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# Maladaptive Avoidance Learning in the Orbitofrontal Cortex in Adolescents With Major Depression

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## ABSTRACT

**BACKGROUND:** Understanding the mechanisms in the brain's incentive network that give rise to symptoms of major depressive disorder (MDD) during adolescence provides new perspectives to address MDD in early stages of development. This functional magnetic resonance imaging study determines whether instrumental vigor and brain responses to appetitive and aversive monetary incentives are altered in adolescent MDD and associated with symptom severity.

**METHODS:** Adolescents with moderate to severe MDD ($n$ = 30, mean age [SD] = 16.1 [1.4] years) and healthy control subjects ($n$ = 33, mean age = 16.2 [1.9] years) matched for age, sex, and IQ performed a monetary incentive delay task. During outcome presentation, prediction error signals were used to study the response and coupling of the incentive network during learning of cue-outcome associations. A computational reinforcement model was used to assess adaptation of response vigor. Brain responses and effective connectivity to model-derived prediction errors were assessed and related to depression severity and anhedonia levels.

**RESULTS:** Participants with MDD behaved according to a more simplistic learning model and exhibited slower learning. Effective connectivity analysis of functional magnetic resonance imaging data revealed that impaired loss error processing in the orbitofrontal cortex was associated with aberrant gain control. Anhedonia scores correlated with loss-related error signals in the posterior insula and habenula.

**CONCLUSIONS:** Adolescent MDD is selectively related to impaired processing of error signals during loss, but not reward, in the orbitofrontal cortex. Aberrant evaluation of loss outcomes might reflect an early mechanism of how negative bias and helplessness manifest in the brain. This approach sheds light on pathomechanisms in MDD and may improve early diagnosis and treatment selection.

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Major depressive disorder (MDD) is among the most prevalent mental health problems in adolescents worldwide (1), with an estimated 12-month prevalence of 7.5% in mid to late adolescence (2). Adolescent MDD increases the risk for substance misuse; can severely impair success in school, social life, and cognitive functions (3); and is a major risk factor for suicide, which is among the leading causes of death at this age (4). Despite these adverse outcomes, relatively little is known about brain mechanisms related to MDD with early onset. Recent evidence suggests that disrupted prediction error (PE) signaling constitutes a potential brain mechanism that promotes the persistence of negative beliefs and anhedonia (5).

It is widely established that the dopaminergic system is fundamental in encoding reward and loss PEs (6), which are crucial in reinforcement learning and decision making. Influential computational models (7,8) suggest that during anticipation of an incentive, an expected value (Q) signal is generated, which is the product of a learned probability and the magnitude of the incentive. During outcome receipt, the difference between the expected value signal and the actual outcome is signaled as PE to update predictions. While the ventral striatum primarily encodes PEs in reward contexts, the anterior insula does so in avoidance or loss contexts (9). Brain regions sensitive to errors in reward and loss contexts are the orbitofrontal cortex (OFC) and the dorsal anterior cingulate cortex (dACC) (10,11).

Previous studies have demonstrated that striatal PE signaling is reduced in adult MDD in reward (12,13) and loss (6) contexts. Therefore, it is crucial to establish whether this aberrant signaling is already present in early-onset MDD or whether deviations in reward and loss processing are a downstream effect of chronicity and burden (6). Studies in young cohorts suggest that blunted reward sensitivity in the ventral striatum predicts symptom deterioration (14,15) and is present in individuals at high familial risk for depression (16,17). In addition, there is emerging evidence of impaired loss sensitivity in the incentive network in high-risk groups (18) that predicts future depressive symptoms (19). However, it remains





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unclear whether atypical learning signals are linked to deficient motivated behavior. Previous studies showed mixed results when applying computational models to behavioral data in adult MDD, with learning rates depending on the task used and the specific learning process probed (20). This clearly indicates that more work is necessary to identify brain mechanisms that give rise to aberrant incentive processing in depression, particularly during development.

In this functional magnetic resonance imaging (fMRI) study, we hypothesized that the encoding of reinforcement learning signals is impaired in adolescent MDD. We employed a monetary incentive delay task (10,21) with varying magnitude (low, high) and valence (reward, loss) to probe the neural circuits supporting PE and expected value processing. On a neural level, we hypothesized 1) decreased reward PE signaling within the striatum in MDD (5,15), 2) a negative association between anhedonia scores and blunted responses to rewards in the striatum and OFC (22), and 3) reduced reactivity of the OFC during loss events (19). Behaviorally, we tested whether response vigor, i.e., adaptive responses to reward and losses of varying magnitudes (23), was differentially modulated in MDD and whether there are differences in the update of value representations in the instrumental learning task.

