

# Orbitofrontal Cortex Activity and Connectivity Predict Future Depression Symptoms in Adolescence

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## ABSTRACT

**BACKGROUND:** Major depressive disorder is a leading cause of disability worldwide; however, little is known about pathological mechanisms involved in its development. Research in adolescent depression has focused on reward sensitivity and striatal mechanisms implementing it. The contribution of loss sensitivity to future depression, as well as the orbitofrontal cortex (OFC) mechanisms critical for processing losses and rewards, remains unexplored. Furthermore, it is unclear whether OFC functioning interacts with familial history in predicting future depression.

**METHODS:** In this longitudinal study, we recorded functional magnetic resonance imaging data while 229 female adolescents with or without parental history of depression completed a monetary gambling task. We examined whether OFC blood oxygen level–dependent response and functional connectivity during loss and win feedback was associated with depression symptoms concurrently and prospectively (9 months later) and whether this relationship was moderated by parental history of depression.

**RESULTS:** Reduced OFC response during loss was associated with higher depression symptoms concurrently and prospectively, even after controlling for concurrent depression, specifically in adolescents with parental history of depression. Similarly, increased OFC-posterior insula connectivity during loss was associated with future depression symptoms, but this relationship was not moderated by parental history of depression.

**CONCLUSIONS:** This study provides the first evidence for loss-related alterations in OFC functioning and its interaction with familial history of depression as possible mechanisms in the development of depression. While the current functional magnetic resonance imaging literature has mainly focused on reward, the current findings underscore the need to include prefrontal loss processing in existing developmental models of depression.

**Keywords:** Adolescence, Depression, fMRI, Loss, Orbitofrontal, Parental history

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Major depressive disorder (MDD) is among the leading causes of disability worldwide. However, knowledge of pathological neural mechanisms involved in the development of MDD is limited, frustrating efforts aimed at early detection and intervention. A promising pathophysiological mechanism in depression is that of sensitivity to losses and rewards, with some studies showing reduced reactivity to rewards (1), increased reactivity to losses (2,3), or reduced reactivity to both rewards and losses (4). Importantly, studies show that these alterations in reward reactivity are evident in children and adolescents at high risk for developing depression (5,6) and prospectively predict worsening of depression symptoms (7–9). However, research on neural correlates of loss or reward sensitivity in adolescent depression is limited in that it has focused almost exclusively on reward sensitivity as well as striatal mechanisms that support it (1,5). In contrast, the role of loss sensitivity and its contribution to future depression remains poorly understood (10,11). This is a critical gap in the literature because loss sensitivity varies across

development (11), contributes significantly to decision making, perhaps more strongly than reward sensitivity (12), and is strongly linked to anxiety and mood disorders (5,13,14).

As part of a distributed network critical for valence processing and valuation (15,16), the orbitofrontal cortex (OFC) plays an important role in processing salience and magnitude of losses as well as rewards (17–21). The OFC represents the complete dimension of subjective valence ranging from unpleasant to pleasant (22,23). Due to strong anatomical connectivity with sensory, striatal, limbic, and insular regions, the OFC plays a critical role in integrating loss- and reward-related information (19,24). Furthermore, adolescence might be a developmentally sensitive period for studying the OFC (25) and its relationship with future depression. Adults with history of or risk for depression show attenuated OFC activity for both rewards (7,26,27) and negative stimuli including losses (28,29) [for a review see (13)]. Relatively less is known about functional and effective connectivity of the OFC in adult depression, with studies showing greater connectivity of the

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OFC with the insula (30), the amygdala (31), and a distributed network including prefrontal and cingulate cortices (32), and this enhanced connectivity is associated with more severe depression symptoms (30,32). Despite prefrontal maturation in adolescence (33), adolescents and adults with and at risk for MDD show a similar pattern of prefrontal resting-state connectivity (34,35). However, it is unclear whether attenuated OFC activity and/or enhanced OFC connectivity during rewards and losses represent a premorbid risk that precedes the onset of symptoms or is the result of depression onset or treatment exposure, indicating a need for longitudinal research on OFC functioning prior to depression onset.

