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Altered Medial Frontal Feedback Learning Signals in Anorexia Nervosa

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ABSTRACT

BACKGROUND: In their relentless pursuit of thinness, individuals with anorexia nervosa (AN) engage in maladaptive behaviors (restrictive food choices and overexercising) that may originate in altered decision making and learning.

METHODS: In this functional magnetic resonance imaging study, we employed computational modeling to elucidate the neural correlates of feedback learning and value-based decision making in 36 female patients with AN and 36 age-matched healthy volunteers (12–24 years). Participants performed a decision task that required adaptation to changing reward contingencies. Data were analyzed within a hierarchical Gaussian filter model that captures interindividual variability in learning under uncertainty.

RESULTS: Behaviorally, patients displayed an increased learning rate specifically after punishments. At the neural level, hemodynamic correlates for the learning rate, expected value, and prediction error did not differ between the groups. However, activity in the posterior medial frontal cortex was elevated in AN following punishment.

CONCLUSIONS: Our findings suggest that the neural underpinning of feedback learning is selectively altered for punishment in AN.

Keywords: Anterior cingulate cortex, Bayesian inference, Computational modeling, fMRI, Hierarchical models, Probabilistic reversal learning

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Anorexia nervosa (AN) is an eating disorder characterized by a relentless pursuit of thinness, mostly by self-starvation. Repeated maladaptive eating behaviors (1,2) and extreme therapy resistance (3) in this enigmatic illness may originate from alterations in reinforcement learning such as increased sensitivity to reward or punishment and associated impairments in decision making (4,5). Aberrant reward-based learning in AN may reflect an entrenched "habit" of restrictive food choice (6,7). Similarly, it has been proposed that primary rewards (food) become conditioned as punishing, and aversive stimuli (hunger) become conditioned as rewarding in the brain reward system of individuals with AN (8). However, the precise mechanisms underlying response to and learning from reward and punshiment in AN are still poorly understood.

AN is consistently associated with low reward reactivity and high punishment sensitivity on clinical scales, although important differences between subtypes (restrictive vs. binging–purging) may exist (9–13). Most laboratory evidence for altered feedback learning and value-based decision making in AN comes from impaired performance in the Iowa Gambling Task (14,15)—a paradigm used to measure choice behavior in the context of outcome (reward vs. punishment) uncertainty. However, reward processing is multifaceted, and the typically reported Iowa Gambling Task "net score" provides little insight into which aspect(s) might be altered in AN. Suggesting that patients with AN may be particularly hypersensitive to punishment, patients also have been found to make less risky choices than healthy control subjects (HCs) in another decision-making paradigm, the Balloon Analogue Risk Task (13). Further evidence comes from neuroimaging studies that found altered reward processing in response to disorder-related stimuli such as food and taste (16–18) and secondary reinforcers (19–23). For example, neural response to punishment (monetary loss) has been found to be elevated in acutely ill adolescents in corticostriatal regions involved in valuation and action selection (21). Alteration in motivational and executive corticostriatal circuitry may also be associated with an impaired ability to flexibly adapt to change (24) and with an apparently excessive amount of self-control (5,25).

To gain a new perspective on feedback learning and decision making in AN, here we applied the methods of computational psychiatry (26) that associate neurobiological signals with defined mechanistic steps such as those needed to estimate the amount of reward associated with alternative behavioral options based on previous feedback. Compared with conventional analysis methods, this approach avoids 1) associating neurobiological signals with subjective reports of patients (which depends on their ability to self-reflect and adequately verbalize mood states or experiences) and 2) the limitations of purely descriptive measures such as error rates.

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Intuitively, we expect healthy subjects to place greater importance on unexpected feedback in a changing environment but to nearly disregard it in a stable one. The latter guards against switching away from the preferred option in the presence of environmental noise, that is, when the differences between expected and received rewards [also called reward prediction errors (27,28)] are not due to a real change of contingencies. To probe these mechanisms in AN, we employed a reversal learning task in which the preferable choice was rewarded probabilistically (in 80% of all choices) and changed only after a learning criterion was achieved, thereby requiring participants to learn from feedback and adapt to changing reward contingencies. To analyze behavior, we compared a hierarchical Gaussian filter (HGF) model (29) with more classical reinforcement learning models (30). In the HGF model, the weight given to prediction errors is encoded in an adaptive subject-specific learning rate that is high for large environmental uncertainty and low for small uncertainty.