## METHODS AND MATERIALS

### Participants

A total of 30 adolescent patients and 33 healthy individuals matched for age, IQ, sex, and handedness participated in this study (Table 1). Participants with MDD were recruited through clinical services. All participants underwent a semistructured clinical interview [Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (24) or Mini-International Neuropsychiatric Interview for Children and Adolescents (25)]. Participants with MDD fulfilled a diagnosis according to the DSM-IV (codes 296.20–296.23, 296.30–296.33). Past and present comorbid diagnoses in patients included anxiety disorders ($n$ = 7), obsessive-compulsive disorder ($n$ = 1), and attention-deficit/hyperactivity disorder ($n$ = 2). Moreover, we assessed a battery of self-report questionnaires, IQ, and working memory of all participants (Table 1). We included total scores and scores from the anhedonia subscale from the German

**Table 1. Clinical and Demographic Characteristics of Study Participants**

| Characteristics | Control Group | MDD Group | Test Statistic | $p$ Value[a] |
|---|---|---|---|---|
| Age, Years, Mean (SD), [Min–Max] | 16.2 (1.9), [11.2–18.8] | 16.1 (1.4), [12.8–18.7] | $U$ = 553.5 | .425 |
| Sex, Males, $n$ (%) | 10 (30%) | 10 (33%) | $\chi^2_1$ = 0.07 | .796 |
| Handedness, Right, $n$ (%) | 32 (97%) | 28 (93%) | $\chi^2_1$ = 0.46 | .500 |
| In-Scanner Movement, FD, mm | 0.18 (0.09) | 0.18 (0.08) | $t_{61}$ = 0.09 | .930 |
| CD-RISC | 72.9 (10.1) | 38.6 (15.6) | $t_{58}$ = 10.16 | < .001 |
| CDI | 8.4 (6.6) | 29.6 (9.3) | $U$ = 38.0 | < .001 |
| Anhedonia | 2.3 (2.2) | 10.5 (2.8) | $U$ = 13.5 | < .001 |
| Negative mood | 2.2 (2.0) | 6.4 (2.4) | $U$ = 88.0 | < .001 |
| Negative self-esteem | 1.0 (1.2) | 5.0 (1.7) | $U$ = 42.0 | < .001 |
| Ineffectiveness | 1.2 (1.2) | 5.0 (1.9) | $U$ = 54.5 | < .001 |
| Interpersonal problems | 1.1 (1.2) | 3.7 (1.5) | U = 74.5 | < .001 |
| Stomach | 0.6 (0.6) | 1.1 (0.8) | U = 301.5 | .018 |
| RIAS IQ | 104.5 (6.9) | 108.0 (8.7) | $t_{60}$ = −1.75 | .079 |
| PSS | 22.4 (6.6) | 28.8 (7.7) | $t_{57}$ = −3.44 | .001 |
| SDQ | 8.8 (5.3) | 16.3 (5.6) | $t_{56}$ = −5.26 | < .001 |
| WISC-IV Digit Span, Forward | 8.9 (2.1) | 8.8 (2.0) | $t_{60}$ = 0.32 | .747 |
| WISC-IV Digit Span, Backward | 8.6 (1.6) | 9.4 (2.0) | $t_{60}$ = −1.70 | .094 |
| WISC-IV Mosaic | 57.0 (5.7) | 59.0 (6.2) | $t_{56}$ = −1.27 | .208 |
| Current Medication, $n$ (%) | | | | |
| No medication | NA | 10 (33%) | NA | NA |
| SSRI | NA | 18 (60%) | NA | NA |
| Dual-action antidepressant[b] | NA | 2 (7%) | NA | NA |
| NERI | NA | 2 (7%) | NA | NA |
| Antipsychotic[c] | NA | 2 (7%) | NA | NA |
| Methylphenidate | NA | 2 (7%) | NA | NA |

Data are presented as mean (SD) unless otherwise indicated.

CDI, Children's Depression Inventory; CD-RISC, Connor-Davidson Resilience Scale; FD, framewise displacement; Max, maximum; MDD, major depressive disorder; Min, minimum; NA, not applicable; NERI, norepinephrine reuptake inhibitor; PSS, Perceived Stress Scale; RIAS, Reynolds Intellectual Assessment Scales; SDQ, Strengths and Difficulties Questionnaire; SSRI, selective serotonin reuptake inhibitor; WISC-IV, Wechsler Intelligence Scale for Children, fourth edition.

[a]Uncorrected $p$ values for between-group comparisons; significance threshold $p < .05$.

[b]Serotonin-noradrenaline reuptake inhibitor.