Finally, depression is etiologically heterogeneous, with evidence suggesting differences in etiopathophysiological processes between more and less familial/genetic forms (36). Familial history of depression is one of the most important risk factors for depression, and it is associated with altered reward sensitivity in adolescents (5,6,37). However, few studies have explored whether abnormalities in OFC functioning interact with vulnerability imposed by familial history of depression to predict future depression. In the current longitudinal study, we used functional magnetic resonance imaging (fMRI) and a monetary gambling task to examine OFC blood oxygen level-dependent response, an indirect measure of neural activity (38), and OFC connectivity during loss and win feedback in a large cohort of female adolescents who were free of lifetime depressive disorders and who were assessed for depression again 9 months later. We hypothesized that 1) attenuated OFC activity and enhanced OFC functional connectivity with striatal, limbic, and insular regions for losses and wins will be correlated with greater depression symptoms concurrently and will predict depression symptoms 9 months later, even after controlling for concurrent depression, 2) parental history of depression (parental-history) will moderate the relationship between OFC activity and connectivity with future depression symptoms, such that the association is stronger for groups with high versus low risk for depression, and 3) measures of OFC activity and connectivity will independently predict depression symptoms in both cross-sectional and prospective analyses.

## METHODS AND MATERIALS

### Participants

A total of 261 female adolescents (mean age = 15 years 3 months, SD = 7 months) and their parents from the larger Adolescent Development of Emotions and Personality Traits project participated in the current study. The project cohort consisted of female adolescents during a developmental stage marked by a sharp increase in depression onset (39–41) (see the Supplement). Participants and their parents gave informed assent and consent, respectively, and all families were financially compensated for participation. After the baseline assessment (wave 1), participants were invited for follow-up clinical assessments every 9 months and fMRI at first follow-up (wave 2). See Supplement for details. Because we aimed to examine predictors of depression, participants with a lifetime history of MDD or dysthymia were excluded during initial screening. The exclusion of 32 participants due to data quality

issues resulted in a final set of 229 subjects, 49 high risk (HR) and 180 low risk (LR), based on whether their participating parents met criteria for a lifetime history of either MDD or dysthymia (Supplement). Additional analyses were conducted defining the HR group based on family history reports of depression in nonparticipating parents (Supplement).

### Clinical Measures

At baseline (wave 1), lifetime history of MDD or dysthymic disorder was determined based on the Structured Clinical Interview for DSM-IV (42) conducted with the participating biological parent (Supplement). Mood and anxiety symptoms in adolescents were measured using a new-generation factor-analytically derived Inventory of Depressive and Anxiety Symptoms (IDAS-II) (43). Relationship of OFC activity was examined with IDAS-II dysphoria scores at wave 2 ( $Dys_{w2}$ ) and wave 3 ( $Dys_{w3}$ ) because this scale captures core symptoms of depression (9,43) as well as other IDAS-II anxiety and depression-related scales (Supplement).

### Experiment Paradigm: The Doors Task

Participants performed a modified version of a previously used forced-choice monetary gambling task (44) to probe neural response to loss- and reward-related monetary feedback (Figure 1A). Participants chose between two doors presented simultaneously and received feedback of loss or win with 50/50 probability (Supplement). The losses were purposefully set at half as large as wins due to prior data suggesting a 2 times loss aversion ratio (45). Choice and response time were recorded. Although the outcome of each trial was predetermined and independent of performance, participants were informed that they could gain between \$0 and \$10 depending on success rate. All participants were paid \$6 after the scan.

