Biological Psychiatry: CNNI

# Archival Report

# Reward Functioning Abnormalities in Adolescents at High Familial Risk for Depressive Disorders

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## ABSTRACT

**BACKGROUND:** A parental history of major depressive disorder (MDD) is an established risk factor for MDD in youth, and clarifying the mechanisms related to familial risk transmission is critical. Aberrant reward processing is a promising biomarker of MDD risk; accordingly, the aim of this study was to test behavioral measures of reward responsiveness and underlying frontostriatal resting activity in healthy adolescents both with (high-risk) and without (low-risk) a maternal history of MDD.

**METHODS:** Low-risk and high-risk 12- to 14-year-old adolescents completed a probabilistic reward task ($n$ = 74 low-risk, $n$ = 27 high-risk) and a resting-state functional magnetic resonance imaging scan ($n$ = 61 low-risk, $n$ = 25 high-risk). Group differences in response bias toward reward and resting ventral striatal and medial prefrontal cortex (mPFC) fractional amplitude of low-frequency fluctuations (fALFFs) were examined. Computational modeling was applied to dissociate reward sensitivity from learning rate.

**RESULTS:** High-risk adolescents showed a blunted response bias compared with low-risk adolescents. Computational modeling analyses revealed that relative to low-risk adolescents, high-risk adolescents exhibited reduced reward sensitivity but similar learning rate. Although there were no group differences in ventral striatal and mPFC fALFFs, groups differed in their relationships between mPFC fALFFs and response bias. Specifically, among high-risk adolescents, higher mPFC fALFFs correlated with a blunted response bias, whereas there was no fALFFs–response bias relationship among low-risk youths.

**CONCLUSIONS:** High-risk adolescents exhibit reward functioning impairments, which are associated with mPFC fALFFs. The blunted response bias–mPFC fALFFs association may reflect an excessive mPFC-mediated suppression of reward-driven behavior, which may potentiate MDD risk.

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A parental history of major depressive disorder (MDD) is a robust risk factor for MDD development (1). Thus, clarifying the mechanisms that may facilitate this familial transmission of risk is an important area of research. Reward processing deficits have emerged as a promising mechanism in this area (2). Early adolescence, particularly the ages spanning 12 to 14, is an important developmental window for studying reward functioning (2), as it is a period of peak sensitivity of reward-related neural regions (3–6) and increased MDD occurrence (7).

Although impaired reward responsiveness characterizes adolescents exhibiting depressive episodes (8,9), behavioral evidence for reward functioning deficits in youths at familial high risk has been mixed. Studies conducted in young children found that high-risk children displayed less positive affect on laboratory tasks relative to low-risk children (10,11). Moreover, a sample of high-risk late adolescents and young adults showed reduced reward seeking compared with low-risk individuals (12). However, other investigators have failed to find blunted reward responsiveness among high-risk offspring or have found this only among offspring already exhibiting depressive symptoms, making it difficult to tease apart familial risk versus symptom contributions to reward-related deficits (8,13,14). Furthermore, considering developmental differences in neural responsivity to rewards (3–6), some research falls outside early adolescence or spans wide age ranges, which may preclude identifying premorbid reward processing deficits (8,10–14). Additionally, no studies have applied computational modeling analyses to better determine which specific reward processes are impaired in high-risk adolescents, which may help clarify inconsistent findings.

Neuroimaging studies examining ventral striatum (VS) and medial prefrontal cortex (mPFC) correlates of reward functioning as well as electrophysiological studies probing reward-related reward positivity/feedback negativity event-related potentials have yielded more consistent findings among youths at familial risk for MDD. Specifically, mirroring activation patterns seen in adolescents with depression (15–19), relative to low-risk youths, high-risk children and adolescents exhibit

 
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reduced VS activation and feedback negativity following rewarding stimuli (16,20–26). With regard to the mPFC, a recent meta-analysis demonstrated evidence for increased mPFC activation during reward processing tasks in MDD (27). However, a study in high-risk young adults reported blunted mPFC activation in response to rewards compared with the low-risk group, suggesting potential differences in individuals with current MDD versus individuals at familial risk for depression (28). The mixed findings may also reflect differences in reward task designs.