[c]Used for behavioral control.

version of the Children's Depression Inventory (26) in our neuroimaging analyses. Healthy control subjects were recruited through schools and volunteer websites. For control subjects, exclusion criteria included any current psychiatric disorder, other major medical illnesses, drug abuse, any MRI contraindication, pregnancy, and a history of brain injury. Three control participants had a past diagnostic work-up for attention-deficit/hyperactivity disorder, but they were currently symptom free and were not taking any medication during the study. All procedures contributing to this work comply with the ethical standards of the ethic committee of the Canton of Zurich, Switzerland (BASEC 2017-02179) and with the Helsinki Declaration of 1975, as revised in 2008. All participants gave their written informed consent; parents or legal guardians gave signed informed consent for children under the age of 14 years. They were reimbursed for participation and informed about the opportunity to additionally win up to CHF 20 during the task.

## Experimental Task

In this study, we used the monetary incentive delay task (Figure S1) to examine incentive processing in different valence and magnitude contexts (21). This fMRI task minimizes cognitive confounds (e.g., solving a task with different strategies) because of the simple decision processes (27). Importantly, it allowed us to assess individual trial-by-trial reward and loss PEs based on the associations participants built up relying on the outcome of the preceding trials, allowing us to distinguish it from outcome processing. Every trial began with the presentation of a cue indicating the level of magnitude (CHF 1, CHF 4) and the valence (reward, loss avoidance, null) for a button press on time (hit). Participants were instructed to use the index finger of their dominant hand to press a button on a 2-button fiberoptic response pad (Current Design, Inc.) as soon as the go-signal target symbol, a star, appeared. In total, each cue was presented 24 times (i.e., 120 trials in total, mean stimulus onset asynchrony = 8500 ms) in two separate MRI runs. We used an adaptive algorithm that adjusted the presentation times of the target to the response time of the participant to ensure a hit rate of ~66%. The cue symbols indicating valence (square, triangle, and circle) were counterbalanced across subjects. A filled symbol indicated a trial with high magnitude (CHF 4), whereas an empty symbol indicated a trial with low magnitude (CHF 1). All participants had a short training session outside the scanner (~2 min) to familiarize themselves with the task, and we ensured that cue-outcome contingencies were understood. The task was implemented in python (pygame; https://www.pygame.org) and presented using video goggles (VisuaStim Digital) with a resolution of 800 × 600 pixels.

Postscan ratings of subjective liking and arousal for rewards and losses were assessed at the end of the scanning session. Participants rated their subjective liking (How much did you like this outcome?) and arousal (How excited were you by the outcome?) on a continuous scale using a slider between 0 (strongly dislike, not aroused) and 100 (strongly like, highly aroused).

## Computational Modeling

The task employed here allows for the assessment of mechanisms that determine behavior (i.e., instrumental response vigor). To assess these quantities, we constructed several competing generative behavioral models that predicted trial-by-trial reaction times for each participant. This allowed us to identify parameters with mechanistic meaning for observed response vigor, the latent representation of value, and the participant-specific learning rate. Even though no learning is necessary to perform this task well, previous studies have found that learning signals continue to be generated even if an association is well-learned (28).

The winning model included the parameters cue salience, i.e., the magnitude of possible outcomes × probability; novelty, i.e., the unsigned PE; a posterror term; a linear term; and the intercept. Group differences between controls and patients were assessed for parameters of the best-fitting model across both groups. A detailed description of the behavioral model, model simulations, and behavioral analysis is provided in the Supplement (Figures S2 and S3, Tables S1–S4).

## Functional MRI Analysis

**Model-Based fMRI—General Linear Model Analysis.** To investigate the trial-by-trial effect of the computational variables derived from the computational model, we used the variables of the best behavioral model across participants (Table S2) and entered expected value and PE as parametric modulators for cue onset and feedback, respectively (Supplemental Methods). Group effects were assessed with two-sample *t* tests, where we entered the contrast images for the expected values and the PEs for healthy control subjects and patients with MDD. The cluster-level significance threshold for the whole-brain group analyses (familywise error–corrected [FWEc]) was set to $p_{FWEc} < .05$ with a cluster-defining threshold of $p_{CDT} < .001$. All fMRI analyses were conducted in SPM12 (version 7487; Wellcome Trust Centre for Neuroimaging, University College London, London, UK); labels for brain regions are based on the Automated Anatomical Atlas (29).

**Effective Connectivity Analysis.** To reveal the functional coupling between regions of the incentive network in participants with and without MDD, we performed a dynamic causal modeling (DCM) analysis (30,31). The regions for this analysis were selected based on 1) previously published findings of incentive processing (9,10,32), 2) findings of studies in participants with a history of and at risk for MDD (18,19), and 3) our second-level general linear model analyses (Figure 1A; Tables S5–S8 and Figures S4–S6). The aforementioned studies have provided compelling evidence that the insula and dACC play a significant role in loss-avoidance learning, a finding we corroborate across groups during reward and loss processing. Furthermore, we found a significant group effect in the OFC that suggested aberrant network dynamics in MDD.

