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Altered medial frontal feedback learning signals in anorexia nervosa

Fabio Bernardoni PhD,[1,2] Daniel Geisler MSc,[1,2] Joseph A. King PhD,[1,2] Amir-Homayoun Javadi PhD,[6] Franziska Ritschel MSc,[1,2] Julia Murr MD, [3] Andrea M.F. Reiter PhD, [4,5] Veit Rössner MD,[1] Michael N. Smolka MD,[7] Stefan Kiebel PhD, [4,7] Stefan Ehrlich* MD [1,2]

[1]Division of Psychological and Social Medicine and Developmental Neuroscience, Faculty of Medicine, Technische Universität Dresden, Dresden, Germany

[2]Eating Disorder Treatment and Research Center, Department of Child and Adolescent Psychiatry, Faculty of Medicine, Technische Universität Dresden, Dresden, Germany

[3]Department of Psychosomatic Therapy, Faculty of Medicine, Technische Universität Dresden, Dresden, Germany

[4]Department of Psychology, Institute of General Psychology, Biopsychology and Methods of Psychology, Technische Universität Dresden, Dresden, Germany

[5]Lifepan Developmental Neuroscience, Technische Universität Dresden

[6]School of Psychology, University of Kent, Canterbury, UK

[7]Department of Psychiatry and Neuroimaging, Technische Universität Dresden, Dresden, Germany

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Corresponding author: Stefan Ehrlich, MD, Technische Universität Dresden, Faculty of Medicine, University Hospital C. G. Carus, Dresden, Division of Psychological and Social Medicine and Developmental Neuroscience, Fetscherstraße 74, 01307 Dresden, Germany, Phone: +49 (0)351 458-15095, Fax: +49 (0)351 458 -5754, Email: Stefan.Ehrlich@uniklinikum-dresden.de

Abstract

Background

In their relentless pursuit of thinness, individuals with anorexia nervosa (AN) engage in maladaptive behaviors (restrictive food choices, over-exercising) which may originate in altered decision-making and learning.

Methods

In this fMRI study we employed computational modelling to elucidate the neural correlates of feedback learning and value-based decision making in 36 female AN patients and 36 age-matched healthy volunteers (12-24 years). Participants performed a decision task which required adaptation to changing reward contingencies. Data were analyzed within a hierarchical Gaussian filter model, which captures inter-individual variability in learning under uncertainty.

Results

Behaviorally, patients displayed an increased learning rate specifically after punishments. At the neural level, hemodynamic correlates for 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.

Conclusion

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

Introduction

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) 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. binge-purging) may exist (9–13). Most laboratory evidence for altered feedback learning and value-based decision making in AN comes from impaired perfomance in the Iowa Gambling Task (IGT; 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 IGT "net score" provides little insight into which aspect(s) might be altered in AN. Suggesting that AN patients may be particularly hypersensitive to punishment, patients have been also found to make less risky choices than healthy controls (HC) in another decision-making paradigm, the Balloon Analogue Risk Task (13). Further evidence comes from neuroimaging studies which found altered reward processing in response to disorder-related stimuli like food or 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 an apparently excessive amount of self-control (5, 25).

To gain a new perspective on feedback learning and decision-making in AN, we here apply the methods of computational psychiatry (26) which 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 to conventional analysis methods, this approach avoids i) associating neurobiological signals with subjective reports of patients (which depends on their ability to self-reflect and adequately verbalize mood states or experiences) and ii) the limitations of purely descriptive measures, such as error rates.

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, i.e. 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 which 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, e.g. posterior medial frontal cortex (pMFC) for learning rate, ventromedial prefrontal cortex (vmPFC) for expected (subjective) value of a choice option and ventral striatum (VS) for 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 HC and that learning from such negative feedback would be linked to altered activation in the pMFC. The pMFC spans the dorsal anterior cingulate cortex (dACC) and pre-supplementary motor area (pre-SMA) 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

72 females participated in this study: 36 acutely underweight AN (12-23 years old) and 36 pairwise age-matched HC (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 (SM 1.1). AN participants were recruited from specialized eating disorder programs and underwent MRI within 96 hours after admission to behaviorally-oriented nutritional rehabilitation programs. Please refer to SM1.1 and SM

1.2 for additional information on inclusion and exclusion criteria and 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 AN participant (and her age-matched partner) had to be excluded due to low performance (SM 1.3 and Figure S1).

Experimental paradigm

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

Computational Modeling

Our computational model followed the meta-Bayesian 'observing the observer' approach (40). 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 option A and B on each trial), using a so-called 'perceptual model'. Subsequently, an 'observational model' predicted the ensuing behavioral responses.