Examining VS and mPFC activity at rest allows for assessment of neural functioning without the confounds of task design differences. Aberrant VS and mPFC functional activity persist even at rest among individuals with and at high familial risk for MDD (29,30). Highlighting the importance of these resting neural abnormalities to MDD pathophysiology, a recent meta-analysis demonstrated that brain functional alterations at rest may be a more robust biomarker of MDD than task-based neural deficits (31). Intrinsic neural activation at rest can be examined by computing the amplitude of low-frequency fluctuations (ALFFs) or fractional ALFFs (fALFFs), a relative measure of ALFFs, derived from dividing the resting amplitude within a given power spectrum (e.g., 0.008–0.09 Hz) by the total power spectrum (32,33). The measurement of fALFFs is less susceptible to physiological noise and has a higher sensitivity and specificity than measurement of ALFFs (32,33). Whereas traditional resting-state functional connectivity approaches examine coactivation patterns between brain regions, ALFF/fALFF values provide an index of the strength of resting activity within a single brain region. Directly pertinent to the current study, several studies have linked ALFFs/fALFFs to aberrant cognitive functioning in MDD along with illness severity, suggesting relevance for MDD pathophysiology (34–38). Relative to healthy control subjects, adults with MDD show greater ALFFs/fALFFs in mPFC and striatal regions (29,30,34,35,37,39–41). However, among depressed adolescents, there is evidence of less striatal fALFFs (42). With respect to at-risk samples, one study found that healthy adult siblings of individuals with MDD showed greater mPFC fALFFs compared with subjects without a sibling with MDD (30). However, to date, no study has examined fALFF alterations in high-risk adolescents with a parental history of MDD. Additionally, no one has examined whether VS and mPFC fALFFs may track premorbid reward processing impairments in high-risk samples. Notably, studies conducted in healthy individuals have demonstrated that VS and mPFC resting activity and coactivation are linked to individual differences in behavioral responses to rewards (43–45), suggesting that VS and mPFC resting fALFFs may serve as promising neural markers underlying reward deficits in high-risk youths.

With the goal of determining whether there are premorbid behavioral and neural alterations impacting reward processes, the current study compared 12- to 14-year-old healthy adolescents at low and high risk for MDD, with risk operationalized as having a maternal MDD history. Group differences in reward responsiveness and reward learning were tested. We expected that high-risk adolescents would exhibit a reduced bias toward a more frequently rewarded stimulus on a probabilistic reward task (PRT) (46) compared with low-risk adolescents. Computational modeling analyses were also conducted on the PRT data to evaluate whether familial risk for MDD is associated with abnormalities in reward sensitivity (an index of consummatory pleasure in response to rewarding stimuli) and/or learning rate (a measure of the ability to learn from rewarding feedback). Although yet to be conducted in healthy at-risk samples, studies using computational modeling to study reward processes have linked MDD to reward sensitivity (but not learning rate) abnormalities (47,48). Thus, we predicted that compared with low-risk adolescents, high-risk adolescents would show impaired reward sensitivity, but intact learning rate.

Moreover, given growing evidence supporting the relevance of VS and mPFC fALFFs to MDD pathophysiology and reward processing deficits, exploratory analyses examining group differences in fALFFs within these regions were conducted. Additionally, relationships between VS and mPFC fALFFs with behavioral measures of reward responsiveness and how these associations may differ as a function of MDD risk status were tested. Although resting-state magnetic resonance imaging (MRI) studies traditionally focus on one common frequency band (e.g., 0.008–0.09 Hz), evidence points to several independent frequency bands, each with their own unique properties and functions (33,34,49,50). Consequently, different frequency bands have uncovered distinct fALFF abnormalities in psychiatric disorders, supporting the importance of assessing multiple frequency bands (34,49,51,52). Pertinent to the current study, low-frequency oscillations in the VS are best characterized by a slow-4, 0.027- to 0.073-Hz band (33,49,50). Supporting the functional relevance of different frequency bands, preclinical studies have shown that slow-4 VS oscillations were selectively modulated by dopaminergic drugs (53–55). Conversely, low-frequency fluctuations in the mPFC are maximal in a slow-5, 0.01- to 0.027-Hz band (33,49,50). Thus, we tested VS and mPFC in their respective maximal frequency bands in addition to supplemental analyses within a 0.008- to 0.09-Hz band. We predicted that high-risk adolescents would show increased VS and mPFC fALFFs compared with low-risk adolescents and that higher fALFFs within these regions would be associated with more impaired reward responsiveness.

## METHODS AND MATERIALS

### Participants

The study enrolled 95 mothers with no lifetime depressive disorders (low-risk) and current mental health disorders and 32 mothers with a lifetime unipolar depressive diagnosis (high-risk) along with their respective 12- to 14-year-old adolescent offspring (for statistical power considerations, see Supplemental Methods). To allow for unambiguous interpretations, exclusion criteria for all adolescents included lifetime mental disorders, current psychotropic medication use, presence of any medical or neurological illnesses, and any MRI contraindications. Two low-risk participants were excluded given a personal history of nonsuicidal self-injury and a current maternal posttraumatic stress disorder diagnosis. A high-risk participant was excluded because of a past MDD episode. An additional 19 low-risk and 4 high-risk adolescents failed to pass quality control criteria for the PRT (see Supplemental Methods). Thus, the final sample included 74