For the DCM analysis, we localized the effects of hits and misses across trials by performing whole-brain contrasts with the Children's Depression Inventory as covariate (Figure S5) and extracted the time series for each subject from activated voxels ($p < .05$, uncorrected) within a 12-mm spherical search volume around the group maxima from the miss-hit (insula [x =

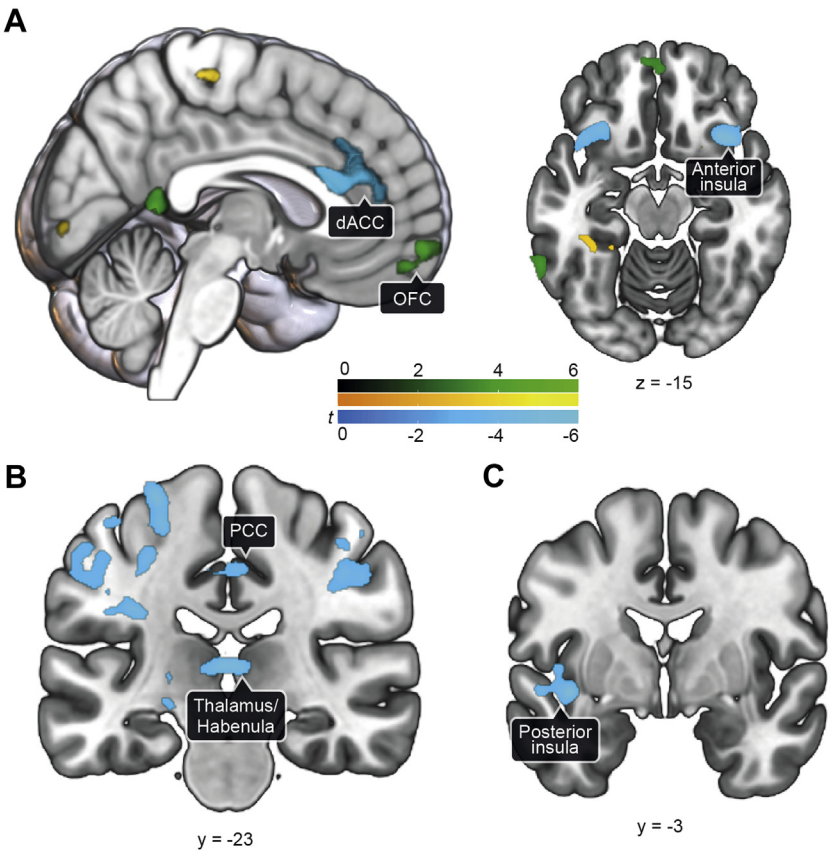


**Figure 1.** **(A)** Effect of loss outcome error $\varphi_t^-$ during feedback presentation across all participants ($n$ = 63). Patients showed significantly reduced responses related to errors during loss compared with control subjects in the orbitofrontal cortex (OFC, green). Consistent effects across groups (positive effect in yellow, negative effect in blue) of outcome error were found in the dorsal anterior cingulate cortex (dACC) and the anterior insula. Details are reported in Table 2 and main effects in Table S5. $p_{FWEc} < .05$, $p_{CDT} < .001$. **(B)** Assessment of the effect of anhedonia within patients ($n$ = 29). A negative relationship between magnitude-modulated loss prediction error $\delta_t^-$-related actitivity and anhedonia scores was observed in a cluster in the medial thalamus/habenula and the posterior cingulate cortex (PCC). **(C)** A significant negative association between anhedonia scores and loss outcome error $\varphi_t^-$-related activity was found in the posterior insula. CDT, cluster-defining threshold; FWEc, familywise error–corrected.

35, y = 18, z = −18 mm Montreal Neurological Institute (MNI)]; dACC [x = 7, y = 36, z = 30 mm MNI]) (Table S8) and the all-events (inferior occipital gyrus [x = 29, y = −80, z = −16 mm MNI]) (Table S10) contrast. The search volume for the OFC comprised the voxels in the active OFC (x = −7, y = 46, z = −16 mm MNI) cluster of the second-level hit-miss contrast (Table S8) (cluster-extent threshold $p_{FWEc} < .05$). If a participant's maximum within the search volume differed from the group maximum, we centered the sphere around the participant's maximum. The first eigenvariate of the time course of all active voxels ($p < .05$) was then extracted and adjusted for any motion effects. One patient and 2 control subjects had to be excluded from this analysis because they did not show any activation in the dACC for the defined threshold.

The feedback regressor was the driving input for the visual region. The model was composed of direct forward connections from the visual area to all other fully interconnected regions. Because the general linear model analysis revealed loss-related group differences in OFC activity (see Results), our main interest was to study network effects during the loss condition; nevertheless, the reward condition was also included to improve the model fit. We included contextual modulation of PEs, magnitude (−1 for low and 1 for high), and their interaction term, i.e., magnitude-sensitive PEs on the self-connections of the regions (see Supplement). In this model, the self-connections embody the change in synaptic gain for a given task context (31). Here, our goal was to identify the network dynamics that give rise to the lower error signal in the OFC in patients with MDD during loss processing. For this, we set up a DCM analysis within the parametric empirical Bayes (PEB) framework.