We compared the performance of three perceptual models. In addition to (i) the widely used Rescorla-Wagner model with constant learning rate, we considered two alternative models: (ii) a HGF (29) because it allowed us to quantify different forms of perceptual uncertainty perceived by the agent and (iii) a Rescorla-Wagner model with an adaptive learning rate (41). Since Bayesian Model Selection (42) revealed that the HGF fitted behavior best across HC and AN patients as well as for both groups separately (Protected Exceedance Probability>.996), it was also chosen to fit the fMRI data (SM1.5 and Table S1).

The HGF (29) used is a Bayesian learning model that allows for individual differences through subject-specific parameters: the *meta-volatility* (θ, 27) and the *tonic log-volatility* (ω). The *meta-volatility* 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:

$$prediction(k) = prediction(k-1) + learning\ rate(k)\ \times prediction\ error(k).$$

As in previous studies (31, 33, 41, 44), 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 SM 1.4. For the implementation and inversion of the HGF, we used the Translational Algorithms for Psychiatry-Advancing Science (TAPAS) package (http://www.translationalneuromodeling.org/tapas/) with v4.10 of the HGF toolbox (using standard priors for the free model parameters).

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111 ***Statistical Analysis***

112 *Behavioral Measures*

113 We subjected eight measures to t-tests with group as independent factor: (i) The total
114 amount of money won, (ii) the number of misses (invalid trials), (iii) the ratio of correct responses,
115 (iv) the rate of contingency switches, (v) the log-model-evidence (LME) associated with the inversion
116 of the HGF for each subject, and the trial-independent subject-specific parameters of the
117 computational model, i.e. (vi) *log-decision noise* $\log(1/\beta)$, (vii) *tonic log-volatility* ω and (viii) *log-*
118 *meta-volatility* $\log(\theta)$.

119 The trial-dependent parameters (expected value $v^{(k)}$, prediction error $\delta^{(k)}$ and learning rate
120 $\alpha^{(k)}$) and the reaction times (RT) were treated each within a $2 \times 2 \times 2$ linear mixed model (after a
121 logit and log transform respectively; SM 1.6) with response (correct/wrong) and feedback
122 (rewarded/punished) as within-subject factors and group (HC/AN) as between-subject factor. Post
123 hoc t-tests were corrected for multiple comparisons using a Bonferroni-correction.

124 ***MRI Data acquisition***

125 Structural and functional images were acquired between 8 and 9 am after an overnight fast
126 using standard sequences with a 3 T whole-body MRI scanner (TRIO; Siemens, Erlangen, Germany)
127 equipped with a standard head coil (details in SM 1.2).

128 ***MRI Data Preprocessing***

129 Functional and structural images were processed using the SPM8 toolbox
130 (http://www.fil.ion.ucl.ac.uk/spm/) within the Nipype framework (45). Preprocessing steps included
131 correcting for slice timing and motion, normalization, smoothing, and noise reduction using CompCor
132 (46). For more details and information regarding image quality control see SM 1.8.

133 ***MRI Data Analysis***

134 *First level analysis*

135 In our main analysis, we implemented three different GLMs. All three models included a
136 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 modelling in a probabilistic reversal learning task (32, 41, 44). In particular, we modulated the (GLM 1) response event (assumed to start one second before the button press) with the expected value of the chosen option $v^{(k)}$, (GLM 2) the learning event (starting at feedback) with the implied learning rate $\alpha^{(k)}$ (31, 41), and (GLM 3) the feedback event (starting at feedback) separately for rewarded and punished trials with the absolute value of the prediction error ($|\delta^{(k)}|$; 25). 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 the 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 CompCor analysis, and one regressor for each motion or intensity outlier volume.

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 ANOVA with group (AN/HC) as between- and feedback (punished/rewarded) as within-subjects factors on the 1st level coefficients from our follow-up GLM using GLMFlex (http://mrtools.mgh.harvard.edu), which allows for the estimation of partitioned errors terms.

We report results as significant at a family-wise error rate FWE level whole-brain corrected using random field theory (47) with a false-positive rate $\alpha < 0.05$. In the case of non-significant whole-brain results in any of the three *a priori* defined ROIs (SM 1.9 and Figure S2) corresponding to the vmPFC ($v_{A,B}^{(k)}$), VS ($\delta^{(k)}$), and pMFC ($\alpha^{(k)}$), we computed small volume corrected (SVC) voxel-wise thresholds (FWE-SVC<.05).