Previous studies in healthy individuals (31–33) and other patient populations (34) have linked specific model parameters to activation in specific brain regions, for example, posterior medial frontal cortex (pMFC) for the learning rate, ventromedial prefrontal cortex (PFC) for the expected (subjective) value of a choice option, and ventral striatum for the prediction error. Given evidence of hypersensitivity to punishment in AN (9–12,21,35,36), we hypothesized that patients' decision making would be more affected by punishments (monetary loss) relative to HCs and that learning from such negative feedback would be linked to altered activation in the pMFC. The pMFC spans the dorsal anterior cingulate cortex and presupplementary motor area and is broadly implicated in reward-based decision making and signaling the need for adjustments when behavioral goals are threatened such as when losses occur (35–37).

METHODS AND MATERIALS

Participants and Procedure

A total of 72 female subjects participated in this study: 36 acutely underweight patients with AN (12–23 years old) and 36 pairwise age-matched HCs (12–24 years old). Case-control age matching was carried out, resulting in a maximum difference of 1.7 years between the individuals within one pair (Supplemental Methods). Participants with AN were recruited from specialized eating disorder programs and underwent magnetic resonance imaging (MRI) within 96 hours after admission to behaviorally oriented nutritional rehabilitation programs. Refer to Supplemental Methods for additional information on inclusion and exclusion criteria and on clinical assessments. Clinical variables are reported in Table 1.

This study was approved by the institutional ethics review board, and all participants (and their guardians if underage) gave written informed consent.

One participant with AN (and her age-matched partner) needed to be excluded due to low performance (Supplemental Methods and Supplemental Figure S1).

Experimental Paradigm

We used a probabilistic reversal learning task adapted from Hampton *et al.* (33) (Figure 1) that includes probabilistic positive and negative monetary feedback and contingency changes according to a learning criterion (see below). In each of the 120 trials, participants needed to choose one of two symbols, referred to as options A and B. One symbol was designated as correct and led to monetary reward (+20 cents) with a probability of 80% and to punishment (−20 cents) in 20% of the cases (probabilistic errors). The choice of the "wrong" symbol led to punishment and reward with inverted probabilities. With a probability of 25%, the contingency reversed (change of the "correct" symbol to the previously "wrong" symbol) after at least four consecutive correct decisions since the last contingency switch.

Table 1. Group Characteristics

	AN		HC		Test Statistics	
	Mean	SD	Mean	SD	*t*	*p*
Demographic Variables						
Age	16.0	2.6	16.3	2.6	−0.5	.662
BMI	14.7	1.3	20.4	2.5	−12.0	< .001
BMI-SDS	−2.1	0.6	0.0	0.8	−11.7	< .001
IQ	111.9	11.1	110.9	10.0	0.4	.673
Handedness	0.5	2.0	1.7	3.7	−1.8	.081
Clinical Variables						
EDI-2 total score	197.4	50.7	139.6	28.0	5.9	< .001
EDI-2 perfectionism	19.6	6.0	15.7	4.2	3.3	.002
BDI-II total score	19.5	11.6	5.5	5.7	6.5	< .001
BIS	22.0	3.7	20.8	3.3	1.12	.269
BAS	39.8	6.3	40.5	4.2	−0.44	.665
JTCI harm avoidance	37.3	11.5	34.1	8.0	1.36	.178
SCL-90-R	74.9	59.8	28.6	26.8	17.4	< .001

Comparisons of demographic and clinical variables were examined using independent two-sample *t* tests. Differences in task-relevant variables were examined using one-way analyses of covariance controlling for IQ. In total, 32 patients were of restrictive subtype and 3 were of binging–purging subtype. All *p* values less than .05 indicate a significant group difference.

AN, anorexia nervosa group; BDI-II, Beck Depression Inventory; BIS/BAS, behavioral inhibition/avoidance scales, computed on a sample of 19 patients with AN and 21 HC subjects; BMI-SDS, body mass index standard deviation score; EDI-2, Eating Disorder Inventory; HC, healthy control group; IQ, intelligence quotient; JTCI, Junior Temperament and Character Inventory values, computed on a sample of 34 patients with AN and 35 HC subjects; SCL-90-R, Symptom Checklist 90-revised.

Computational Modeling

Our computational model followed the meta-Bayesian "observing the observer" approach (38). Accordingly, an active decision-making agent makes inferences about the hidden "state of affairs" based on the feedback associated with each option (here the expected values of options A and B on each trial) using a so-called perceptual model. Subsequently, an "observational model" predicted the ensuing behavioral responses.