### Behavioral Data Analyses

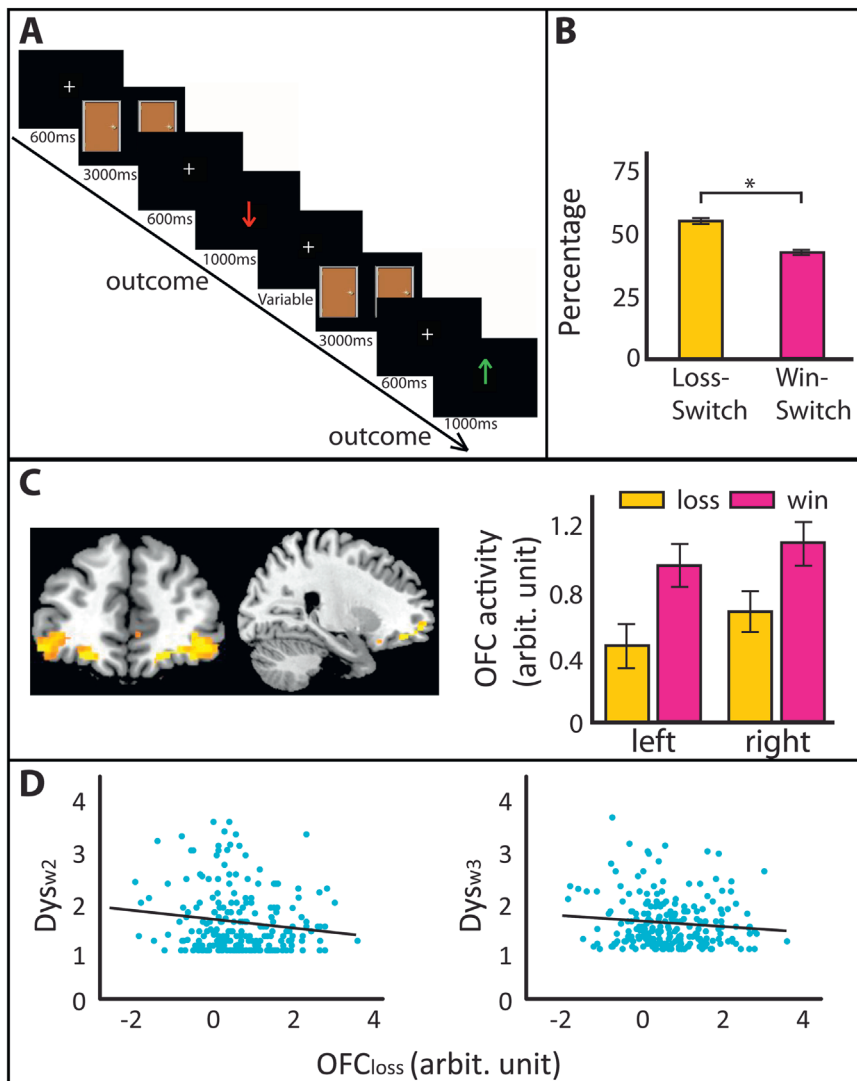
For each subject, we computed the percentage of times the subject switched the choice of door on the next trial ( $n + 1$ ) based on whether the door in the current trial ( $n$ ) yielded loss feedback (loss-switch) or win feedback (win-switch). We compared win-switch and loss-switch using a paired-samples  $t$  test. We also examined choices across time (Supplement).

### fMRI Data Acquisition and Preprocessing

Whole-brain functional and structural MRI images were acquired using gradient echo T2\*-weighted echo planar images on a Siemens Trio 3T MRI whole-body scanner (Siemens, Erlangen, Germany). All functional images were spatially realigned, motion corrected, normalized to standardized space, and spatially smoothed using Statistical Parametric Mapping software (SPM8; <http://www.fil.ion.ucl.ac.uk/spm/software/spm8/>). See the Supplement for details regarding image parameters and preprocessing.

### fMRI Data Analyses

**Subject-Level Model.** A general linear model was estimated by convolving blood oxygenation level-dependent hemodynamic response function with stick ( $\delta$ ) function



**Figure 1.** Monetary gambling task and orbital-frontal cortex (OFC) activity. **(A)** Experimental paradigm. Participants performed a gambling task in which each trial began with the presentation of two identical doors on the left and right sides of the screen simultaneously. Participants were asked to choose between the two doors by clicking one of two buttons corresponding to the left or right door on a magnetic resonance imaging-compatible button box. After a short delay, a predetermined feedback of either loss (red downward arrow indicating  $-25\text{c}$ ) or win (green upward arrow indicating  $+50\text{c}$ ) was revealed. **(B)** Behavioral results. The percentage of loss feedback (Loss-Switch) was significantly higher than that of win feedback (Win-Switch). Error bars represent standard error of the mean, and asterisk (\*) indicates  $p < .001$ . **(C)** OFC activity to losses and wins. Increased left OFC activity (peak coordinates:  $x = -22, y = 46, z = -14$ ) and right OFC activity (peak coordinates:  $x = 24, y = 44, z = -14$ ) was seen for loss and win conditions across all participants ( $p < .05$ , familywise error corrected). The bar graphs show averaged contrast estimates for loss and win conditions for left and right OFC. Error bars represent 95% confidence interval. **(D)** Correlation between OFC activity to loss and depression symptoms. Decreased loss-related OFC activity ( $\text{OFC}_{\text{loss}}$ ) is associated with increased concurrent depression symptoms ( $\text{Dys}_{\text{sw}2}$ ) in the left panel and increased depression symptoms 9 months later ( $\text{Dys}_{\text{sw}3}$ ) in the right panel.

aligned to the onset of feedback for the loss and win conditions (see the [Supplement](#) for details). Contrast maps based on the subject-level per-voxel parameter estimate ( $\beta$ ) maps representing the magnitude of blood oxygen level-dependent response associated with each condition were subjected to group-level  $t$  tests to obtain group-level per-voxel contrast maps of loss or win larger than baseline.