Results

Sample Characteristics

There were no significant differences in age, IQ, or handedness score between the pairwise matched groups of AN and HC. However, as expected, AN had lower body mass index (BMI), higher eating disorder symptom and depression scores (Table 1). Differences in the Behavioral Inhibition Scale (BIS) 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 questionaire data, that included the one used for the present study, AN patients had a significantly higher BIS and HA (SM 2.1).

Behavioral and Modeling Data

The results of the ANOVA 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 and the number of misses. The LME and the subject-specific model parameters (inverse log-decision noise $\log(\beta)$, *tonic log-volatility* ω and *log-meta-volatility* $\log(\theta)$) 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 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 [(44, 48); SM 2.3]. Most importantly, a group×feedback interaction indicating a higher learning rate on punished trials in AN was found [$F(1,8262.6)=6.6$, $p=0.010$; Figure 2]. This effect was not influenced by age (SM 2.3, Table S4). Further explorative analyses indicated that increased learning rate after punishment in AN might be related to eating disorder symptoms, but is not driven by HA or extreme underweight (SM 2.3, Table S6).

Imaging Data

In line with previous studies (31), BOLD activity in the pMFC correlated with the changing (time-dependent) learning rate $\alpha^{(k)}$ (Figures 3a, S5). Also as in previous studies (32, 33), activation in the vmPFC correlated with the changing expected value $v^{(k)}$ (Figure S3). Furthermore, BOLD activation in the VS correlated with the changing prediction error $|\delta^{(k)}|$ separately in rewarded and punished trials [Figure S3, (32, 33, 41, 44)]. Together, these findings corroborate our task and

analytical approach. Other significant activations are reported in Table S4. No group differences were found at FWE or FWE-SVC level.

More important regarding our hypotheses, given (i) the behavioral findings indicative of an increased learning rate in AN on punished trials (Figure 2), (ii) previous evidence of elevated sensitivity to punishment in AN (9, 12), and (iii) the linear correlation between learning rate and BOLD activity in pMFC as in previous studies (31, 41), we predicted altered activation in AN in the region associated with learning rate, specifically after punishments. To test this hypothesis, we calculated a 2(group) x2(feedback) ANOVA. Critically, while no group difference in the pMFC was revealed on win trials, the BOLD response was elevated in this region in AN on punished trials. This group difference overlapped the cluster in which BOLD activity correlated with learning rate (Figures 3b, S4, Table S8; see also Figure S5). To investigate possible causal relationships, we conducted mediation analysis using the SPSS PROCESS toolbox (49). However, no mediation effects of the learning rate on the pMFC activation or vice versa were detected (SM 2.4, Tables S9). Moreover, no correlation between pMFC activation and BMI-SDS, BDI-II, EDI-2 or HA scores was evident in AN (FWE-SVC).

Discussion

We used computational modelling in combination with fMRI to provide insight into the neural mechanisms underlying decision-making and feedback learning in young, acutely ill AN patients. 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 classical reinforcement learning models (30). However, AN patients were characterized by an increased learning rate on punished trials; possibly indicating hypersensitivity to punishment which has been observed clinically and empirically in AN (10, 12, 35). This finding suggests that when AN patients experience negative feedback, they question their beliefs to a greater degree than HC. 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, 41), we found a significant correlation between learning rate and BOLD activation in the pMFC, a region involved in outcome evaluation and initiating adaptive adjustments accordingly (31, 38, 50). Most importantly, 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 AN converges with recent evidence attributing a role of this region to the pathophysiology of the disorder. For example adolescent AN patients exhibited an elevated neural response to punishment in the “cognitive” zone of the dACC relative to HC 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 AN. Altered pMFC activity has also been reported during temporal reward discounting (19, 51) and during inhibitory processing (52). Moreover, a recent resting-state functional connectivity study (53), found reduced connectivity between pMFC and the executive control network in adolescent AN. While these studies suggest altered pMFC functioning in AN, the direction of group differences vary and the possible interpretations range from altered conflict monitoring, excessive cognitive control and increased neural efficiency. Structurally, volume reductions in the ACC (including portions of the pMFC) in acutely ill AN have been related to deficits in perceptual organization and conceptual reasoning, while the degree of normalization during treatment was linked to clinical outcome (54). Using SPECT, reduced regional cerebral blood flow in the dACC extending into the pre-SMA was observed during the acute phase of the illness and after weight recovery (55). Our study gives additional support for

functional pMFC alterations in acutely ill AN using a novel approach that had been applied successfully in other disorders before (42–44). Taken together, our behavioral and imaging findings suggest thatthe 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 modelling study of IGT performance found a "recency bias" in AN captured by a learning/memory parameter (58). 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 increased learning rate in AN. The current evidence of altered decision-making in response to negative feedback is in line with 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 don't include negative feedback, at least in adolescents (19, 59). Nonetheless, these findings were made in predominately 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 ones (21, 51), 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 (60). 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, predispose (future) AN patients to change their nutritional habits and activity levels to lose weight (61). Indeed, it has been found that increased HA persists after recovery in AN, raising the possibility that such a trait exists premorbidly (62, 63).

