable. Participant Demographic, Clinical, and Behavioral Variables

Variable	High-Risk (n=20)	Low-Risk (n=25)
Age, years, mean (SD)	12.74 (2.85)	11.75 (2.37)
Gender, Female, N (%)	13 (65%)	15 (60%)
Right Handedness, N (%)	18 (90%)	24 (96%)
Tanner Stage, mean (SD)	2.72 (.77)	2.32 (.97)
Socioeconomic Status, mean (SD)	4.11 (1.31)	3.90 (1.61)
Full Scale IQ, mean (SD)	111.31 (9.70)	115.12 (17.21)
YMRS, mean (SD)	1.25 (1.21)	1.13 (1.29)
CDRS, mean (SD)	20.1 (3.34)	19.54 (2.70)
CGAS, mean (SD)*	89.92 (5.49)	85.65 (5.22)
MASC T-score (SD)	43.56 (11.78)	44.99 (9.81)
BIS – Attentional Impulsivity	14.52 (2.9)	14.00 (2.62)
BIS – Motor Impulsivity	20.84 (3.17)	19.73 (3.24)
BIS – Nonplanning Impulsivity	24.37 (5.49)	23.59 (3.80)
DOTS-R Approach-Withdrawal Score*	22.1 (3.78)	19.28 (3.27)
MID Reaction Time for Rewards, mean (SD)	210.99 (26.82)	205.15 (31.75)
MID Reaction Time for Losses, mean (SD)	210.47 (26.15)	210.23 (21.31)
MID Reaction Time for Control, mean (SD)	215.86 (24.00)	210.90 (31.20)
MID Accuracy for Rewards, % (mean correct hits)	72% (24)	78% (26)
MID Accuracy for Losses, % (mean correct hits)	72% (24)	73% (25)
MID Accuracy for Control, % (mean correct hits)	70% (23)	71% (24)

* Significant at $p<.05$. SD = standard deviation; IQ = Intellectual Quotient; YMRS = Young Mania Rating Scale; CDRS = Childhood Depression Rating Scale; CGAS = Clinical Global Assessment Scale; MASC = Multidimensional Anxiety Scale for Children; BIS = Barratt Impulsiveness Scale, DOTS-R = Dimensions of Temperament-Revised, MID = Monetary Incentive Delay Task Behavioral Performance, RT = reaction time