On the first level, the full DCM model of each participant was estimated iteratively in an empirical Bayesian inversion scheme (31). The individual DCM parameters from the first level were then entered in the second-level PEB model to determine 1) the differences between the MDD group and the control group and 2) the group mean. This analysis was carried out separately for intrinsic and modulatory connections. We performed Bayesian model reduction to iteratively discard those model parameters not contributing to the model evidence. Then, we averaged the parameters of the best PEB models weighted by the posterior probability of the respective model. A PEB model parameter was considered significant when exceeding a 95% posterior probability of being present versus absent based on the model evidence (31,33). Leave-one-out cross-validation was used to assess whether the predicted and actual group effect showed an independent out-of-sample correlation.

## RESULTS

### Altered Learning of Cue-Outcome Associations in MDD

Bayesian model comparison revealed that the response model including cue salience and novelty terms using a single

**Table 2. Group Differences Between Patients With MDD and Healthy Control Subjects for $\varphi_t^-$ Processing**

| | MNI Coordinates, mm | | | Significant Activation | | Peak |
|---|---|---|---|---|---|---|
| Brain Region | x | y | z | $p_{FWEc}$ | k | *Z* |
| Controls > MDD | | | | | | |
| Precuneus_L | −3 | −46 | 10 | .022 | 128 | 4.67 |
| Frontal_Sup_2_R | 17 | 28 | 44 | .046 | 108 | 4.48 |
| Temporal_Mid_L | −67 | −50 | −6 | .000 | 269 | 4.24 |
| Angular_L | −55 | −64 | 24 | .006 | 166 | 4.08 |
| Temporal_Mid_R | 65 | −10 | −16 | .034 | 116 | 4.05 |
| Frontal_Med_Orb_L | −3 | 60 | −8 | .019 | 132 | 3.93 |
| MDD > Controls (NS) | | | | | | |

Significance level at whole-brain cluster-level $p_{FWEc} < .05$, cluster-defining threshold $p_{CDT} < .001$. Main effects are reported in Table S5.
k, cluster size; FWEc, familywise error–corrected; L, left; MDD, major depressive disorder; Med, medial; Mid, middle; MNI, Montreal Neurological Institute; NS, not significant; Orb, orbital; R, right; Sup, superior.

learning rate fitted the response data best across groups. Nevertheless, we found that in patients, the simpler model with a single learning rate performed better (posterior probability = 57.7%) (Table S2), whereas a more complex model with separate learning rates for rewards and losses fitted data better in control subjects only (posterior probability = 51.6%). However, while we found this difference among groups, the difference between the simple and the more complex model was not very strong (Bayes factor = 2.00), and thus we decided to continue the analysis with the simpler model because this performed best for both groups. A between-group comparison of the learning rate of the best-fitting model across all participants showed that the learning rate was marginally lower in MDD ($\alpha$: MDD, 0.050 [SD = 0.021]; control subjects, 0.052 [SD = 0.012]; $U = 617$; $p = .095$). This difference was significant after removing 1 outlier from to the MDD group (Grubb's test: $G = 6.107$, $U = 0.389$, $p < 10^{-11}$; $\alpha$: MDD, 0.046 [SD = 0.009]; control subjects, 0.052 [SD = 0.012]; $t_{60} = 2.04$; $p = .046$) (Supplemental Methods). The response model parameters, in particular cue salience and novelty, did not differ between groups (all $p > .10$) (Table S4). These results demonstrate a nondiscriminable value update mechanism underlying adolescent MDD for both reward and loss conditions, while there was positive evidence that control subjects' response vigor was best described by a more flexible dual update model for both valences. In addition, the comparison of the learning rate shows that participants with MDD changed their value expectations slower across the task.

## OFC Gain Control Explains Atypical Aversive Outcome Signaling in MDD

When processing loss feedback, participants with MDD showed a significantly lower response to the outcome error signal $\varphi_t^-$ in the OFC (Figure 1 and Table 2). While this region reflected a signal encoding the difference between subjective belief of the outcome and the actual outcome in reward and loss in control subjects (Table S5), patients only expressed this signal during rewarding and not loss-avoidance trials.

