Orbitofrontal Cortex Activity and Connectivity Predict Future Depression Symptoms in Adolescence

Supplemental Information

Supplementary Methods and Materials

Participants

The parent ADEPT study is a longitudinal project designed to examine personality traits and first onset of depression, approved by the Institutional Review Board at Stony Brook University. The parent ADEPT cohort consisted of 550 adolescent females (13.0 to 15.5 years of age at baseline assessment, mean age = 14 years, 5 months; *SD* = 7 months) and one of their biological parents as informants (93.1% mothers) that were recruited from the community. The cohort consisted of 80.5% Caucasian, 5.1% African-American, 8.4% Latino, 2.5% Asian, 0.4% Native American, and 3.1% "Others". Inclusion criteria included fluency in English, capable of reading and comprehending questionnaires, and consent for participation from a biological parent. For detailed description of recruitment procedures please refer to previous publications (1, 2).

After completing the baseline assessment (wave1), participants were invited for follow-up assessments every 9 months. At the first follow-up assessment (wave2), all participants were invited to participate in the fMRI study. The fMRI sample (N = 261) consisted of all participants who were willing to participate and met basic eligibility criteria for MRI (e.g., without metal implants, braces, claustrophobia, etc.). Difference in severity of depression between the fMRI subsample and participants who were not scanned were minimal (see results below), suggesting little if any bias.

A total of 32 participants were excluded due to technical problems (N = 2), data processing errors (N = 7), incomplete fMRI data (N = 7), excessive movement (N = 3, for details see fMRI data analysis below), low fMRI image quality (N = 6), and lack of behavioral response data (N = 4). Given that the main aim of the current study was to examine neural correlates that predict *future* severity of depression, we further excluded participants who developed MDD or Dysthymia by the time of the fMRI assessment (incidence between wave1 and wave2, N = 2) or obtained depression symptom severity scores that were outliers at the time of fMRI scan (> 3 SD above the group mean of the IDAS-II dysphoria subscale, see the Clinical Measures section, N = 1).

Among the final 229 subjects, mothers were the participating parent for 216 adolescents and fathers were the participating parent for 13 adolescents. Among 49 HR participants, 47 mothers and 2 fathers met criteria for a lifetime history of either MDD or dysthymia (Parental-History) on the SCID assessment. The remaining 180 participants constituted the LR group since their participating parent was free of a lifetime history of MDD or dysthymia. Due to practical constraints, the SCID assessment was done in the participating parent only and HR and LR groups were created based on this assessment. However, keeping in mind that the non-participating parent may have a history of depression, we asked the participating parent whether the non-participating biological parent ‘ever felt sad, blue, or depressed for most of the time for two weeks or more without including times of physical illness, or mourning after a death,’ a question on the family health screen (FHS (3)). We then created another HR group based on whether the participating parent qualified for a SCID depression diagnosis or endorsed a history of depression in the non-participating parent on FHS. An additional 13 participants were categorized in the HR group, resulting in 62 participants for HR and 167 for LR group. Overall,

among the 229 participants, 220 had complete wave2 IDAS-II dysphoria dimension score (Dys_{w2}), 224 had complete wave3 IDAS-II dysphoria dimension score (Dys_{w3}), and 217 had both wave2 and wave3 scores. These variations affect the degrees of freedom in the data analyses reported.

Clinical Measures

The SCID interviews were video-recorded. Inter-rater reliability for parental unipolar depression was high ($\kappa = .73$), based on 25 recordings. Study interviewers were trained and supervised by clinical psychologists (DK, RK, and GP). The absence of lifetime depressive disorders in the adolescents was confirmed using the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version (K-SADS-PL) (4). The IDAS-II consists of 99-items rated on a 1 (Not at all) to 5 (Extremely) scale. IDAS-II scales show excellent internal consistency across multiple samples, with most showing coefficient alphas above .80 in adolescents (5) and other populations (6). We used the average item response on the 10-item dysphoria scale to measure depression symptom severity, and prorated if missing no more than 1 item (α was .90 for both Dys_{w2} and Dys_{w3}, respectively).

Participation in the fMRI portion of the study was voluntary, which may introduce bias. To test for such bias, we conducted independent samples *t*-tests comparing the dysphoria scores from wave1 and wave2 for the subsample that participated in fMRI versus the subsample that did not participate in fMRI (see results).