At the neurobiological level, PET imaging studies found associations between HA and 5-HT functioning in various eating disorders (62). Interestingly, a low 5-HT state, probably due to reduced

tryptophan intake because of food restriction (63–65) has been suggested for acute AN (62). In healthy participants (66), it was found that acute tryptophan depletion (ATD), 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 AN (62, 67), future studies in weight-recovered AN targeting the pMFC during feedback learning are 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 AN and HC. 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 Rescorla-Wagner models (either with fixed or flexible learning rate) suggesting that, equally to controls, AN patients place differential importance on prediction errors depending on their perception of environmental volatility. Note that for other psychiatric disorders such as binge eating disorder (57), schizophrenia (68) or alcoholism (69), Bayesian Model Selection indicated that patients' behavior was guided by different (typically less efficient) decision-making strategies. For example, in adolescent ADHD, patients choice behavior was better explained by a Rescorla-Wagner model with constant learning rate whereas for HC the HGF provided a better fit (56). Previous computational modeling studies in AN (16, 70) 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 has 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 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 (SM 2.3, 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 present study, presumably because of lack of statistical power (SM 2.1), and the expected correlation between HA and learning rate after punishment was not found (SM 2.3). Therefore, alternative explanations of increased learning rate in AN inlcuding impaired memory (58) and uncertainty regarding present beliefs are also plausible. However, an increased learning rate specifically after punishments indicates that an exaggerated importance is placed to 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 (71) 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 present results in patients with acute AN, a stronger focus on increasing self-confidence (72) and the ability to tolerate criticism might foster therapeutic success.

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Figure Legends

Figure 1. Top: Time course of the experiment. First, two abstract stimuli were presented. The participant had up to 2s time to make a choice. After the participant had selected one stimulus (by left or right button press), a fixation cross was presented for 4s. Finally, positive or negative feedback (monetary reward or punishment) was displayed for 1s followed by a jittered inter-trial interval (fixation cross) for 4 to 8s. **Bottom left**: **The Hierarchical Gaussian Filter (HGF).** Graphical representation of the perceptual (HGF) 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 the *meta-volatility* and ω the *tonic log-volatility*. x_1 is the probability of reward for each option A and B, x_2 is the tendency towards reward and x_3 is the time-dependent part of the log-volatility. y are the responses given by the participant. In our observational model y does not depend directly on the environmental volatility x_3. **Bottom right**: **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 SM1.4. 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 on the entire sample plus minus the standard deviation (see Table 2).

Figure 2. Increased learning rate after punishment in AN. The critical group×feedback interaction (significant also after Bonferroni correction across the four tested models p(corrected) = 0.40) was followed up with post-hoc comparisons which revealed that learning rate is greater in AN than in HC on punished trials (mean difference (SE) = 0.083(0.036)). Error bars reflect 95% confidence level intervals.

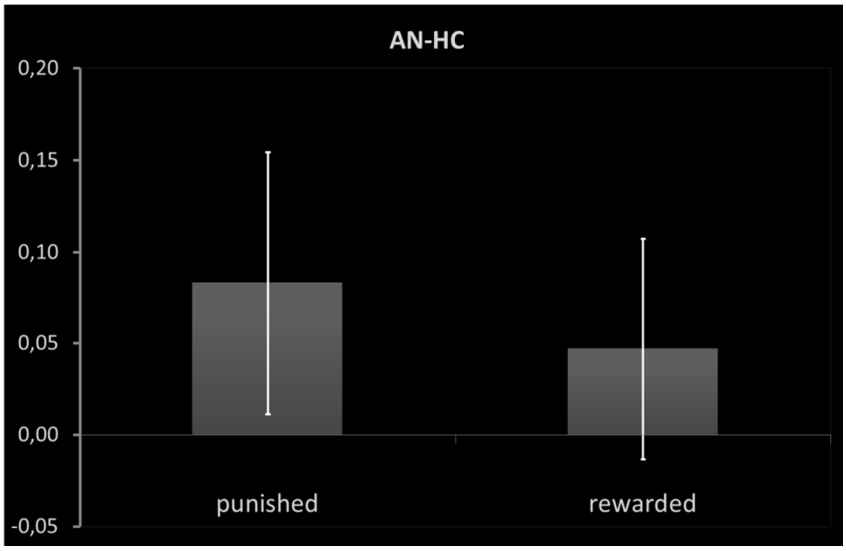

Figure 3. a: Correlation of BOLD activity after feedback with learning rate α. Learning rate was computed within a Hierarchical Gaussian Filter and the expected pattern of activation in the pMFC (31, 41) across all participants (whole-brain one-sample t-test) was reproduced. **b: Increased BOLD activity in AN following punishment.** Increased BOLD activity in AN relative to HC 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 Table S4. We display regions where the signal is significant at a FWE<.05 level determined with random field theory. The color scale shows one sample t-test values.