To further scrutinize the origin of this effect, we performed a DCM analysis (Figure 2 and Table 3). Bayesian model averaging showed that the effect of loss magnitude on the self-inhibition parameter of the OFC was significantly more negative in MDD, i.e., the region was more disinhibited during processing the outcome of high compared with low loss. These results indicate that MDD is related to aberrant gain control in the OFC, specifically in high-loss contexts. Moreover, self-inhibition of the dACC was significantly lower across task conditions in the MDD group. The posterior mean of the group effect on self-inhibition of the OFC was significantly related to the learning rate across all participants (Spearman's $\rho = 0.295$, $p = .023$, $n = 59$), but not in the dACC ($\rho = -0.135$, $p = .301$, $n = 59$). A leave-one-out cross-validation using the loss magnitude–dependent

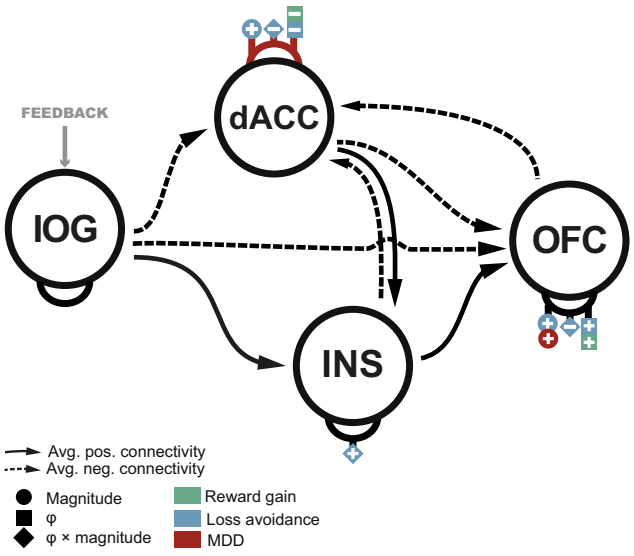


**Figure 2.** Effective connectivity during reward and loss feedback processing. There was a significant group effect of the factor loss magnitude on the self-inhibition parameter in the orbitofrontal cortex (OFC), indicating aberrant input sensitivity during feedback in loss-avoidance contexts in adolescent major depressive disorder (MDD). Cross-validation showed that this effective connectivity parameter was able to predict the group variable indicated by a significant out-of-sample correlation. Importantly, this parameter was associated with the learning rate of participants, which was lower in adolescents with MDD. The arrows reflect the posterior estimates of the second-level parametric empirical Bayes model after Bayesian model reduction. Self-connections are depicted as a half-circle on each region. Solid lines indicate positive effective connectivity, whereas dashed lines represent negative effective connectivity. Details of the results are reported in Table 3. dACC, dorsal anterior cingulate cortex; INS, anterior insula; IOG, inferior occipital gyrus; φ, outcome error.

**Table 3. Average Connectivity During Feedback Phase Obtained by Bayesian Model Averaging of PEB Model Parameters**

| Connection Type | Commonalities | PP Commonalities | Depression | PP Depression |
|---|---|---|---|---|
| Endogenous Parameters | | | | |
| OFC → Insula | 0 | 0 | 0 | 0 |
| OFC → dACC | −0.195 | 1 | 0.04 | 0.66 |
| dACC → Insula | 0.812 | 1 | 0 | 0 |
| dACC → OFC | −0.345 | 1 | 0 | 0 |
| Insula → OFC | 0.284 | 1 | 0 | 0 |
| Insula → dACC | −0.084 | 1 | −0.049 | 0.85 |
| IOG → Insula | 0.144 | 1 | 0 | 0 |
| IOG → dACC | −0.228 | 1 | 0.017 | 0.53 |
| IOG → OFC | −0.108 | 1 | −0.013 | 0.58 |
| Self-Inhibition Parameters | | | | |
| OFC → OFC | −0.467 | 1 | | |
| Insula → Insula | 0.311 | 1 | | |
| dACC → dACC | −0.288 | 1 | −0.139 | 1 |
| IOG → IOG | 1.740 | 1 | | |
| Modulatory Parameters | | | | |
| Insula → Insula, $\varphi_t^+$ | 0 | 0 | 0 | 0 |
| Insula → Insula, $M^+$ | 0 | 0 | 0 | 0 |
| Insula → Insula, $\varphi_t^+ \times M^+$ | 0 | 0 | 0 | 0 |
| Insula → Insula, $\varphi_t^-$ | 0 | 0 | 0 | 0 |
| Insula → Insula, $M^-$ | 0 | 0 | 0 | 0 |
| Insula → Insula, $\varphi_t^- \times M^-$ | −0.482 | 1 | 0 | 0 |
| dACC → dACC, $\varphi_t^+$ | 1.506 | 1 | 0 | 0 |
| dACC → dACC, $M^+$ | −0.103 | 0.55 | 0 | 0 |
| dACC → dACC, $\varphi_t^+ \times M^+$ | 0 | 0 | 0.194 | 0.89 |
| dACC → dACC, $\varphi_t^-$ | 1.986 | 1 | 0 | 0 |
| dACC → dACC, $M^-$ | −0.628 | 1 | 0 | 0 |
| dACC → dACC, $\varphi_t^- \times M^-$ | −0.308 | 0.99 | 0 | 0 |
| OFC → OFC, $\varphi_t^+$ | 1.506 | 1 | 0.351 | 0.90 |
| OFC → OFC, $M^+$ | 0.148 | 0.54 | 0 | 0 |
| OFC → OFC, $\varphi_t^+ \times M^+$ | 0 | 0 | −0.140 | 0.51 |
| OFC → OFC, $\varphi_t^-$ | −0.748 | 1 | 0 | 0 |
| OFC → OFC, $M^-$ | −0.495 | 1 | −0.663 | 1 |
| OFC → OFC, $\varphi_t^- \times M^-$ | 0.781 | 1 | 0 | 0 |
| Input Parameter | | | | |
| Feedback → IOG | 4.287 | 1 | −0.208 | 0.64 |