**Region of Interest Analysis.** We first identified OFC voxels that are sensitive to loss or win by examining results of the group-level  $t$  test for loss- or win-related activity within an anatomically defined OFC mask (see the [Supplement](#) for details) at the threshold of  $p < .05$ , familywise error (FWE) corrected. We confirmed that the OFC cluster also survived a more stringent whole-brain threshold of  $p < .05$ , FWE corrected (see the [Supplement](#) for whole-brain results). The maximum probability atlas of Desai DD and Desai DKD maps in FreeSurfer (46,47) was used to check the probability of each resultant cluster as belonging to the OFC. For significant

clusters with a high probability of belonging to the OFC, we separately averaged across voxels in each cluster for loss-related ( $\text{OFC}_{\text{loss}}$ ) and win-related ( $\text{OFC}_{\text{win}}$ ) responses to obtain a mean contrast value as the unbiased summary statistic that was used for examining the association with clinical measures in SPSS, version 22 (IBM Corp., Armonk, NY). Similar region of interest analyses were conducted in striatum and a control region that correlated with concurrent depression ([Supplement](#)).

**Functional Connectivity Analyses.** Functional connectivity during loss and win conditions was examined using a generalized form of psychophysiological interaction analysis implemented in the SPM8 package (48–50) (see the [Supplement](#) for details). The right OFC seed region for connectivity analyses was identified functionally as the region that was most responsive to the task and depression symptoms above. Psychophysiological interaction analysis generated the per-voxel parameter estimate ( $\beta$ ) maps representing the magnitude of functional connectivity between the OFC

seed region and voxelwise activation in the brain as a function of loss and win conditions for each subject. These condition-related  $\beta$  maps were compared at the group level using  $t$  tests at a threshold of  $p < .05$ , whole-brain FWE corrected (voxelwise) for multiple comparisons. We then extracted the averaged contrast values for connectivity of the OFC during loss and win, which were used for correlation and regression with self-report measures in SPSS. The significance of these correlations was determined if the  $r$  value survived Bonferroni correction for multiple clusters ( $\alpha = .05/\text{number of clusters}$ ).

**Association of OFC Activity and Connectivity With Depression Symptoms.** We examined our a priori hypothesis regarding the relationship between task-related OFC activity and connectivity with self-report symptom measures across all participants. First, OFC<sub>loss</sub> and OFC<sub>win</sub> activity or connectivity summary measures derived from significant clusters as described above were correlated with participants' self-reported depression symptoms from the wave concurrent with fMRI data acquisition (Dys<sub>w2</sub>) as well as the wave 9 months later (Dys<sub>w3</sub>). Next, we examined whether the relationship of OFC<sub>loss</sub>, OFC<sub>win</sub>, or OFC connectivity with Dys<sub>w3</sub> was moderated by parental-history even after controlling for Dys<sub>w2</sub>. Accordingly, a hierarchical regression was conducted to predict Dys<sub>w3</sub> using OFC activity or connectivity, parental-history, participant's age at the scan (age), and Dys<sub>w2</sub> at step 1 and the interaction between OFC response or connectivity and parental-history at step 2. After establishing the significant interaction effect, we conducted two regression analyses for the HR and LR groups separately, using OFC response to predict Dys<sub>w3</sub> when controlling for age and Dys<sub>w2</sub>. Finally, because loss/punishment and reward share commonalities in terms of underlying psychological and neural mechanisms (51–53), we also examined whether OFC<sub>loss</sub> or OFC connectivity during loss uniquely predicted future depression even when controlling for OFC<sub>win</sub>. Hence, another hierarchical regression analysis was conducted predicting Dys<sub>w3</sub> using OFC<sub>loss</sub>, OFC<sub>win</sub>, parental-history, Dys<sub>w2</sub>, and age at step 1 and using OFC<sub>loss</sub>  $\times$  parental-history as well as OFC<sub>win</sub>  $\times$  parental-history at step 2. We also examined the relationship of OFC response with other IDAS-II depression and anxiety measures (Supplement).

**Cross-Validation Tests.** To test the robustness of the association between OFC response and Dys<sub>w3</sub> for the HR group, we conducted a 1000 times 3-fold cross-validation analysis on the participants in the HR group. We first obtained the residuals of Dys<sub>w3</sub> regressing out Dys<sub>w2</sub> so that later cross-validation results were not driven by high correlation between Dys<sub>w2</sub> and Dys<sub>w3</sub>. See the Supplement for details of the cross-validation analysis.