**Table 1. Demographic and Clinical Characteristics of Healthy Adolescents at High and Low Familial Risk for Major Depressive Disorder**

| | Low Risk ($n$ = 74) | High Risk ($n$ = 27) | $t/\chi^2$ ($df$) | $p$ |
|---|---|---|---|---|
| Sex, Female, % | 63.5 | 63.0 | 0.003 (1) | .959 |
| Age, Years, Mean (SD) | 12.95 (0.86) | 13.19 (0.79) | −1.267 (99) | .208 |
| Tanner Scale, Mean (SD) | 3.10 (0.59) | 3.10 (0.66) | −0.002 (99) | .998 |
| Ethnicity, White, % | 86.5 | 85.2 | 0.028 (1) | .867 |
| Family Income, % | | | 0.053 (1) | .818 |
| ≤ $100,000 | 24.3 | 29.6 | – | – |
| > $100,000 | 64.9 | 70.4 | – | – |
| Unreported | 10.8 | 0.0 | – | – |
| Depression Symptoms, Mean (SD)[a] | 5.78 (6.73) | 8.30 (8.11) | −1.755 (99) | .082 |
| Anhedonia Symptoms, Mean (SD)[b] | 20.60 (4.72) | 21.37 (4.26) | −0.746 (99) | .458 |
| Anxiety Symptoms, Mean (SD)[c] | 34.12 (11.51) | 42.05 (12.82) | −2.970 (99) | .004 |
| Lifetime Maternal MDD, % | 0 | 96.3 | – | – |
| Maternal Depressive Disorder NOS, % | 0 | 3.7 | – | – |
| Maternal Current Depressive Episode, % | 0 | 7.4 | – | – |
| Maternal Single Depressive Episode, % | 0 | 48.1 | – | – |
| Maternal Recurrent Depressive Episode, % | 0 | 51.9 | – | – |
| Maternal Current Panic Disorder, % | 0 | 0 | – | – |
| Maternal Past Panic Disorder, % | 0 | 3.7 | – | – |
| Maternal Current Social Phobia, % | 0 | 7.4 | – | – |
| Maternal Past Social Phobia, % | 1.4 | 18.5 | – | – |
| Maternal Current Specific Phobia, % | 0 | 7.4 | – | – |
| Maternal Past Specific Phobia, % | 1.4 | 7.4 | – | – |
| Maternal GAD, % | 0 | 18.5 | – | – |
| Maternal Current PTSD, % | 0 | 3.7 | – | – |
| Maternal Past PTSD, % | 0 | 11.1 | – | – |
| Maternal Current Alcohol/Substance, % | 0 | 0 | – | – |
| Maternal Past Alcohol/Substance, % | 6.8 | 22.2 | – | – |

Current Alcohol/Substance, current alcohol/substance use abuse or dependence; GAD, generalized anxiety disorder; MDD, major depressive disorder; NOS, not otherwise specified; Past Alcohol/Substance, past alcohol/substance use abuse or dependence; PTSD, posttraumatic stress disorder.

[a]Depressive symptoms were measured with the Mood and Feelings Questionnaire.

[b]Anhedonia symptoms were measured with the Snaith-Hamilton Pleasure Scale.

[c]Anxiety symptoms were measured with the Multidimensional Anxiety Scale for Children.

low-risk mother-adolescent ($n$ = 47 female, $n$ = 27 male) dyads and 27 high-risk mother-adolescent ($n$ = 17 female, $n$ = 10 male) dyads. Demographic information and maternal clinical characteristics are summarized in Table 1 (see Supplemental Methods for more information about maternal inclusion/exclusion criteria).

## Procedures

The study was approved by the Partners Institutional Review Board. Adolescents assented, and their mothers provided written consent. During the first visit, mothers completed a clinical diagnostic interview regarding personal lifetime mental disorders. Adolescents were administered a diagnostic interview about lifetime mental disorders, completed self-report symptom questionnaires, and performed the PRT. Adolescents were invited for a second session involving structural (56), resting-state functional MRI (fMRI), and task-based fMRI (57,58) scans. Adolescents received $80 and their parents received $20 for their participation.

## Clinical Instruments

**Diagnostic Interviews.** Adolescents were administered the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (59), a semistructured interview that assesses adolescent DSM-IV lifetime mental disorders. Mothers were administered the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (60), which assessed lifetime mental disorders. Recorded interviews were randomly selected (Schedule for Affective Disorders and Schizophrenia for School-Age Children, $n$ = 10, and Structured Clinical Interview for DSM-IV-TR Axis I Disorders, $n$ = 10, evenly split between high-risk and low-risk dyads), for interrater reliability analyses. Reliability was excellent (Schedule for Affective Disorders and Schizophrenia for School-Age Children mean $\kappa$ = 1.00; Structured Clinical Interview for DSM-IV-TR Axis I Disorders mean $\kappa$ = .918).