We compared the performances of three perceptual models. In addition to the widely used Rescorla-Wagner model with constant learning rate, we considered two alternative models: an HGF (29) because it allowed us to quantify different forms of perceptual uncertainty perceived by the

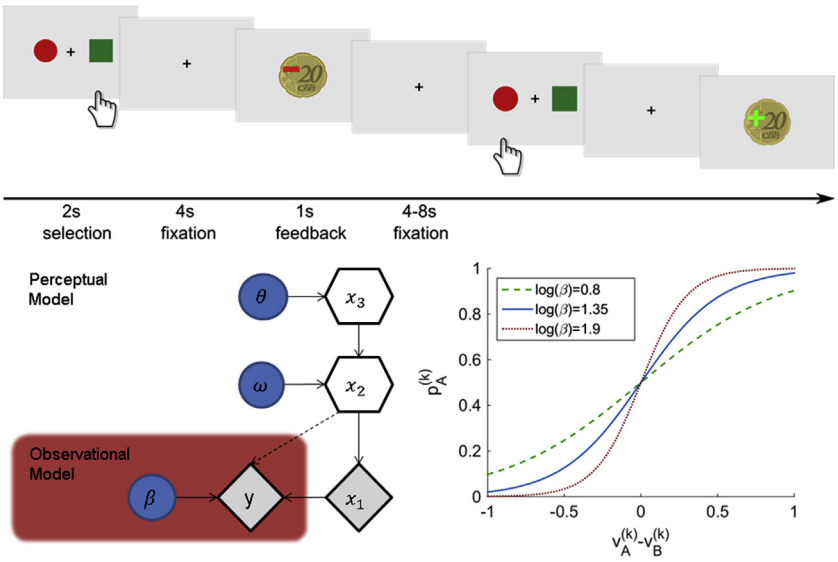

Figure 1. (Top panel) Time course of the experiment. First, two abstract stimuli were presented. The participant had up to 2 seconds to make a choice. After the participant had selected one stimulus (by left or right button press), a fixation cross was presented for 4 seconds. Finally, positive or negative feedback (monetary reward or punishment) was displayed for 1 second, followed by a jittered intertrial interval (fixation cross) for 4 to 8 seconds. (Bottom left panel) The hierarchical Gaussian filter: Graphical representation of the perceptual (hierarchical Gaussian filter) model used in this work. Polygons represent quantities that change with time, while circles denote time-independent, subject-specific parameters. Arrows indicate dependency of one variable on another. While hexagons represent states that satisfy the Markov property, such that the state at trial k also depends on the state at $k-1$, diamonds contain quantities that do change with time but do not depend on their previous state. β is the inverse decision noise, θ is the metavolatility, and ω is the tonic log volatility. x_1 is the probability of reward for each option (A or B), x_2 is the tendency toward reward, and x_3 is the time-dependent part of the log-volatility. y is the response given by the participant. In our observational model, y does not depend directly on the environmental volatility x_3. (Bottom right panel) The softmax choice rule: Probability that option A is chosen according to the observational model used in this work (softmax). $v_A^{(k)}-v_B^{(k)}$ can be computed from x_1 (see Supplemental Methods). A small value of decision noise ($1/\beta$) implies that the most valuable option is chosen with high probability. The β values chosen correspond to the mean of the entire sample plus or minus the standard deviation (see Table 2).

agent, and a Rescorla-Wagner model with an adaptive learning rate (39). Because Bayesian model selection (40) revealed that the HGF fitted behavior best across HCs and patients with AN, as well as for both groups separately (protected exceedance probability $>$ .996), it was also chosen to fit the functional MRI (fMRI) data (Supplemental Methods and Supplemental Table S1).

The HGF (29) used is a Bayesian learning model that allows for individual differences through subject-specific parameters: the metavolatility (θ) (27) and the tonic log volatility (ω). The metavolatility determines how fast the environmental volatility is assumed to change, while the tonic log volatility is a constant component of the log volatility and therefore has a modulating effect on the learning rate. The update equations for the expected values of each option are similar to those in basic reinforcement learning models:

$$\text{prediction}(k) = \text{prediction}(k-1) + \text{learning rate}(k) \times \text{prediction error}(k)$$

As in previous studies (31,33,39,41), we used prediction errors $\delta^{(k)}$, implied learning rates $\alpha^{(k)}$, and expected values of the chosen option $v^{(k)}$ as parametric modulators in the fMRI analysis.

The probability of an option to be chosen was a softmax function of its inferred expected value relative to the other option, which introduces another subject-specific parameter, the decision noise ($1/\beta$) (Figure 1).