## RESULTS

### Loss Feedback Influences Behavior Differently Than Win Feedback

There was a significantly higher percentage of switching choices following loss feedback (loss-switch, mean = 55.48%, SD = 18.02) than following win feedback (win-switch,

mean = 42.99%, SD = 18.43) ( $t_{228} = 6.85, p < .001$ ) (Figure 1B). Hence, participants avoided choosing the same door that yielded loss feedback, an effect that grew stronger over the course of the experiment (second half vs. first half) (Supplement). We did not see a difference in loss-switch ( $t_{227} = -0.114, p = .909$ ) and win-switch ( $t_{227} = -1.013, p = .191$ ) between the HR and LR groups.

### OFC Reactivity to Loss and Win Feedback

Voxelwise  $t$  tests across all participants showed significant bilateral OFC activation to loss (OFC<sub>loss</sub>) and win (OFC<sub>win</sub>) feedback ( $p < .05$ , FWE corrected) (Figure 1C). Overall activity in this region showed no difference between HR and LR for OFC<sub>loss</sub> (mean difference = 0.03,  $t_{227} = 0.176, p = .861$  for left OFC; mean difference = 0.05,  $t_{227} = .308, p = .759$  for right OFC) or for OFC<sub>win</sub> (mean difference = 0.097,  $t_{227} = .670, p = .505$  for left OFC; mean difference = 0.14,  $t_{227} = 1.08, p = .284$  for right OFC). See the Supplement for whole-brain task activation results.

### OFC Reactivity Correlates With Concurrent and Future Depression Symptoms

In the full sample, reduced right OFC<sub>loss</sub> activity was associated with higher Dys<sub>w2</sub> ( $r = -.14, p = .041$ ) and Dys<sub>w3</sub> ( $r = -.14, p = .031$ ) symptoms (Figure 1D and Table 1). In contrast, OFC<sub>win</sub> was not significantly correlated with either Dys<sub>w2</sub> or Dys<sub>w3</sub> symptoms (Table 1).

### OFC Reactivity to Loss Predicts Future Depression Symptoms as a Function of Parental-History

Hierarchical regression revealed a significant OFC<sub>loss</sub>  $\times$  parental-history interaction (Table 2), indicating that reduced OFC<sub>loss</sub> predicted increased Dys<sub>w3</sub> even after controlling for age and Dys<sub>w2</sub>, a relationship that was stronger for HR adolescents than for LR adolescents (Figure 2A). Next, two regression analyses controlling for age and Dys<sub>w2</sub> for HR and LR separately confirmed a significant effect of OFC<sub>loss</sub> for the HR group ( $\beta = -.275, p = .010$ ) but not for the LR group ( $\beta = -.031, p = .635$ ). Furthermore, the OFC<sub>loss</sub>  $\times$  parental-history interaction predicted Dys<sub>w3</sub> even after controlling for OFC<sub>win</sub>

**Table 1. Correlations Between Orbitofrontal Cortex Response to Loss and Depression Measures**

Group	Correlation With Dys <sub>w2</sub>		Correlation With Dys <sub>w3</sub>	
	Loss	Win	Loss	Win
Full Sample (Right)	-.14*	-.06	-.14*	-.06
Full Sample (Left)	-.06	.02	-.09	-.01
Right				
HR	-.26	.24	-.44 <sup>a</sup>	-.22
LR	-.10	.03	-.05	-.03
Left				
HR	-.01	.13	-.22	-.15
LR	-.07	.06	-.05	-.02

Dys<sub>w2</sub>, Inventory of Depressive and Anxiety Symptoms dysphoria on wave 2; Dys<sub>w3</sub>, Inventory of Depressive and Anxiety Symptoms dysphoria on wave 3; HR, high-risk group; LR, low-risk group.

<sup>a</sup> $p < .05$ .



**Table 2. Orbitofrontal Cortex Response to Loss Predicting Future Depression**

Predictor	$R^2$	$F$	$\beta$	$p$
Model at Step 1				
Overall model	.356	30.815	–	<.001
OFC <sub>loss</sub>	–	2.868	–.093	.092
Parental-history	–	1.975	.077	.161
Age	–	2.721	.091	.101
Dys <sub>w2</sub>	–	109.940	.577	<.001
Model at Step 2 $R^2$ change = .012, $p$ = .041				
Overall model	.365	25.857	–	<.001
OFC <sub>loss</sub>	–	6.226	–.157	.013
Parental-history	–	1.929	.076	.166
Age	–	2.606	.088	.108
Dys <sub>w2</sub>	–	108.151	.570	<.001
OFC <sub>loss</sub> × parental-history	–	4.222	–.128	.041

Dys<sub>w2</sub>, Inventory of Depressive and Anxiety Symptoms dysphoria on wave 2; OFC<sub>loss</sub>, orbitofrontal cortex response to loss; parental-history, parental history of depression.