**Adolescent Self-reported Measures.** Adolescents completed the Tanner scale (61), a measure of pubertal status, along with the Mood and Feelings Questionnaire (62), Snaith-

Hamilton Pleasure Scale (63), and Multidimensional Anxiety Scale for Children (64) to assess for depression, anhedonia, and anxiety symptoms, respectively (for more information about clinical measures, see the Supplement). The internal consistency for all clinical symptom measures ranged from good to excellent (Mood and Feelings Questionnaire $\alpha$ = .915; Snaith-Hamilton Pleasure Scale $\alpha$ = .844; Multidimensional Anxiety Scale for Children $\alpha$ = .829).

### Probabilistic Reward Task

Participants completed a 15-minute computer-based version of the social reward PRT (46). The PRT utilizes signal detection theory to assess a person's propensity to modify behavior based on reinforcement history. The PRT task consisted of 2 blocks of 100 trials each. Each trial began with a 500-ms fixation cross followed by a 500-ms face without a mouth. Next, a short mouth (10 mm) or a long mouth (11 mm) was presented briefly on the face for 100 ms. Participants were then asked to determine whether a short mouth or a long mouth was presented with a key press. In each block, social praise feedback was provided for 40 trials with a correct response ("Correct! You are doing well on this task" along with an image of a medal with "Good Job" written on it). Participants were told to respond as quickly and accurately as possible and that not all correct responses would be followed by feedback. Long and short mouths were presented with equal frequency. However, without the participant's knowledge, one mouth length was rewarded 3 times more frequently (the rich stimulus) than the other mouth length (the lean stimulus).

### Behavioral Data Processing

For detailed information about PRT quality control procedures, see Supplemental Methods. After the quality control procedures, response bias and discriminability were computed using the following equations:

$$\text{Response bias: } \log b = \frac{1}{2}\log\left(\frac{\text{Rich}_{\text{correct}} * \text{Lean}_{\text{incorrect}}}{\text{Rich}_{\text{incorrect}} * \text{Lean}_{\text{correct}}}\right)$$

$$\text{Discriminability: } \log d = \frac{1}{2}\log\left(\frac{\text{Rich}_{\text{correct}} * \text{Lean}_{\text{correct}}}{\text{Rich}_{\text{incorrect}} * \text{Lean}_{\text{incorrect}}}\right)$$

To allow computations for instances in which there was zero in the formula, 0.5 was added to every cell in the matrix (46). Mean accuracy and reaction time also were computed.

### Computational Modeling

Consistent with prior work (47,48,65), a series of reinforcement learning models were fitted to the PRT choice data to separate the influence of reward sensitivity and learning rate on performance (see Supplemental Methods).

### fMRI Acquisition and Preprocessing

Imaging acquisition and fMRI preprocessing details are in Supplemental Methods. Structural and 5-minute resting-state fMRI scans were collected on a 3T TIM Trio MRI scanner (Siemens Healthcare AG, Erlangen, Germany). Participants viewed a black screen and were instructed to keep their eyes open. Participants with >20% of their volumes marked as motion-related outliers were removed from fMRI analyses, resulting in exclusion from all fMRI analyses of 14 adolescents in the low-risk group and 2 adolescents in the high-risk. Thus, the final sample for fMRI analyses included 61 low-risk adolescents and 25 high-risk adolescents.

### fALFF Analysis

The CONN toolbox (66) was used to conduct the fALFF analysis. Data were passed through both slow-4 (0.027–0.073 Hz) and slow-5 (0.01–0.027 Hz) frequency band filters, along with a third, more typical resting-state band pass filter (0.008–0.09 Hz) to test whether putative findings would generalize to a broader filter (findings reported in Supplement). For each voxel, the filtered time series was transformed to the frequency domain using a discrete cosine transform. A voxelwise fALFF analysis was conducted by calculating the average square root of power within each of the 3 frequency bands of interest separately for each voxel and dividing by the total power spectrum. All fALFF maps were standardized into subject-level *z* score maps. Mean fALFF measures within predefined bilateral VS and mPFC region of interest masks were extracted using the function spm_summarise (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/). The VS fALFF measure was extracted from the slow-4 *z* score normalized fALFF map, and the mPFC fALFF measure was extracted from the slow-5 *z* score normalized fALFF map. The bilateral VS mask was derived from the Oxford-GSK Imanova structural anatomical striatal atlas (67), and the mPFC mask was derived from a prior resting-state fMRI meta-analysis of MDD (68).