For a precise definition of the models and their update equations, see Supplemental Methods. For the implementation and inversion of the HGF, we used the Translational Algorithms for Psychiatry-Advancing Science package (http://www.translationalneuromodeling.org/tapas/) with version 4.10 of the HGF toolbox (using standard priors for the free model parameters).

Statistical Analysis

Behavioral Measures. We subjected eight measures to t tests with group as an independent factor: 1) the total amount of money won, 2) the number of misses (invalid trials), 3) the ratio of correct responses, 4) the rate of contingency switches, and 5) the log model evidence associated with the inversion of the HGF for each subject as well as the trial-independent, subject-specific parameters of the computational model, that is, 6) log-decision noise log ($1/\beta$), 7) tonic log-volatility ω, and 8) log metavolatility log θ.

The trial-dependent parameters [expected value $v^{(k)}$, prediction error $\delta^{(k)}$, and learning rate $\alpha^{(k)}$] and the reaction times were each treated within a $2 \times 2 \times 2$ linear mixed model (after a logit and log transform, respectively; see Supplemental Methods) with response (correct/wrong) and feedback (rewarded/punished) as within-subject factors and group (HC/AN) as a between-subject factor. Post hoc t tests were corrected for multiple comparisons using a Bonferroni correction.

MRI Data Acquisition. Structural and functional images were acquired between 8 and 9 AM after an overnight fast using standard sequences with a 3T whole-body MRI scanner (TRIO; Siemens, Erlangen, Germany) equipped with a standard head coil (details in Supplemental Methods).

MRI Data Preprocessing. Functional and structural images were processed using the SPM8 toolbox (http://www.fil.ion.ucl.ac.uk/spm/) within the Nipype framework (42). Preprocessing steps included correcting for slice timing and motion, normalization, smoothing, and noise reduction using a component-based noise correction method (43). For more details and information regarding image quality control, see Supplemental Methods.

MRI Data Analysis: First-Level Analysis. In our main analysis, we implemented three different general linear models (GLMs). All three models included a binary and a parametric modulation regressor of interest (trial-dependent parameter of the HGF), each associated with an event lasting for 1 second and convolved with a canonical hemodynamic response function, as in previous studies applying computational modeling in a probabilistic reversal learning task (32,39,41). In particular, we modulated the GLM 1 response event (assumed to start 1 second before the button press) with the expected value of the chosen option $v^{(k)}$, the GLM 2 learning event (starting at feedback) with the implied learning rate $\alpha^{(k)}$ (31,39), and the GLM 3 feedback event (starting at feedback) separately for rewarded and punished trials with the absolute value of the prediction error $|\delta^{(k)}|$ (39). Follow-up analysis considered a fourth GLM with two binary regressors of interest (and no parametric modulator) starting at feedback and lasting for 1 second, separating the rewarded and punished trials. Additional nuisance regressors in all four models were the event of stimulus presentation (lasting 0 seconds), six realignment parameters, six principal noise components from the component-based noise correction analysis, and one regressor for each motion or intensity outlier volume.

MRI Data Analysis: Second-Level Analysis. To verify that the task elicited the expected activation patterns, we first conducted whole-brain one-sample *t* tests on the regression weights of the parametric modulators of the first-level GLMs. To test for group differences, we then conducted independent-samples *t* tests on activation regressors and parametric modulators. We also implemented a whole-brain 2 × 2 mixed-factorial analysis of variance with group (AN/HC) as a between-subjects factor and feedback (punished/rewarded) as a within-subjects factor on the first-level coefficients from our follow-up GLM using GLMFlex (http://mrtools.mgh.harvard.edu), which allows for the estimation of partitioned error terms.

We report results as significant at a familywise error (FWE) rate level whole-brain corrected using random field theory (44) with a false-positive rate of $\alpha < .05$. In the case of nonsignificant whole-brain results in any of the three a priori defined regions of interest (Supplemental Methods and Supplemental Figure S2) corresponding to the ventromedial PFC $[v^{(k)}_{A,B}]$, ventral striatum $[\delta^{(k)}]$, and pMFC $[\alpha^{(k)}]$, we computed small volume corrected (SVC) voxelwise thresholds (FWE–SVC < .05).

RESULTS

Sample Characteristics

There were no significant differences in age, IQ, or handedness score between the pairwise matched AN and HC groups. However, as expected, patients with AN had lower body mass index and higher eating disorder symptom and depression scores (Table 1). Differences in the Behavioral Inhibition Scale or Junior Temperament and Character Inventory subscale harm avoidance (HA) were not significant in the sample with neuroimaging data. However, in a larger sample with questionnaire data that included the one used for the current study, patients with AN had significantly higher Behavioral Inhibition Scale and HA scores (Supplemental Results).