(Table 3). These results were confirmed with the HR group created using participating parents' Structured Clinical Interview for DSM-IV and family history reports of depression in the nonparticipating parents (Supplement). Similar findings were not observed for striatum and a control region as well as other IDAS measures except for lassitude (Supplement).

**Cross-Validation Test of OFC Predicting Future Depression Symptoms**

The predictive power of OFC<sub>loss</sub> for the HR group was supported with a stringent 1000 times 3-fold cross-validation test that showed a moderate correlation (mean  $r$  = .33) between the estimated and observed Dys<sub>w3</sub> scores for the HR group, such that 99.6% of the  $r$  values generated over

**Table 3. Orbitofrontal Cortex Response to Loss and Win Predicting Future Depression**

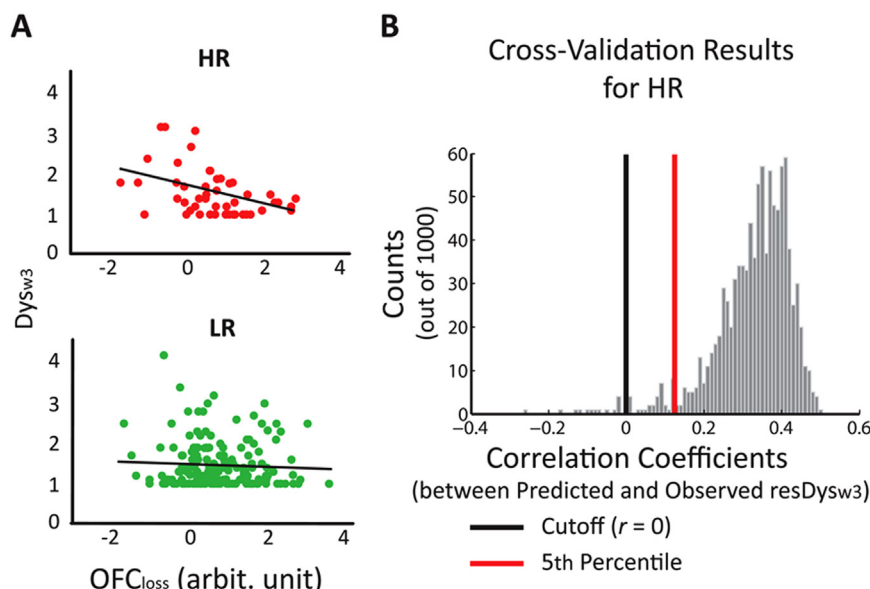
Predictor	$R^2$	$F$	$\beta$	$p$
Model at Step 1				
Overall model	.354	18.681	–	<.001
OFC <sub>loss</sub>	–	6.446	–.130	.084
OFC <sub>win</sub>	–	1.342	.054	.473
Parental-history	–	1.170	.073	.184
Age	–	2.858	.095	.087
Dys <sub>w2</sub>	–	108.707	.575	<.001
Model at Step 2 $R^2$ change = .016, $p$ = .072				
Overall model	.364	18.681	–	<.001
OFC <sub>loss</sub>	–	6.446	–.214	.012
OFC <sub>win</sub>	–	1.342	.132	.248
Parental-history	–	1.170	.060	.281
Age	–	2.858	.093	.092
Dys <sub>w2</sub>	–	108.707	.573	<.001
OFC <sub>loss</sub> × parental-history	–	5.202	–.191	.024
OFC <sub>win</sub> × parental-history	–	1.508	–.139	.221

Dys<sub>w2</sub>, Inventory of Depressive and Anxiety Symptoms dysphoria on wave 2; OFC<sub>loss</sub>, orbitofrontal cortex response to loss; OFC<sub>win</sub>, orbitofrontal cortex response to win; parental-history, parental history of depression.

1000 iterations were above zero (Figure 2B). Similar results were seen with a 5-fold version of the analysis (Supplement).