Experiment Paradigm: the Doors Task

The gambling task was presented using E-Prime software (7). The entire experiment consisted of 46 trials (23 loss trials and 23 win trials) presented in an event-related manner in 1 scanning session spanning ~ 424 s. Outcome of each trial was predetermined and the trials were presented in a pseudo-randomized order. For all participants, the experiment started and ended with a fixation cross presented for 18.9 s. Each loss or win trial started with a fixation cross displayed for 600 ms, followed by two doors displayed for 3 s, another fixation cross for 600 ms, and finally the outcome of participant's choice displayed for 1 s. At the end of each trial (and before next trial started) a fixation cross was displayed for a jittered time interval ranging from 1.1 to 7.4 s. Participants were instructed that if they did not make a decision within 3 s, the computer would make a random selection for them.

Behavioral Data Analyses

We also examined if participants' choices changed over the course of the experiment and if this change differed by Parental-History. To do so, we divided the 46 trials (23 win and 23 loss trials) into the first and second half of the experiment and computed the number of switches following win feedback (Win-Switch) and the number of switches following loss feedback (Loss-Switch) for the first and second half of the experiment. A 2 (first versus second half) x 2 (HR versus LR) repeated-measures ANOVA was conducted comparing the number of switches for the win condition and loss condition for the HR versus LR groups.

fMRI Data Acquisition and Preprocessing

To enhance signal recovery, we used an integrated parallel acquisition technique known as Generalized Autocalibrating Partially Parallel Acquisition (GRAPPA). Imaging parameters included a repetition time (TR) of 2.1s, echo time (TE) of 23 ms, slice thickness of 3.5 mm, in-plane resolution of 2.3 x 2.3 mm, field of view (FOV) of 224 mm x 224 mm, and a matrix size of 96 x 96 x 37. High-resolution structural images were collected using a T1-weighted MPRAGE pulse sequence (TR = 1.9 s, TE = 2.53 ms, flip angle = 9°, slice thickness = 1 mm, in-plane resolution = 1×1 mm) for normalizing images from each participant to a common space.

The initial 6 volumes were discarded for spin saturation. The ArtRepair toolbox (8, 9) was used to correct motion artifacts by replacing affected volumes with a volume interpolated from the nearest unaffected volumes. Volumes with rapid movement above 1mm were identified and excluded, and the entire participant's data was discarded if over 20% of the total volumes showed movement above 1mm. For each participant, the motion-corrected data were spatially realigned to the first volume. The T1-weighted structural image was co-registered to the mean functional image averaged across the realigned data, and segmented into maps of gray matter, white matter and cerebrospinal fluid (CSF), thereby generating the realignment parameters needed to normalize to the Montreal Neurological Institute (MNI) EPI brain template. The same normalization parameters were then applied to the realigned functional data to bring the images to MNI space. Finally, the functional data was spatially smoothed with an isotropic Gaussian kernel of full-width half-maximum (FWHM) of 6 mm^3.

fMRI Data Analyses

Subject-level model. The GLM model included a 128 s high-pass filter to remove low-frequency fluctuations and a first order autoregression AR (1) to account for temporal non-sphericity due to autocorrelations. In order to account for the effects of participant movement, the model also included motion-related regressors, including 6 regressors for rigid body motion parameters estimated during realignment, and regressors indicating volumes of excessive movement identified by ArtRepair motion correction. The fixation periods within each trial as well as the fixation blocks at the beginning and end of the experiment were not modeled and constituted the implicit baseline.

OFC ROI analysis. In line with earlier studies, our anatomical OFC mask consisted of bilateral superior orbital gyrus, bilateral middle orbital gyrus, bilateral inferior orbital gyrus, bilateral medial orbital gyrus, and bilateral rectal gyrus selected from Automated Anatomical Labeling (AAL) (10, 11) from the Wake Forest University (WFU) PickAtlas (12).

Striatum ROI analyses. Keeping in mind the existing literature regarding HR versus LR group differences in reward-related striatal activity (13, 14), we compared striatal response to wins in HR and LR groups using an anatomically defined striatum mask comprising of bilateral caudate, bilateral putamen, and bilateral pallidum selected from Automated Anatomical Labeling (AAL) (10, 11) from the Wake Forest University (WFU) PickAtlas (12). The resultant mask covers both dorsal and ventral striatum. We also defined task-sensitive striatal ROIs using criteria identical to OFC ROIs and subjected them to correlation and regression analyses with self-report measures.