Behavioral and Modeling Data

The results of the analysis of variance on behavioral measures and on trial-independent model parameters (and of the Mann-Whitney test on ω) are summarized in Table 2. There were no group differences for the number of correct answers and contingency reversals, for the total win trials, and the number of misses. The log model evidence and the subject-specific model parameters [inverse log-decision noise log (β), tonic log-volatility ω, and log metavolatility log (θ)] also did not differ between the groups.

The results of the 2 (HC/AN) × 2 (rewarded/punished) × 2 (correct/wrong) mixed model on the trial-dependent model parameters and the reaction times are summarized in Table 3 (see also Supplemental Table S5). The expected main effects and interactions of feedback and response on the learning rate, the prediction error, and the expected value were reproduced [(41,45); see also Supplemental Results]. Most important, a group × feedback interaction indicating a higher learning rate on punished trials in patients with AN was found ($F_{1,8262.6} = 6.6$, $p = .010$) (Figure 2). This effect was not influenced by age (Supplemental Results and Supplemental Table S4). Further explorative analyses indicated that an increased learning rate after punishment in patients with AN is not driven by HA or extreme underweight (Supplemental Results and Supplemental Table S6).

Imaging Data

In line with previous studies (31), blood oxygen level–dependent (BOLD) activity in the pMFC correlated with the changing (time-dependent) learning rate $\alpha^{(k)}$ (Figure 3A and Supplemental Figure S5). Also as in previous studies (32,33), activation in the ventromedial PFC correlated with the

Table 2. Analysis of Variance on Trial-Independent Parameters

	AN		HC		Test Statistics	
	Mean	SD	Mean	SD	*F*	*p*
Behavioral Measures						
Correct answers	81.3	6.1	82.1	8.0	0.18	.675
Contingency reversal	9.2	1.4	8.7	1.9	1.27	.264
Perceptual Model Parameters						
Tonic log-volatility (ω)	−1.15	0.59	−1.62	1.54	2.86	.095
Log metavolatility [log (θ)]	−5.87	1.38	−6.01	0.64	0.313	.578
Observational Model Parameter						
Log decision-noise [–log (β)]	−1.33	0.53	−1.39	0.59	0.197	.659
Quality of Fit						
Log model evidence	−52.2	14.2	−52.9	15.5	0.036	.850

The individual parameters from the hierarchical Gaussian filter perceptual model and softmax observational model were subjected to an analysis of variance with group as an independent factor. For the tonic log-volatility (ω), a Mann-Whitney test found no group differences ($U = 612.5$, $p = .089$, two tailed). *p* Values less than .05 indicate a significant group difference. See Supplemental Figure S1 for more details on performance parameters.

AN, anorexia nervosa group; HC, healthy control group.

Table 3. Mixed-Factor Analysis of Variance on Trial-Dependent Parameters

	Learning Rate			Prediction Error		
Effect	*df*	*F*	*p*	*df*	*F*	*p*
Response	1, 8264	24.4	< .001	1, 8275	823	< .001
Feedback	1, 8263	692.5	< .001	1, 8260	13419	< .001
Group	1, 69.3	3.8	.055	1, 83.7	0.827	.366
Response × Feedback	1, 8263	265.1	< .001	1, 8260	21.4	< .001
Feedback × Group	1, 8263	6.6	.010	1, 8260	1.64	.200
Response × Group	1, 8264	0.02	.891	1, 8275	0.002	.964
Response × Feedback × Group	1, 8263	0.46	.498	1, 8260	1.925	.165
	Expected Value			Reaction Time		
Effect	*df*	*F*	*p*	*df*	*F*	*p*
Response	1, 8282	927.0	< .001	1, 8274	9.99	.002
Feedback	1, 8272	10.7	.001	1, 8270	1.06	.303
Group	1, 77.6	0.926	.339	1, 71.6	0.425	.517
Response × Feedback	1, 8273	.002	.962	1, 8270	0.052	.819
Feedback × Group	1, 8272	0.051	.822	1, 8270	0.139	.709
Response × Group	1, 8282	0.841	.359	1, 8274	0.577	.448
Response × Feedback × Group	1, 8273	1.35	.246	1, 8270	0.821	.365

The individual trial-dependent parameters from the hierarchical Gaussian filter perceptual model and the reaction times were subjected to a 2 × 2 × 2 analysis of variance after a logit and log transformation, respectively (see Supplemental Methods) with group, response, and feedback as factors. We provide *F* and *p* values for the main effects and interactions. Reaction times did not differ between the groups, but there was a main effect of response. The post hoc test revealed that reaction time was longer on those trials where a wrong answer was given.

changing expected value $v^{(k)}$ (Supplemental Figure S3). Furthermore, BOLD activation in the ventral striatum correlated with the changing prediction error $|\delta^{(k)}|$ separately in rewarded and punished trials [Supplemental Figure S3; see also (32,33,39,41)]. Together, these findings corroborate our task and analytical approach. Other significant activations are reported in Supplemental Table S4. No group differences were found at the FWE or FWE–SVC level.