**Functional Connectivity Between OFC and Insula During Loss Predicts Future Depression Symptoms**

Voxelwise  $t$  tests across all participants for loss or win conditions showed significant OFC connectivity with bilateral caudate and insula ( $p$  < .05, whole-brain FWE corrected) (Supplemental Figure S4 and Table 4). Only stronger OFC-posterior insula connectivity for loss was marginally associated with increased Dys<sub>w2</sub> ( $r$  = .12,  $p$  = .083) and significantly



**Figure 2.** Orbitofrontal cortex (OFC) activity to loss interacts with parental history of depression to predict future depression symptoms. (A) Parental history of depression moderates the relationship between OFC activity to loss and future depression symptoms. The top panel shows a significant correlation between OFC activity to loss (OFC<sub>loss</sub>) and depression symptoms 9 months later (Dys<sub>w3</sub>) for the high-risk (HR) group, whereas the bottom panel shows no correlation between the two for the low-risk (LR) group. (B) Cross-validation analysis of OFC activity to loss predicting future depression for the HR group. Distribution of the Pearson's correlation coefficients between predicted and observed residuals of Dys<sub>w3</sub> (resDys<sub>w3</sub>) obtained from the 1000 times 3-fold cross-validation analysis is shown. The distribution shows that > 95% (the red line marks the 5th percentile) of the correlations are > 0 (indicated by the black line).

**Table 4. Correlation Between Loss-Related Orbitofrontal Cortex Functional Connectivity With Depression Measures**

Region	Peak (x, y, z)	Correlation With Dys <sub>w3</sub>	
		Loss	Win
Caudate (Right)	12, -4, 16	.06	.01
Caudate (Left)	-12, -6, 16	.00	-.02
Insula (Right)	30, 24, -2	.10	.08
Insula (Right)	36, -8, 12	.20 <sup>a</sup>	.08
Insula (Left)	-34, -10, 8	-.00	-.01

Dys<sub>w3</sub>, Inventory of Depressive and Anxiety Symptoms dysphoria on wave 3.

<sup>a</sup> $p < .05$ , Bonferroni corrected for five clusters ( $\alpha = .05/5$ ).

associated with increased Dys<sub>w3</sub> ( $r = .20, p = .003$ ) (Table 4). Hierarchical regression showed a significant main effect of OFC-posterior insula connectivity for loss ( $\beta = .13, p = .020$ ) but no main effect of parental-history ( $\beta = .07, p = .206$ ) or interaction between OFC-posterior insula connectivity for loss and parental-history ( $\beta = -.08, p = .210$ ) in predicting Dys<sub>w3</sub> when controlling age and Dys<sub>w2</sub>. Furthermore, OFC-posterior insula connectivity for loss remained significant ( $\beta = .128, p = .022$ ) even when controlling for win connectivity ( $\beta = .055, p = .319$ ), demonstrating the unique contribution of OFC-posterior insula connectivity for loss to Dys<sub>w3</sub>.

A hierarchical regression model revealed that adding OFC-posterior insula connectivity for loss enhanced predictive power over and above OFC<sub>loss</sub>, parental-history, age, Dys<sub>w2</sub>, and OFC<sub>loss</sub>  $\times$  parental-history in predicting Dys<sub>w3</sub> ( $\Delta R^2 = .02, p = .009$ ), with a significant effect of OFC-posterior insula connectivity for loss ( $\beta = .143, p = .009$ ), whereas both OFC<sub>loss</sub> ( $\beta = -.167, p = .008$ ) and OFC<sub>loss</sub>  $\times$  parental-history ( $\beta = -.145, p = .020$ ) remain significant. This result indicates that OFC activity and connectivity for loss account for unique variance in Dys<sub>w3</sub>.

## DISCUSSION

The role of the OFC in the representation of primary and abstract reinforcers as well as adaptive decision-making is well established (18,19,23,24); however, its role in reward- or loss-related decision making in adolescent depression remains unknown. The current study provides the first evidence that alterations in OFC activity predict future depression symptoms in never-depressed female adolescents who are at high familial risk for developing depression, indicating that aberrant OFC activity and connectivity may represent a vulnerability factor for depression. Due to the OFC's role in the representation and integration of motivationally salient information (22,23), flexible value-based computation (54–59), and adaptive decision making (60–62), the current findings have the potential to clarify how complex representations of loss and reward, as well as their integration, contribute to the development of future depression.