Control ROI analysis. In order to determine whether the OFC activity was uniquely associated with future depression, we also examined a ‘control’ region in the brain that

correlated with concurrent depression (Dys_{w2}) and conducted similar analyses as with our anatomical OFC ROI. Besides OFC, we found that anterior cingulate cortex (ACC, x = 12, y = 50, z = 20) correlated with Dys_{w2} at a threshold of p = .005, uncorrected. We extracted the average activation in response to loss across all voxels in the ACC cluster for each subject (ACC_{loss}) and subjected this averaged ROI score to the same analyses strategy as with the OFC ROI.

Functional connectivity analyses. PPI analyses estimate the contribution of an interaction between a psychological factor (change in loss or win experimental conditions) and a physiological factor (activity in the OFC seed region) to the activity in each voxel in the brain. This basic analysis method is extended to the generalized form of context-dependent psychophysiological interaction analyses (gPPI (15)), which enables modeling of connectivity differences by group and condition, thus increasing flexibility of statistical modeling over standard PPI methods. Statistical testing of gPPI comparing it to standard PPI methods found that gPPI improved model fit and sensitivity to true positive findings (15-17).

For each subject, we computed the 'psychological' term by convolving the condition onset times for loss and win conditions separately with the canonical HRF, and the 'physiological' term was estimated as the first eigenvariate time series of the BOLD signal extracted from the right OFC seed region. This represents the average BOLD signal weighted by the voxel significance. To compute the 'psychophysiological' interaction term, time series was first de-convolved with the hemodynamic signal (18) to model out the effects of the canonical HRF. The deconvolved physiological factor was multiplied by the psychological variable and re-convolved with the HRF, giving the interaction term. The PPI analyses were conducted by

regressing activity in each voxel against the interaction term while controlling for variance associated with the psychological and physiological main effects.

Association between OFC response and other IDAS measures. To determine that OFC_{loss} bears a unique relationship with depression but not anxiety measures that are highly comorbid with depression, we also tested OFC_{loss} correlation with an anxiety measures in IDAS-Panic for wave2 and wave3 respectively. Additionally, we also examined whether OFC_{loss} was associated with w2 and w3 depression-relevant scales and whether OFC_{loss} predicts w3 depression-relevant scales in the HR but not in LR group, even after controlling for Age and the same scale at w2. Accordingly, we ran two regression analyses using OFC_{loss}, Age and w2 scale to predict w3 scale for HR and LR separately for each of the 6 depression-relevant IDAS-II scales: lassitude, suicidality, insomnia, appetite-gain, appetite-loss, and well-being. As was in the main text, for scales that were significant, we followed up with a functional connectivity analysis.

Cross-validation tests. To estimate predictive power, we conducted a 1000 times 3-fold-cross-validation (3-fold-CV) test. While keeping enough data for training, a 3-fold-CV analysis is able to utilize a reasonable subsample for testing (about 15 subjects in testing set). K-fold cross-validation test has been widely used to yield relatively unbiased performance estimates, with the caveat of higher variance due to arbitrary partitioning of the training and testing data. Recent research has shown that the high variance issue can be resolved by conducting the k-fold cross-validation repeatedly (19). Each of the 1000 iterations contains three steps. First, the participants were randomly assigned into 3 bins. Second, a 3-fold-CV was conducted, using 2 bins for training (about 30 participants) and the remaining bin (about 15 participants) for testing at each time, and this was repeated for 3 iterations exhausting the training-testing combinations. During each of the 3 iterations, the training set was used to obtain regression weights of OFC

response and Age in predicting $resDys_{w3}$. Then we entered the testing participants' scores into the resulting equation, yielding a predicted $resDys_{w3}$ score for each of the testing participants. We next correlated these predicted $resDys_{w3}$ scores with observed $resDys_{w3}$ for each iteration, resulting in 3 correlation values, which were then averaged to obtain a mean correlation value finishing the current 3-fold-CV. Finally, in order to stabilize the final correlation value, this 3-fold-CV was conducted 1000 times, yielding a distribution of 1000 correlation values. The averaged correlation across all 1000 correlation values was used as the final estimate of the predictive power. Because the 1000 correlation values were not independent from each other, a non-parametric approach was used to determine the significance. If more than 95% of the distribution was above zero, indicating that > 95% of the 3-fold-CV values yielded positive correlations, we rejected the null hypothesis of no correlation between predicted and observed $resDys_{w3}$ scores for the HR group. The same analyses were conducted for the LR group. We also conducted a 5-fold version of the analysis which yielded the same results.