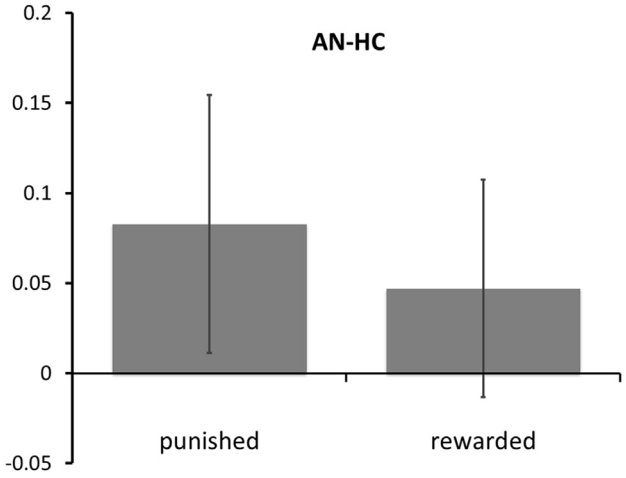

Figure 2. Increased learning rate after punishment in anorexia nervosa (AN). The critical group × feedback interaction [also significant after Bonferroni correction across the four tested models *p*(corrected) = .04] was followed up with post hoc comparisons revealing that the learning rate is greater in the AN group than in the healthy control (HC) group on punished trials [mean difference (SE) = 0.083 (0.036)]. Error bars reflect 95% confidence level intervals.

More important regarding our hypotheses, given 1) the behavioral findings indicative of an increased learning rate in patients with AN on punished trials (Figure 2), 2) previous evidence of elevated sensitivity to punishment in patients with AN (9,12), and 3) the linear correlation between the learning rate and BOLD activity in pMFC as in previous studies (31,39), we predicted altered activation in patients with AN in the region associated with the learning rate, specifically after punishments. To test this hypothesis, we calculated a 2 (group) × 2 (feedback) analysis of variance. Critically, while no group difference in the pMFC was revealed on win trials, the BOLD response was elevated in this region in patients with AN on punished trials. This group difference overlapped the cluster in which BOLD activity correlated with the learning rate (Figure 3B, Supplemental Figure S4, and Supplemental Table S8; see also Supplemental Figure S5). To investigate possible causal relationships, we conducted mediation analysis using the SPSS PROCESS toolbox (46). However, no mediation effects of the learning rate on the pMFC activation or vice versa were detected (Supplemental Results and Supplemental Table S9). Moreover, exploratory analysis revealed no correlation between pMFC activation and body mass index standard deviation score, Beck Depression Inventory, Eating Disorder Inventory, or HA scores in patients with AN (FWE–SVC).

DISCUSSION

We used computational modeling in combination with fMRI to provide insight into the neural mechanisms underlying decision making and feedback learning in young, acutely ill patients with AN. Bayesian model comparison (methods) demonstrated better fit between a recently developed HGF model (29) and the behavioral data for both the AN and HC groups than more