Our finding showing that decreased OFC response to loss in adolescents is associated with increased depression symptoms is consistent with findings in adult depression showing that reduced superior frontal gyrus activity in response to loss is associated with increased depressive rumination symptoms (28). Reduced frontal activity in response to loss in depression

has been interpreted as indicative of increased sensitivity to loss (28). However, the relationship between the direction of OFC activity and the direction of loss sensitivity can be studied only by manipulating levels or magnitude of loss, which few studies have done. In one study, the OFC as well as other regions involved in loss or reward processing showed parametrically increasing activity with increasing gains and parametrically decreasing activity with increasing losses, with a steeper negative slope for increasing losses compared with a corresponding positive slope for increasing gains, consistent with the pattern of loss aversion (63). Another study found this pattern for the medial parts of the OFC but not for the lateral OFC (18). Because greater sensitivity to loss has been linked to depressive symptoms (64), reductions in OFC activity that predict future depression in our study may be indicative of greater sensitivity to loss; however, further studies that parametrically modulate the magnitude of losses and examine its relationship with severity of depression symptoms are needed.

The role that the OFC plays in integrating information regarding negative and positive motivational values of stimuli and subsequent decision making is attributed to its strong anatomical connectivity with higher sensory cortices of all modalities and reciprocal connections with areas such as amygdala, hippocampus, and striatum (24,65). In the current study, we found that increased functional connectivity of the OFC with posterior insula during loss was associated with concurrent and future depression even when controlling for concurrent depression. Unlike OFC activity, the relationship between OFC connectivity and future depression was not moderated by a parental history of depression, indicating that it may be a vulnerability factor independent of familial history of depression. Evidence suggests that posterior insula receives sensory information across modalities (66) and supports the primary cortical representation of interoceptive signals (67), playing an important role in emotional awareness (68). In line with this role of posterior insula, the functional connectivity of the OFC and posterior insula in response to loss may be indicative of integration of the value of loss with its emotional and interoceptive awareness, with a stronger integration predicting more severe future depression symptoms.

While the OFC was responsive to both loss and win in the current study, it is interesting that OFC activity and connectivity changes in response to loss, but not to win, predicted concurrent and future depression symptoms. Exploring the role of both loss and reward sensitivity is critical to understanding how adolescents make choices to engage in or avoid real-life situations, why these choices may differ across development, and how they contribute to the development of internalizing and externalizing disorders. Economic models of decision making have suggested that losses actually loom larger than gains for most individuals, including adolescents (10); that is, the aversiveness of a potential loss is greater than the desirability of an equal potential gain, referred to as loss aversion. Keeping in mind this difference, the loss magnitude in our task was half the reward magnitude in an attempt to make the subjective magnitude of the two conditions comparable. Despite this, we found that, behaviorally, participants show very different patterns of responding following win and loss feedback. Neurally, decreased OFC response to losses

uniquely predicted future depression, over and above response to wins, which is consistent with previous findings in other regions (69), indicating the importance of this measure as a vulnerability factor in the development of depression. Overall, the stronger relationship between the OFC and future depression symptoms may be because losses (compared with wins) have a significantly greater effect on decision making, which may contribute to future depression symptoms in adolescents.

Our study is limited because history of depression was thoroughly assessed only in the participating parent. To address this limitation, we confirmed that our results remained the same when the risk groups were defined based on a history of depression in participating and nonparticipating parents (see Supplement). In addition, a follow-up duration longer than 9 months may be helpful in studying adolescents meeting criteria for depression diagnosis. While our study highlights how neural reactivity to reward or loss feedback predicts depression, future studies using more complex paradigms are needed to pinpoint which specific aspects of motivational processing are impaired. These include tasks examining neural reactivity during anticipation as well as changing magnitude of rewards and losses. In addition, tasks involving more complex contingency learning and choice behavioral models (70–72), particularly with more trials, would allow researchers to tease apart trial-by-trial effects (72).

Adolescence is a high-risk time for onset of depression, and this period also coincides with active development of the OFC (73). Research shows that a relatively delayed developmental trajectory of the OFC compared with the striatum may underlie aberrant decision making in adolescents (25). In addition, compared with adults, adolescents generally show an increased response in subcortical regions to emotionally salient stimuli, paired with a decreased response in frontal regions when cognitive control or regulation is required (74). Furthermore, keeping in mind the complexity and abstractness of reinforcers that adolescents experience, such as praise, peer acceptance, and peer rejection, the OFC is an ideal candidate for investigation of loss and reward sensitivity in adolescent depression. Our study provides initial evidence for decreased OFC activity and increased OFC-insula connectivity during loss processing as possible mechanisms that are involved in the development of future depression. Furthermore, decreased OFC activity interacts with risk due to parental history of depression to predict future depression symptoms. In a reward literature that has focused largely on subcortical mechanisms, the current findings underscore the need to include the role of prefrontal loss processing in existing developmental models of depression. The current findings also highlight the need for studies on the developmental progression of loss processing as well as its different components and their contribution to decision making in real-life situations and ultimately to the development of depressive disorders.

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