### Group-Level Statistics

Group differences in age, number of motion outliers, pubertal status, depression, anhedonia, and anxiety symptoms were examined with independent-sample *t* tests. Group differences in gender, ethnicity, and family income were examined via $\chi^2$ tests. A set of Pearson correlations were conducted to characterize relationships between symptom measures.

To examine group differences in response bias and discriminability, we conducted 2 separate group (high, low) × block (1, 2) mixed model analyses of covariance (ANCOVAs). Given that there were significant group differences in anxiety symptoms, which may influence reward processing (69), anxiety symptoms were included as a covariate in all statistical models. The 2 analysis of covariance tests conducted on traditional PRT metrics (response bias, discriminability) were Bonferroni-corrected for multiple comparisons ($p < .025$).

Two separate ANCOVAs were conducted to examine group differences in reward sensitivity and learning rate parameters. These 2 tests were Bonferroni-corrected for multiple comparisons ($p < .025$). Finally, 2 secondary group × block × stimulus (rich, lean) mixed model ANCOVAs were conducted to assess group differences in accuracy rates and reaction time, respectively.

To characterize relationships between response bias, group status, and fALFF measures, we conducted 2 exploratory multiple linear regressions, with mean slow-4 VS fALFF and slow-5 mPFC fALFF values each serving as the dependent variable and group, response bias, and group × response bias being predictors as well as covarying for anxiety symptoms.

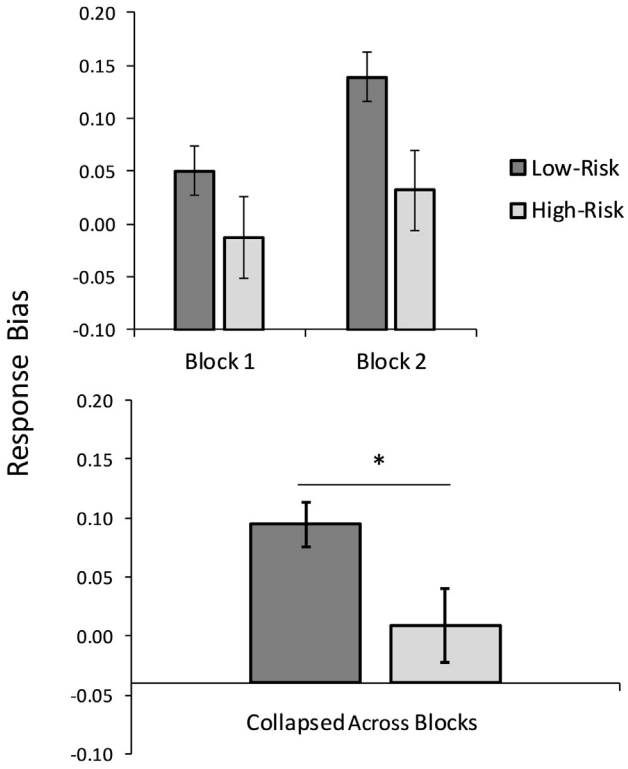


**Figure 1.** The high-risk adolescent group ($n$ = 27) showed an overall significantly reduced response bias toward a more frequently rewarded stimulus relative to the low-risk group ($n$ = 74). *$p$ < .05.

Complementary multiple linear regressions were run again within the 0.008- to 0.09-Hz frequency band for both VS and mPFC regions. Another set of secondary multiple linear regressions was conducted to examine possible associations between mean slow-4 VS fALFF and slow-5 mPFC fALFF values with the computational modeling derived reward sensitivity and learning rate parameters. Given that fALFF analyses were exploratory, all results are displayed uncorrected for multiple comparisons.

## RESULTS

### Participants' Characteristics and Individual Differences

Descriptive statistics are summarized in Table 1. High-risk and low-risk adolescents did not significantly differ in gender, age, pubertal development, ethnicity, or family income. Additionally, high-risk and low-risk adolescents did not significantly differ in depression (Mood and Feelings Questionnaire) and anhedonia (Snaith-Hamilton Pleasure Scale) symptoms; however, the high-risk group reported greater anxiety symptom (Multidimensional Anxiety Scale for Children) levels than the low-risk group, albeit in a range that was not clinically impairing. There were no significant group differences in motion-related fMRI outliers (see Supplemental Results). For correlations between symptom measures, see Supplemental Results.

### Probabilistic Reward Task

**Response Bias.** There was a significant main effect of group, with high-risk adolescents showing a lower overall response bias compared with low-risk adolescents ($F_{1,98}$ = 5.302, $p$ = .023, $\eta_p^2$ = .051) (Figure 1). There also was a main effect of anxiety that did not survive correction for multiple comparisons, with higher anxiety levels being associated with a greater response bias ($F_{1,98}$ = 5.053, $p$ = .027, $\eta_p^2$ = .049). There was no significant main effect of block or group × block interaction (all $F$s < 1.000, $p$s > .300).