Tables

Table 1. Group characteristics. Comparisons of demographic and clinical variables were examined using independent two-sample t-tests, differences in task relevant variables were examind using one-way ANCOVAs controlling for IQ. Means and standard deviations (SD) are given.

	AN		**HC**		**test statistics**	
	Mean	SD	Mean	SD		
Demographic variables					**T**	**p**
Age	16.0	2.6	16.3	2.6	-0.5	0.662
BMI	14.7	1.3	20.4	2.5	-12.0	<0.001
BMI-SDS	-2.1	0.6	0.0	0.8	-11.7	<0.001
IQ	111.9	11.1	110.9	10.0	0.4	0.673
Handedness	0.5	2.0	1.7	3.7	-1.8	0.081
Clinical variables					**T**	**p**
EDI-2 total score	197.4	50.7	139.6	28.0	5.9	<0.001
EDI-2 perfectionism	19.6	6.0	15.7	4.2	3.3	0.002
BDI-II total score	19.5	11.6	5.5	5.7	6.5	<0.001
BIS	22.0	3.7	20.8	3.3	1.12	0.269
BAS	39.8	6.3	40.5	4.2	-0.44	0.665
JTCI harm avoidance	37.3	11.5	34.1	8.0	1.36	0.178
SCL-90-R	74.9	59.8	28.6	26.8	17.4	<0.001

AN=anorexia nervosa patients; HC=healthy controls; BMI-SDS=body mass index standard deviation score; IQ=intelligence quotient; EDI-2=Eating disorder inventory; BDI-II=Beck Depression Inventory; SCL-90-R = revised Symptom Checklist 90, BIS-BAS= behavioral avoidance/inhibition (BIS/BAS) scales, computed on a sample of 19 AN and 21 HC, JTCI=Junior Temperament und Character Inventory values, computed on a sample of 34 AN and

35 HC. 32 patients were of restrictive subtype and 3 of binge-purge. *P*-values below 0.05 indicates a significant group difference.

Table 2. ANOVA on trial independent parameters. The individual parameters from the HGF perceptual model and softmax observational model were subjected to an ANOVA with group as independent factor. Group means and standard deviations (SD) are given. For the *tonic log-volatility* (ω), a Mann-Whitney test found no group differences (U=612.5, p(2-tailed)=0.089).

	AN		**HC**		**test statistics**	
	Mean	SD	Mean	SD	Group	
Behavioral measures					**F**	**p**
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					**F**	**p**
tonic log-volatility $[\omega]$	-1.15	.59	-1.62	1.54	2.86	.095
Log *meta-volatility* $[\log(\theta)]$	-5.87	1.38	-6.01	.64	.313	.578
Observational model parameter					**F**	**p**
Log *decision-noise* $[-log(\beta)]$	-1.33	.53	-1.39	.59	.197	.659
Quality of Fit					**F**	**p**
Log Model Evidence	-52.2	14.2	-52.9	15.5	.036	.850

AN=anorexia nervosa patients; HC=healthy controls; *P*-values below 0.05 indicate a significant group difference. See Figure S1 for more details on performance parameters.

Table 3. Mixed factor ANOVA on trial dependent parameters. The individual trial dependent parameters from the HGF perceptual model and the reaction times were subjected to a 2×2×2 ANOVA after a logit and log transformation respectively (see SM 1.6) 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.

Effect	**learning rate**			**prediction error**		
	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	.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	.02	.891	1,8275	.002	.964
response×feedback×group	1,8263	.46	.498	1,8260	1.925	.165

Effect	**expected value**			**reaction times**		
	df	F	p	df	F	p
response	1,8282	927	<.001	1,8274	9.99	.002
feedback	1,8272	10.7	.001	1,8270	1.06	.303
group	1,77.6	.926	.339	1,71.6	.425	.517
response×feedback	1,8273	.002	.962	1,8270	.052	.819
feedback×group	1,8272	.051	.822	1,8270	.139	.709
response×group	1,8282	.841	.359	1,8274	.577	.448
response×feedback×group	1,8273	1.35	.246	1,8270	.821	.365