Supplementary Results

Depression Measures

There was no significant difference in Dys_{w2} between subsample that participated in fMRI (M = 1.63, SD = .72) and the subsample that declined to participate (M = 1.69, SD = .75; t_{496} = -.89, p = .375). Similarly, no difference was seen for Dys_{w1} between the fMRI subsample (M = 1.63, SD = .71) and the subsample that did not participate in fMRI (M = 1.65, SD = .71; t_{545} = -.33, p = .744), indicating that fMRI subsample was representative of the entire cohort in terms of depression scores.

Overall, depression symptom severity declined slightly from wave2 to wave3 (Dys_{w2}: M = 15.79, SD = 6.48; Dys_{w3}: M = 14.79, SD = 5.70; t_{216} = 2.654, p = .009), which differed by Parental-History. For LR group, there was a significant decrease from wave2 to wave3 (Dys_{w2}: M = 15.78, SD = 6.51; Dys_{w3}: M = 14.57, SD = 5.61; t_{169} = 2.733, p = .007). In contrast, HR youth showed no change over time ($Dys_{w2:}$ M = 15.84, SD = 6.43; Dys_{w3}: M = 15.59, SD = 5.97; t_{46} = .369, p = .714). Relatively similar levels of depression in HR and LR youths may be attributable to the exclusion of participants who developed a depressive disorder at screening and wave 2, thus truncating the dysphoria scores of the high-risk group.

Behavioral Measures

The repeated-measures ANOVA showed a significant main effect of experimental time point, with a higher number of Loss-Switch trials for the second than the first half of the experiment (F(1, 227) = 292.74, p < .001), and a significantly lower number of Win-Switch trials for the second than the first half of the experiment (F(1, 227) = 124.01, p < .001). There was no main effect of Parental History or interaction between time point and Parental History. These results indicate that not only did the participants change their choices more frequently following loss feedback than win feedback overall, as reported in the main text, but also that this effect was even stronger for the second than the first half of the experiment. Following loss feedback, participants changed choices more frequently for the second half than the first half of the experiment. In contrast, following win feedback, they kept the same choice more frequently for the second half than the first half of the experiment. These results demonstrate a strong and persistent effect of feedback modulated behavioral performance. This effect was not significantly different between HR and LR groups.

fMRI Measures

Whole brain analyses. Whole brain task effects for win- and loss-related activity are shown in Supplementary Table S1.

Relationship Between OFC Reactivity and Future Depression Symptoms in HR Group

Using HR group defined by participating parent qualifying for a SCID depression diagnosis or endorsing depression in the non-participating parent, Pearson's correlation coefficient revealed a significant correlation between OFC_{loss} and Dys_{w3} (r = -.37, p = .003) and trending correlation with Dys_{w2} (r = -.21, p = .101) for HR group. These correlations were not significant for LR group (r = -.05, p = .523 for Dys_{w3}, and r = -.11, p = .190 for Dys_{w2}). As in the results reported in the main text, regression analyses using OFC_{loss} to predict Dys_{w3}, controlling for Dys_{w2} and Age for each group separately revealed a significant effect for OFC_{loss} for the HR (b = -.13, p = .013) but not for LR group (b = -.02, p = .692).

Given the literature suggesting differential contribution of parental versus maternal depression to child psychopathology (20), we conducted our main analyses with participants for whom the mother was the participating parent. This resulted in 46 HR participants and 166 LR participants. Our main findings remained similar. Specifically, OFC_{loss} was significantly correlated with Dys_{w3} (r = -.42, p = .004) and marginally correlated with Dys_{w2} (r = -.25, p = .095) for the HR group, whereas no correlation was found between OFC_{loss} and Dys_{w3} (r = -.07, p = .385) or Dys_{w2} (r = -.11, p = .162) for the LR group. Furthermore, OFC_{loss} predicted Dys_{w3} after controlling for Dys_{w2} and Age only for HR group (b = -.26, p = .015) but not for the LR group (b = -.04, p = .523). Finally, the exclusion of additional participants did not affect the

result of OFC_{loss} connectivity with posterior insula (b = .16, p = .006) in predicting Dys_{w3} after controlling for Dys_{w2} and Age.