**Discriminability.** The main effects of group ($F_{1,98}$ = 0.063, $p$ = .803, $\eta_p^2$ = .001), block ($F_{1,98}$ = 0.510, $p$ = .477, $\eta_p^2$ = .005), and group × block interaction ($F_{1,98}$ = 0.002, $p$ = .964, $\eta_p^2$ < .001) were not significant. There were no significant main effects or interactions with anxiety (all $F$s < 2.100, $p$s >.100). See Supplemental Results and Figure S1 for results from secondary accuracy and reaction time variables.

### Computational Modeling of PRT

The ANCOVA revealed a significant main effect of group on the reward sensitivity parameter ($F_{1,98}$ = 5.891, $p$ = .017, $\eta_p^2$ = .057) owing to lower reward sensitivity in the high-risk group compared with the low-risk group (Figure 2). There was no significant main effect of anxiety ($F_{1,98}$ = 1.991, $p$ = .161). Groups did not differ in learning rate ($F_{1,98}$ = 0.429, $p$ = .514, $\eta_p^2$ = .004), and there was no significant effect of anxiety ($F_{1,98}$ = 0.969, $p$ = .327).

### Exploratory fALFF Results

There were no group differences in mean slow-4 frequency band VS fALFF values (β = −.040, $B$ = −0.020, $t$ = −0.346, $p$ = .730, $f^2$ = 0.001). Additionally, there were no significant associations between mean VS fALFF values and response bias, and there were no group differences in slow-4 VS–response bias associations ($p$s > .300). However, there was a significant main effect of anxiety, with higher levels of anxiety being associated with greater slow-4 VS fALFFs (β = .235, $B$ = 0.004, $t$ = 2.022, partial $r$ = .219, $p$ = .046, $f^2$ = 0.050) (Figure 3). With respect to slow-5 mPFC fALFFs, there were no significant group differences (β = −.060, $B$ = −0.043, $t$ = −0.512, $p$ = .610, $f^2$ = 0.003). There was a trend for a group × response bias interaction on slow-5 frequency band mPFC fALFFs (β = −.237, $B$ = −1.100, $t$ = −1.902, $p$ = .061, $f^2$ = 0.04). Follow-up multiple regressions examining each group separately demonstrated that among the high-risk adolescents, a lower response bias was associated with higher mPFC fALFFs (β = −.510, $B$ = −1.131, $t$ = −2.777, partial $r$ = −.509, $p$ = .011) (Figure 4), but a nonsignificant association among low-risk adolescents (β = −.017, $B$ = −0.033, $t$ = −0.121, partial $r$ = −.016, $p$ = .904). There was no significant main effect of response bias or anxiety symptoms on slow-5 mPFC fALFFs ($p$s > .500). This same pattern of results was found when examining VS and mPFC fALFFs with the traditional 0.008- to 0.09-Hz band (see Supplemental Results).

Secondary multiple regressions with computational modeling parameters did not show associations between reward sensitivity or learning rate parameters with mPFC or VS fALFFs (all $p$s > .150). Additionally, there were no group

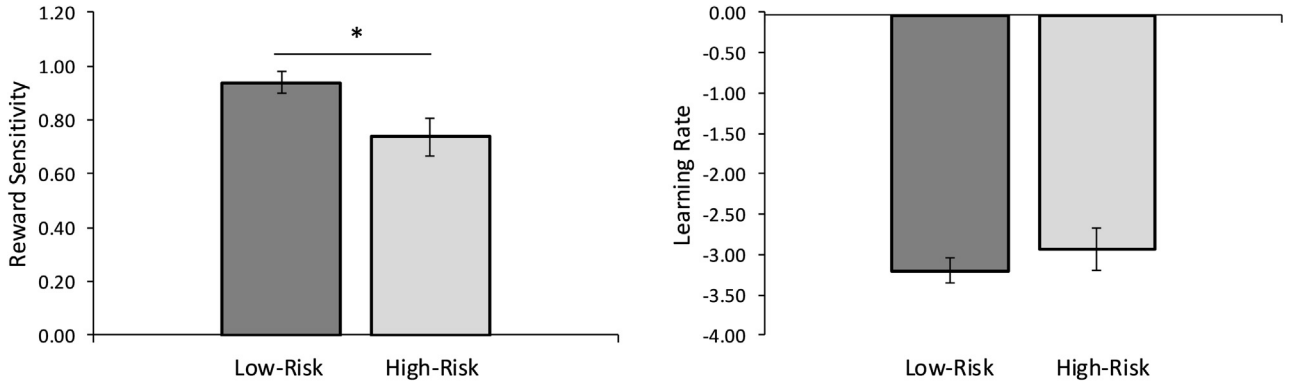


**Figure 2.** Computational modeling analyses revealed that the high-risk adolescent group ($n$ = 27) exhibited a reduction in reward sensitivity (i.e., consummatory pleasure), but not learning rate (i.e., learning from rewarding feedback) compared with the low-risk adolescent group ($n$ = 74). Note that parameters were analyzed in the transformed space to avoid issues with non-Gaussianity; larger magnitude indicates better ability. *$p < .05$.

differences in associations between the computational modeling–derived parameters and mPFC or VS fALFFs (all $p$s $> .100$). Tables S1–S10 contain the full model results for all PRT and imaging analyses.