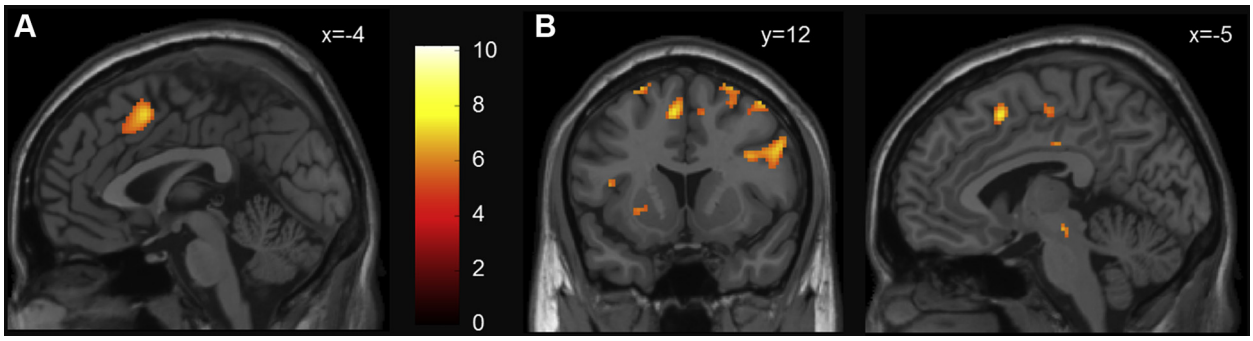

Figure 3. **(A)** Correlation of blood oxygen level–dependent activity after feedback with learning rate α. Learning rate was computed within a hierarchical Gaussian filter, and the expected pattern of activation in the posterior medial frontal cortex (31,39) across all participants (whole-brain one-sample *t* test) was reproduced. **(B)** Increased blood oxygen level–dependent activity in anorexia nervosa following punishment. Increased blood oxygen level–dependent activity in the anorexia nervosa group relative to the healthy control group following punishment as revealed by a whole-brain independent-samples *t* test is depicted on the same slice. A list with the peaks of activation is reported in Supplemental Table S4. We display regions where the signal is significant at a familywise error $< .05$ level determined with random field theory. The color scale shows one-sample *t*-test values.

classical reinforcement learning models (30). However, patients with AN were characterized by an increased learning rate on punished trials, possibly indicating hypersensitivity to punishment that has been observed clinically and empirically in AN (10,12,35). This finding suggests that when patients with AN experience negative feedback, they question their beliefs to a greater degree than HCs. On a neural level, time-dependent parameters of feedback learning correlated with BOLD activity in the same brain regions in both groups. In particular, consistent with previous model-based fMRI studies of decision making and feedback learning in healthy participants (31,39), we found a significant correlation between the learning rate and BOLD activation in the pMFC, a region involved in outcome evaluation and initiating adaptive adjustments accordingly (31,47,48). Most important, mirroring the behavioral group difference, BOLD activation was increased in this region in AN after punishment.

Our finding of increased pMFC activation after punishment in patients with AN converges with recent evidence attributing a role of this region to the pathophysiology of the disorder. For example, adolescent patients with AN exhibited an elevated neural response to punishment in the "cognitive" zone of the dorsal anterior cingulate cortex relative to HCs in a monetary guessing task (21). Conversely, Zastrow *et al.* (24) found decreased pMFC activation specifically on "shift" trials of a target detection task in patients with AN. Altered pMFC activity has also been reported during temporal reward discounting (19,49) and during inhibitory processing (50). Moreover, a recent resting-state functional connectivity study (51) found reduced connectivity between pMFC and the executive control network in adolescent patients with AN. While these studies suggest altered pMFC functioning in AN, the direction of group differences varies and the possible interpretations include altered conflict monitoring, excessive cognitive control, and increased neural efficiency. Structurally, volume reductions in the anterior cingulate cortex (including portions of the pMFC) in acutely ill patients with AN have been related to deficits in perceptual organization and conceptual reasoning, while the degree of normalization during treatment was linked to clinical outcome (52). Using single-photon emission computed tomography, reduced regional cerebral blood flow in the dorsal anterior cingulate cortex extending into the presupplementary motor area was observed during the acute phase of the illness and after weight recovery (53). Our study gives additional support for functional pMFC alterations in acutely ill patients with AN using a novel approach that had been applied successfully in other disorders before (40,41,54). Taken together, our behavioral and imaging findings suggest that the elevated pMFC response in AN may help to explain the abnormally rapid learning rate following punishment.

Restrictive food choice and extreme resistance to treatment are just two examples of altered decision making in AN. While previous laboratory investigations (14,15) were relatively limited in their ability to isolate specific alterations, a recent cognitive modeling study of Iowa Gambling Task performance found a "recency bias" in AN captured by a learning/memory parameter (55). Although the model did not uncover a group difference in a feedback sensitivity parameter, the finding that patients tended to base their decisions on recent experience is commensurate with our finding of an increased learning rate in patients with AN. The current evidence of altered decision making in response to negative feedback is in line with the notion of altered reinforcement learning in AN (1–5,8) and, considered in light of similar recent findings (13), is suggestive of a particular sensitivity to punishment. Decision making may be intact, however, in paradigms that do not include negative feedback, at least in adolescents (19,56). Nonetheless, these findings were made in predominantly restrictive AN, and future studies are needed to clarify potential subtype differences in reward and punishment sensitivity (10,11). Furthermore, given the presumption that AN is characterized by altered general reward-related decision making (4,8,19) and the lack of group differences in this respect in both the current study and other recent studies (21,49), future research is also needed to clarify under which conditions the neural substrates of reward processing are aberrant in AN.