Between-region connections are in units of Hz. Self-connections, where the source and target are the same, are the log of scaling parameters that multiply up or down the default value of −0.5 Hz. $n = 60$.

dACC, dorsal anterior cingulate cortex; IOG, inferior occipital gyrus; M, magnitude; OFC, orbitofrontal cortex; PEB, parametric empirical Bayes; PP, posterior probability; φ, error signal.

difference in self-connection strength in the OFC explained a significant amount of the intersubject variability between MDD and controls, showing an independent out-of-sample correlation of $r_{58} = 0.38$, $p = .001$.

## Neural Correlates of Depression Severity and Anhedonia

Regression analysis of anhedonia scores within patients revealed significant associations in brain signaling of learning variables for loss. Particularly, we found that magnitude-modulated loss PE signaling $\delta_t^-$ was associated negatively with anhedonia scores in the medial thalamus/habenula, posterior cingulate cortex, postcentral gyrus, and fusiform gyrus (Table S6; Figure 1B). The loss-related outcome error signal $\varphi_t^-$ in the posterior insula was associated negatively with anhedonia scores (peak $Z = 4.73$, $p_{FWEc} < .001$) (Table S6; Figure 1C). No within-patient associations were observed for reward-related signals.

## No Effects of Selective Serotonin Reuptake Inhibitors on Brain Activity in Participants With MDD

We conducted additional analyses comparing effects of the learning parameters, δ, φ, and Q to see if there were systematic

differences of brain activity related to selective serotonin reuptake inhibitor (SSRI) medication. We compared groups of 18 patients medicated with SSRIs to 10 other patients (unmedicated or no SSRI). However, general linear model analyses of expected values and PE did not reveal any significant group differences. No clusters survived ($p_{FWEc} < .05$) a threshold of $p_{CDT} < .001$ or a more lenient cluster-defining threshold of $p_{CDT} < .005$. Moreover, DCM parameter values of the OFC and dACC were assessed for SSRI effects. To this end, we extracted the individual posterior means for each patient and split them into two groups (SSRI, other or no medication). However, we did not find a significant difference between patients taking SSRIs and others in the OFC ($t_{26} = -1.44$, $p = .162$) or the dACC ($t_{26} = -0.08$, $p = .936$). Note that 1 patient was excluded from this analysis because their medication history was not disclosed.

## DISCUSSION

In this study, we used a combination of computational modeling, fMRI, and connectivity analysis to study reward and loss processing in adolescent MDD. We demonstrated that adolescent MDD is associated with 1) aberrant gain control in the OFC during loss feedback processing and 2) anhedonia-related reduction of representation of loss outcomes in the posterior insula and habenula, but we found no evidence for aberrant reward PE processing in the ventral striatum and the medial prefrontal cortex. Thus, this work provides novel insights into the neurobiological foundation of altered learning mechanisms in loss avoidance in early-onset MDD.

Our computational modeling approach revealed differences in behavioral adaptation that were reflected in the learning rate to update one's belief about prospective receipt of reward and loss. By testing a series of behavioral models, we showed that participants with MDD adapted their instrumental vigor according to a simpler learning model with a single learning rate for reward and loss and that they also updated the expected values slower than control subjects. While this does not indicate a different learning mechanism in MDD per se, it suggests that instrumental behavior does not rely on differential update rates to adapt behavior for approaching reward and avoiding loss. The speed of learning depends on the perceived volatility of the environment (34), which has been suggested to be affected in anhedonia and anxiety (35), the latter being a highly prevalent comorbidity in depression (36). Reduced learning and updating of one's belief system and hence an inability to update and hold an appropriate structure of possible aversive outcomes might provide the basis for a biased evaluation of the environment.