### Follow-up Sensitivity Analyses

All of the above analyses were run again including gender as a factor/predictor and controlling for depression and anhedonia symptoms. Additionally, we reran the analyses without low-risk participants who had a parent with a past psychiatric diagnosis. The results remained intact under both sets of follow-up analyses (see Tables S11–S20).

## DISCUSSION

The primary aim of this study was to test reward system functioning in healthy adolescents at low and high risk for MDD owing to a maternal history of depression. Consistent with our hypotheses, compared with the low-risk adolescents, high-risk adolescents showed reward functioning impairments as manifested in reduced response bias toward a more frequently rewarded stimulus. Importantly, these group differences survived when controlling for clinical symptoms and thus were not unduly influenced by symptomatic differences.

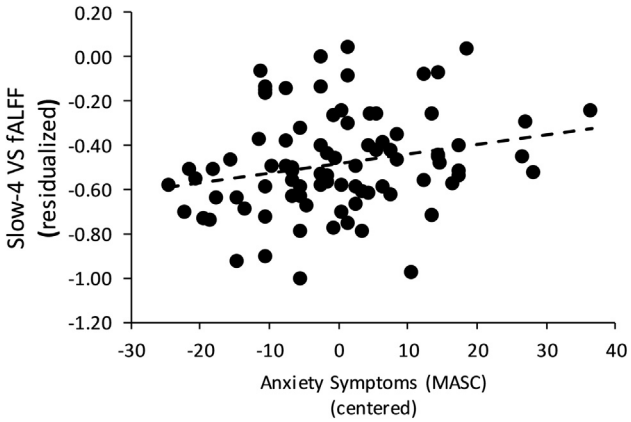


**Figure 3.** Higher levels of anxiety on the Multidimensional Anxiety Scale for Children (MASC) were associated with greater mean ventral striatum (VS) fractional amplitude of low-frequency fluctuation (fALFF) values.

To further understand the mechanisms that may be driving group differences in reward functioning, we conducted computational modeling analyses based on a reinforcement learning model. We tested 2 possible mechanisms—reward sensitivity (a measure of consummatory pleasure) and learning rate (an index of the ability to learn from rewarding feedback). Results indicated that high-risk adolescents were characterized by lower reward sensitivity, but an intact learning rate compared with low-risk adolescents. This suggests that although high-risk and low-risk adolescents showed comparable learning rates, high-risk adolescents may find the rewarding information to be less salient, pleasurable, and motivating, which is consistent with prior research implicating reward sensitivity, but not learning rate, in MDD pathophysiology and treatment response (47,48,65). Together, this suggests that reward processing impairments may be a premorbid vulnerability marker for MDD especially prominent during early adolescence. To the best of our knowledge, this is the first study to test reward sensitivity versus learning rate impairments among individuals at risk for MDD, and the computational modeling clarified that reduced pleasure in response to rewarding feedback may be the more salient reward-related risk marker present before illness onset.

Alterations in resting VS and mPFC fALFFs, potentially underlying reward responsiveness impairments in high-risk offspring, were also probed. Contrary to our hypotheses, we did not find group differences in VS and mPFC fALFFs. Only one study has examined resting fALFFs in a high-risk sample, with results demonstrating that high-risk adults show greater mPFC fALFFs compared with low-risk adults (30). Given the sparse work in high-risk samples, it is possible that our findings indicate that VS and mPFC fALFF disruptions emerge after MDD onset. It is also possible that aberrant frontostriatal fALFFs are not evident during adolescence yet or are unique to sibling-risk transmission, as the prior positive finding was exhibited in siblings of adults with MDD. Future work is needed to address these possibilities. However, higher anxiety levels were linked to VS fALFFs, which is consistent with prior work linking anxiety pathology to resting striatal dysfunction (70,71).