Striatum ROI Analyses

A between group *t*-test comparing win-related striatal activity for HR and LR groups showed attenuated striatal activity in response to win for HR compared to LR (p < .005, uncorrected). When HR was defined based on participating parent qualifying for a SCID depression diagnosis or endorsing family history of depression in non-participating biological parent on FHS, the between-group t-test again showed a significant attenuation in striatal response to win for HR compared to LR group (Figure S2, p < .05, corrected for multiple comparisons via cluster size correction, initial threshold p < .005, cluster size = 71 voxels).

Additionally, as in the OFC analyses, we extracted BOLD activity from the striatum based on the task-effect of win or loss > baseline, at p < .05, FWE-corrected for multiple comparisons. Three clusters survived the threshold. We followed the same processing steps as used in the OFC analyses to extract striatal data. We then examined the correlations between extracted striatal activity and dysphoria (Dys_{w2} and Dys_{w3}) as well as the 6 depression-relevant scales across participants and for HR and LR separately. The results did not reveal association between dysphoria and win-related striatal BOLD response. As for the other depression-relevant scales, only w3 appetite-gain showed a significant correlation when examined across subjects (r = -.14, p = .035) but this relationship did not differ by group.

Association Between OFC_{loss} and Other IDAS Scales

Both Dys_{w2} and Dys_{w3} were highly correlated with $Panic_{w2}$ (r = .71, p < .001, and r = .70, p < .001 respectively). However, OFC_{loss} was not significantly correlated with $Panic_{w2}$: r = -.08, p = .27, $Panic_{w3}$: r = -.05, p = .49. Similarly, OFC-insula connectivity was not correlated with $Panic_{w2}$: r = .12, p = .09, $Panic_{w3}$: r = .12, p = .08. Among the 6 depression-relevant scales, OFC_{loss} was positively correlated with well-being for w2 (r = .14, p = .038) and w3 (r = .13, p = .05) across all participants. On the other hand, when split by group, OFC_{loss} was correlated with lassitude for w3 (r = -.38, p = .008) but not w2 for HR but not LR. There was no significant correlation either for HR or LR for the remaining 5 scales. Regression analyses results confirmed a significant interaction effect for the lassitude scale, but not with the other 5 scales, with OFC_{loss} predicting lassitude for w3 (b = -.23, p = .006) for the HR group but not for LR group (b = .02, p = .724). However, OFC-posterior insula connectivity did not predict lassitude for w3. These results indicate that the interaction between Parental History and OFC_{loss} activity was specifically associated with dysphoria and lassitude, and OFC_{loss} connectivity was associated specifically with dysphoria which was not affected by Parental History.

Control Region Analysis

ACC_{loss} was correlated with Dys_{w2} (r = -.22, p = .001) and Dys_{w3} (r = - .19, p = .005). However, unlike OFC_{loss}, ACC_{loss} and the interaction of ACC_{loss} with Parental-Hx did not predict Dys_{w3} when controlling for Dys_{w2} (Supplementary Table S2).

Prediction and Cross-validation Tests

To evaluate incremental predictive power of OFC_{loss}, we correlated predicted and observed future $resDys_{w3}$ scores. The correlation was significant for HR (r = .44, p = .002), but not for LR (r = .11, p = .169) group, with the two correlations being significantly different (p = .033). In addition to the 1000 times 3-fold-CV, we also conducted a 1000 times 5-fold-CV. The 5-fold-CV version yielded a mean correlation between the predicted and the observed $resDys_{w3}$ of r = .37, with 100% of iterated r values above zero. In contrast to the highly consistent positive correlations shown in the HR group, the mean correlation for the LR group was considerably lower (r = - .01 for the 3-fold-CV, with only 50 % above zero; r = .02 for the 5-fold-CV, with only 64% above zero).