While our study was not designed to clarify whether altered decision making causes AN or is a temporary effect of acute illness, correlation between punishment sensitivity and attachment insecurity has been reported (57). This suggests

that, together with attachment style, a decision-making strategy geared toward loss avoidance may develop early in life. Speculatively, oversensitivity to negative feedback may contribute to the onset of AN. For example, negative comments from peers regarding physical appearance might be given exaggerated importance as an effect of an increased learning rate and, consequently, might predispose (future) patients with AN to change their nutritional habits and activity levels to lose weight (58). Indeed, it has been found that increased HA persists after recovery in AN, raising the possibility that such a trait exists premorbidly (59,60).

At the neurobiological level, positron emission tomography imaging studies have found associations between HA and 5-hydroxytryptamine (5-HT, serotonin) functioning in various eating disorders (59). Interestingly, a low 5-HT state, probably due to reduced tryptophan intake because of food restriction (60–62), has been suggested for acute AN (62). In healthy participants (63), it was found that acute tryptophan depletion, a method for transiently reducing cerebral 5-HT levels, was associated with increased BOLD responses in a region of the dorsomedial PFC overlapping the pMFC during a probabilistic reversal learning task, especially after punishment. Given the role of 5-HT in altered neural mechanisms during feedback learning and evidence suggesting normal or even increased 5-HT levels in recovered patients with AN (59,64), future studies in weight-recovered AN targeting the pMFC during feedback learning would be of great interest.

At a more qualitative level, our model-based approach suggests that learning and decision making activate the same brain regions similarly in both the AN and HC groups. This finding fits neatly with our model comparison; by using different computational models of feedback learning, we found that the behavior of both groups was better explained by the Bayesian HGF model than by Rescorla-Wagner models (with either a fixed or flexible learning rate), suggesting that, equally to HCs, patients with AN place differential importance on prediction errors depending on their perception of environmental volatility. Note that for other psychiatric disorders such as binge eating disorder (65), schizophrenia (66), and alcoholism (67), Bayesian model selection indicated that patients' behavior was guided by different (typically less efficient) decision-making strategies. For example, in adolescent attention-deficit/hyperactivity disorder, patients' choice behavior was better explained by a Rescorla-Wagner model with a constant learning rate, whereas for HCs the HGF provided a better fit (68). Previous computational modeling studies in AN (16,69) used a temporal difference model with a fixed learning rate (28) to derive prediction error measures in passive taste reward learning tasks, but model parameters and model comparison data were not reported in these studies.

Our study needs to be seen in the light of the following limitations. First, we focused on young (mostly adolescent) patients with acute AN. While this has the advantage of minimizing secondary effects of prolonged malnutrition on cognition, it provides no indication as to whether parameters such as the learning rate can be seen as biological markers. Therefore, studies measuring patients longitudinally after weight restoration or complete recovery are needed. However, although patients were in a state of undernutrition, they did not show reduced performance and the behavioral results were not driven by particularly underweight patients (Supplemental Results and Supplemental Table S6). Second, although we compared three computational models of behavior and identified one with best fit for both groups (suggesting that the general strategies employed in AN are normal), there may be better models that lead to different conclusions. Third, although our sample size was large relative to most fMRI studies in AN and the employed task had a comparable number of trials as in similar clinical studies (21), the power of our study to detect all relevant between-group effects (e.g., reward related) may be limited, and future studies with more observations in larger samples are needed. Fourth, the group difference in self-reported HA was not significant in the current study, presumably because of a lack of statistical power (Supplemental Results), and the expected correlation between HA and learning rate after punishment was not found (Supplemental Results). Therefore, alternative explanations of an increased learning rate in AN including impaired memory (55) and uncertainty regarding current beliefs, are also plausible. However, an increased learning rate specifically after punishments indicates that an exaggerated importance is placed on negative feedback despite uncertainty due to the probabilistic nature of contingencies.

Computational approaches focusing on learning mechanisms appear to be particularly promising with respect to the detection of basic mechanisms contributing to the development and maintenance of mental disorders. Altered decision making has been linked to treatment outcome in AN (70), and quantification of individual differences in learning mechanisms have the potential to guide the development of new therapeutic strategies that directly aim at the modification of such behavior patterns. Given the current results in patients with acute AN, a stronger focus on increasing self-confidence (71) and the ability to tolerate criticism might foster therapeutic success.

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