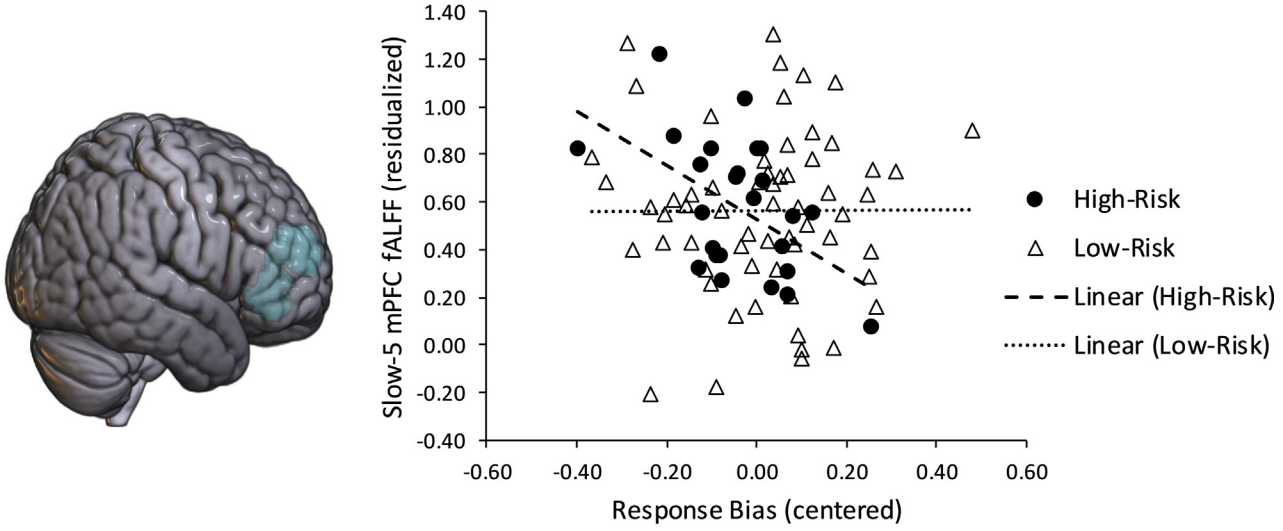


**Figure 4.** Among high-risk adolescents ($n$ = 25), a lower response bias to the more frequently rewarded stimulus was significantly associated with higher mean slow-5 frequency band resting medial prefrontal cortex (mPFC) fractional amplitude of low-frequency fluctuation (fALFF) values. There were no significant fALFF–response bias associations in the low-risk group ($n$ = 61).

Additionally, there were group differences in how mPFC fALFFs related to reward response bias. Specifically, among the high-risk adolescents, higher mPFC fALFFs were linked to a lower response bias. Conversely, there were no significant fALFF and response bias associations among low-risk adolescents.

Preclinical work has established that mPFC hyperactivation can suppress adaptive responses to rewarding stimuli (72,73). Consistent with this work, a study conducted in healthy adults showed that higher mPFC fALFFs were linked to lower positive affect and psychological resilience (74). Thus, it is possible that the negative association between mPFC fALFFs and response bias among high-risk adolescents may reflect an excessive mPFC-mediated top-down regulation of reward-driven behavior. The mPFC is also a core hub of the default mode network, a network shown to be especially active during rest and linked to self-referential processes (75). Prior work has consistently reported that the default mode network is hyperconnected in MDD (68), and this hyperconnectivity has been linked to rumination (75). Thus, among high-risk adolescents, heightened resting-state mPFC activity also may be a marker of maladaptive self-focus that is serving to drive attention away from externally rewarding stimuli in the environment.

While the association between response bias and mPFC fALFFs among high-risk adolescents is preliminary, our results suggest that adolescents with a maternal risk for MDD paired with a reduced reward response bias and hyperactive mPFC resting activity may be especially vulnerable to the development of future depressive episodes. Consistent with this assertion, longitudinal studies found that high-risk adolescents who engaged in less reward seeking or exhibited blunted reward positivity were more likely to experience depressive symptoms at a follow-up assessment (9,76). Given that this is the first study to link fALFFs with reward processes, future work will be needed to corroborate the findings.

Our study has several strengths, including a focus on an early adolescent developmental period marked by enhanced reward neural system sensitivity (3–6). Additionally, all adolescents were free of psychopathology and psychotropic medication, which allowed for testing whether dysfunctional reward functioning might serve as a premorbid risk factor. However, there were limitations, including the relatively small sample of high-risk adolescents compared with the larger sample of low-risk adolescents. Moreover, although focusing on healthy high-risk adolescents strengthened the ability to test aberrant reward processes before illness onset, it may also dampen generalizability of the findings. Despite these limitations, our study provides critical evidence of reward processing impairments in a sample of healthy adolescents at high risk for MDD. This work supports research establishing reward dysfunction as a premorbid vulnerability marker for MDD and lays the foundation for future longitudinal work to determine whether premorbid reward processing abnormalities among high-risk adolescents predict later emergence of depressive episodes.

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