Supplementary Discussion

Despite no group differences in depression levels of HR and LR groups (see Supplementary Results) we found stronger relationship of loss-related OFC activity and connectivity with concurrent and future depression in HR group. However, the same relationship was not observed with symptoms of anxiety, which are highly comorbid with depression. Furthermore, the relationship to future depression was specific to OFC and not seen for another 'control' region in ACC that also correlated with concurrent depression. Our study focused on task-sensitive regions in lateral OFC that are implicated in assigning value to a choice (21) as opposed to ventromedial prefrontal cortex which is also implicated in depression (22) but involved in initiation of the decisions (21). Our findings may indicate depression-related vulnerability at the valuation and choice-value association stage rather than decision stage but

future studies manipulating both the valuation and decision aspects of loss processing are needed to confirm this interpretation.

Supplementary Tables and Figures

Table S1. Whole brain task effects

	Peak Coordinates					
	x	**y**	**z**	**Cluster Size**	**t**	**p**
Win						
Middle Cingulate (L) (include bilateral OFC)	-2	2	38	21808	19.48	<.001
Inferior Parietal (R)	50	-52	48	1951	18.05	<.001
Inferior Parietal (L)	-46	-52	50	1293	17.65	<.001
Vermis	-44	-72	-28	4749	14.36	<.001
Middle Temporal (L)	-64	-36	0	1241	12.49	<.001
Middle Occipital (L)	-50	-76	6	78	9.46	<.001
Parahippocampal (R)	18	-22	-14	121	7.42	<.001
Vermis	0	-36	-24	20	6.89	<.001
Cerebellum (R)	16	-34	-22	88	6.75	<.001
Cerebellum (L)	-12	-38	-20	49	6.23	<.001
Lingual (R)	12	-42	-4	17	5.67	.002
Loss						
Inferior Parietal (R)	50	-54	52	1598	16.62	<.001
Superior Frontal Gyrus, medial part (L) (include right OFC)	0	28	38	5864	14.53	<.001
Inferior Parietal (L)	-48	-52	48	842	13.21	<.001
Insula (R)	34	18	-6	466	11.03	<.001

	Peak Coordinates					
	x	**y**	**z**	**Cluster Size**	**t**	**p**
OFC (L)	-44	18	-10	397	11.02	<.001
Cerebellum (L)	-46	-68	-26	398	10.69	<.001
Middle Temporal (L)	62	-30	-4	463	10.08	<.001
Lingual (L)	-2	-66	-2	500	9.33	<.001
Middle Frontal (L)	-46	26	36	391	8.97	<.001
Middle Frontal(L)	-38	54	10	514	8.91	<.001
Cerebellum (R)	36	-58	-30	287	8.88	<.001
Precuneus (R)	4	-66	52	218	8.71	<.001
Anterior Cingulate (R)	4	-30	6	218	8.65	<.001
Middle Temporal (L)	-62	-36	0	415	8.57	<.001
Middle Temporal (R)	54	-70	2	37	7.33	<.001
OFC (L)	-22	48	-14	25	7.15	<.001
Middle Frontal (L)	-36	8	58	42	5.71	.001

Regions showing significant activation at $p < .05$, FWE-corrected for multiple comparisons. Clusters with size > 10 voxels are reported.

Table S2. Regression results of ACC activity to loss in predicting future depression

Predictors	**R^2**	**F**	**b**	***p***
Overall Model	.345	23.793	---	< .001
ACC_{loss}	---	.447	-.042	.504
Parental-History	---	1.881	.076	.172
Age	---	2.777	.093	.097
Dys_{w2}	---	103.045	.579	< .001
ACC_{loss} x Parental-History	---	.016	-.126	.900

ACC_{loss} = ACC activity to loss; Parental-History = Parental history of depression; and Dysw2 = IDAS-II dysphoria on wave2