On the neural level, we linked these differences in value representation updates derived from the computational model to neural feedback processing. While in control subjects OFC activity was related to an outcome error signal across task conditions, this was absent in participants with MDD during loss processing. Effective connectivity analysis further showed that this effect was primarily driven by aberrant gain control in the OFC, specifically the sensitivity tuning in varying magnitude contexts. Gain in the OFC is modulated by various neurotransmitters (37), but there is evidence that dopamine plays a role in learning approach and avoidance behavior (9), supported by dense dopaminergic projections to the OFC (38). This gain control might be critical to modulating the activity of the OFC during error processing in reward (39) and loss (11) contexts, updating neural representations of value (40), and maintaining a representation of the task structure (41). The latter entails updating an estimate of certainty for a specific outcome, which seems to fail in adolescent MDD when evaluating unexpected outcomes in avoidance learning. Strikingly, we found a significant negative association between learning rate and gain control of the OFC during loss processing.

Although altered OFC activity and connectivity for aversive stimuli has been reported in various paradigms in adults with MDD (42,43), the few studies investigating adult MDD with the monetary incentive delay task did not report changes in loss-related processing (44,45). On the other hand, a longitudinal study in adolescents at risk for MDD (19) showed that loss-related OFC-insula connectivity predicted depressive symptoms 9 months later. This suggests that altered OFC function during loss processing could be specific for early-onset depression. However, more research on OFC connectivity changes over the course of the disorder from adolescence into adulthood is needed. In accordance with Jin *et al.* (19), we also showed that decreased loss error signaling in the posterior insula was related to anhedonia. While the encoding of magnitude-modulated loss PE signals did not significantly differ between groups, a within-patient analysis revealed that blood oxygen level–dependent responses related to loss PE in a cluster composed of the medial thalamus and habenula were significantly negatively associated with anhedonia. Previous work has implicated impaired habenula function and morphology in depression and anhedonia (6,46). Thus, altered loss processing could reflect an important factor that contributes to increased susceptibility to adolescent MDD.

Recent computational accounts on depression suggest that it is related to an aberrant cognitive prior that underlies negative bias in evaluation of the state of the environment (47). An overgeneralization of one's own states might eventually lead to helplessness behavior, where negative outcomes are associated with poor performance and where failure of oneself and positive outcomes are regarded as mere random events. Our results could indicate that a negative prior about the outcome is not updated owing to dysfunction in the OFC, and this might contribute to maintaining a negative bias and a feeling of loss of control over outcomes. The latter is consistent with the differences of negative arousal derived from the postscan ratings, where participants with MDD expressed more relief (i.e., more deactivation) in rewarding outcomes and more fear (i.e., more activation) during loss outcomes. However, unlike in adult depression (48), computational modeling did not indicate that this higher range of negative arousal significantly affected response vigor in MDD.

Contrary to our hypothesis, we did not find any evidence of impact of depression on PE processing in rewarding contexts as previous studies in adult MDD (6,12,13). Here, we postulate that two factors could have led to this null finding. First, in our monetary incentive delay task, participants did not have to learn anything to perform well. This design was employed to minimize confounds of 1) brain maturation and development within participant groups (49) and 2) diagnosis (50) on learning performance, which could be difficult to disentangle in more

complex learning paradigms. Nevertheless, our results are in concordance with previous findings of intact reward PE signaling in a nonlearning task in adult MDD (51). Second, there is evidence that impairments of reward PE signaling are related to the number of depressive episodes across the lifetime (6). This might explain the results in participants with an early onset as in our study and could indicate that previous reports of impaired reward PE signaling errors are related to the chronicity of the disorder.

It has to be considered that the majority of participants with depression were receiving antidepressive medication (Table 1). It is possible that intake of SSRIs might have affected error signaling and learning of cue-outcome associations (52). Based on this assumption, we would expect blunting of reward responses due to the administration of SSRIs. However, additional control analyses of brain activity and connectivity comparing participants with MDD with ($n$ = 18) and without ($n$ = 10) SSRI intake revealed no significant effect. Although we cannot fully rule out that medication had an effect based on these rather small subsamples, we consider it unlikely that this was the case in this study. Nevertheless, the different medication status of patients should be considered when interpreting the results, and further investigation of effects of SSRIs in depression is warranted. Moreover, we note that it is not possible to make causal inferences using a cross-sectional design, and future work should assess larger, longitudinal samples to shed light on the neural mechanisms that could give rise to MDD in adolescence.

In conclusion, this is the first study to our knowledge to show that adolescent MDD is associated with specific impairments of error processing in loss-avoidance contexts, whereas reward sensitivity is intact. Given the critical role of evaluating an action that led to an unexpected aversive outcome, this deficit could be directly related to severe difficulties in decision making and in social life and by contributing to the development and persistence of a negative bias in depression. Our study provides a first important step toward identifying computational mechanisms in adolescent MDD and paves the way for establishing computational assays (53) that will facilitate the translation into clinical practice.

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