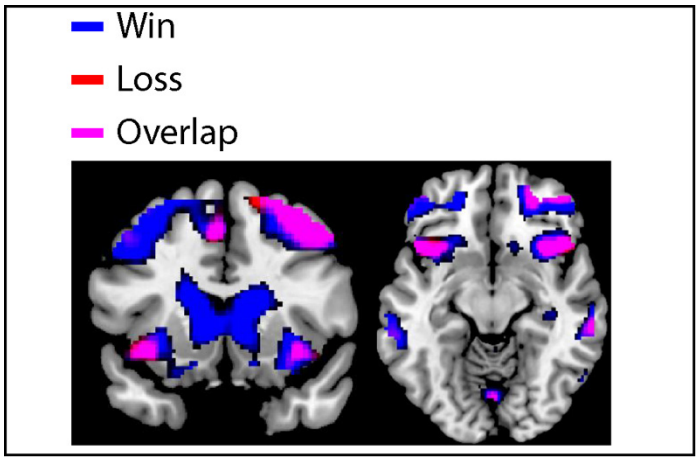

Figure S1. Whole brain task effects. Displayed at $p = 0.05$ FWE-corrected.

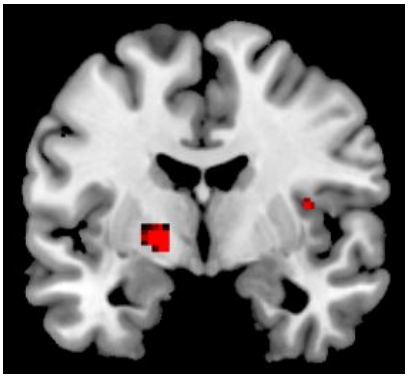

Figure S2. Attenuated striatal activity for HR compared to LR. Displayed at $p < .005$ uncorrected, cluster size = 71 voxels.

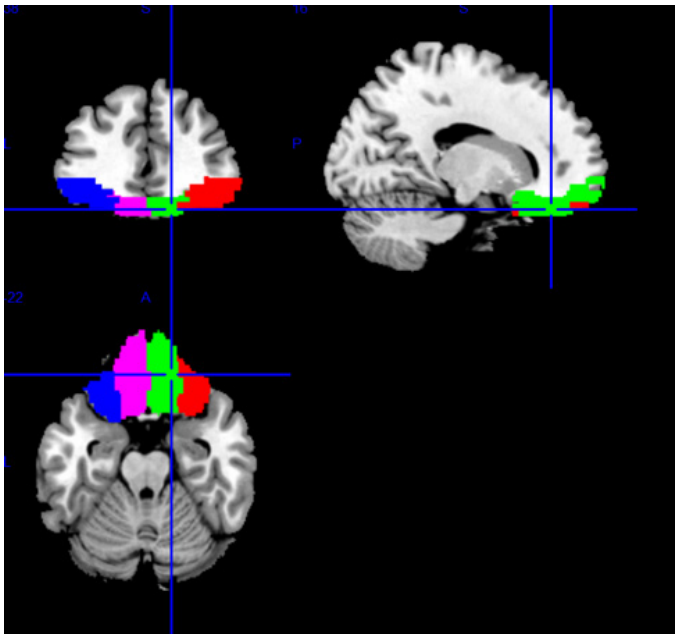

Figure S3. Anatomical mask of OFC.

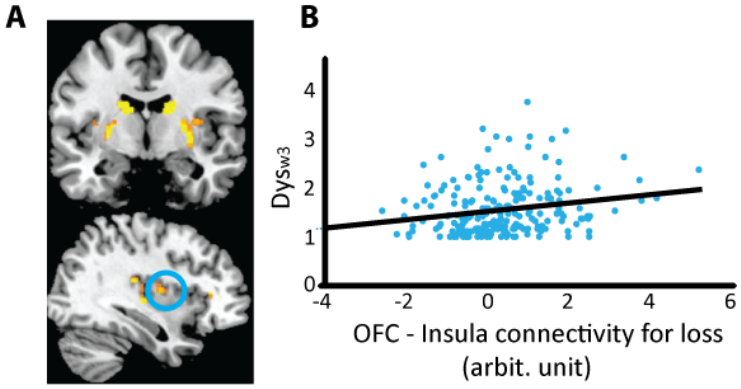

Figure S4. OFC functional connectivity for loss feedback. A. During loss feedback, OFC shows greater functional connectivity with bilateral caudate and bilateral insula ($p < .05$, FWE corrected) across all participants. **B.** The functional connectivity between OFC and right insula (blue circled region in **A**) in response to loss was significantly correlated Dys_{w3} score, even after controlling for $Dys_{w2.}$

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