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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, 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.

1 Introduction

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

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

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

33 Intuitively, we expect healthy subjects to place greater importance on unexpected feedback
34 in a changing environment, but to nearly disregard it in a stable one. The latter guards against

35 switching away from the preferred option in the presence of environmental noise, i.e. when the
36 differences between expected and received rewards (also called reward prediction errors (27, 28))
37 are not due to a real change of contingencies. To probe these mechanisms in AN, we employed a
38 reversal learning task in which the preferable choice was rewarded probabilistically (in 80% of all
39 choices) and changed only after a learning criterion was achieved; thereby requiring participants to
40 learn from feedback and adapt to changing reward contingencies. To analyze behavior, we compared
41 a hierarchical Gaussian filter (HGF) model (29) with more classical reinforcement learning models
42 (30). In the HGF model, the weight given to prediction errors is encoded in an adaptive subject-
43 specific learning rate which is high for large environmental uncertainty, and low for small
44 uncertainty.
45 Previous studies in healthy individuals (31–33) and other patient populations (34) have linked specific
46 model parameters to activation in specific brain regions, e.g. posterior medial frontal cortex (pmMFC)
47 for learning rate, ventromedial prefrontal cortex (vmPFC) for expected (subjective) value of a choice
48 option and ventral striatum (VS) for prediction error. Given evidence of hypersensitivity to
49 punishment in AN (9–12, 21, 35, 36), we hypothesized that patients' decision-making would be more
50 affected by punishments (monetary loss) relative to HC and that learning from such negative
51 feedback would be linked to altered activation in the pmMFC. The pmMFC spans the dorsal anterior
52 cingulate cortex (dACC) and pre-supplementary motor area (pre-SMA) and is broadly implicated in
53 reward-based decision-making and signaling the need for adjustments when behavioral goals are
54 threatened such as when losses occur (35–37).

55

56 **Methods and Materials**

57 ***Participants and Procedure***

58 72 females participated in this study: 36 acutely underweight AN (12-23 years old) and 36
59 pairwise age-matched HC (12-24 years old). Case-control age-matching was carried out resulting in a
60 maximum difference of 1.7 years between the individuals within one pair (SM 1.1). AN participants
61 were recruited from specialized eating disorder programs and underwent MRI within 96 hours after
62 admission to behaviorally-oriented nutritional rehabilitation programs. Please refer to SM1.1 and SM

63 1.2 for additional information on inclusion and exclusion criteria and clinical assessments. Clinical
64 variables are reported in Table 1.

65 This study was approved by the Institutional Ethics Review Board and all participants (and
66 their guardians if underage) gave written informed consent.

67 One AN participant (and her age-matched partner) had to be excluded due to low
68 performance (SM 1.3 and Figure S1).

69

70 ***Experimental paradigm***

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

80 ***Computational Modeling***

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

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

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

99
$$prediction(k) = prediction(k - 1) + learning\ rate(k) \times prediction\ error(k).$$

100 As in previous studies (31, 33, 41, 44), we used prediction errors ($\delta^{(k)}$), implied learning
101 rates ($\alpha^{(k)}$), and expected values of the chosen option $v^{(k)}$ as parametric modulators in the fMRI
102 analysis.

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

106 For a precise definition of the models and their update equations, see SM 1.4. For the
107 implementation and inversion of the HGF, we used the Translational Algorithms for Psychiatry-
108 Advancing Science (TAPAS) package (<http://www.translationalneuromodeling.org/tapas/>) with v4.10
109 of the HGF toolbox (using standard priors for the free model parameters).

110

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),

137 each associated with an event lasting for 1 second and convolved with a canonical hemodynamic
138 response function, as in previous studies applying computational modelling in a probabilistic reversal
139 learning task (32, 41, 44). In particular, we modulated the (GLM 1) response event (assumed to start
140 one second before the button press) with the expected value of the chosen option $v^{(k)}$, (GLM 2) the
141 learning event (starting at feedback) with the implied learning rate $\alpha^{(k)}$ (31, 41), and (GLM 3) the
142 feedback event (starting at feedback) separately for rewarded and punished trials with the absolute
143 value of the prediction error ($|\delta^{(k)}|$; 25). Follow-up analysis considered a fourth GLM with two binary
144 regressors of interest (and no parametric modulator), starting at feedback and lasting for 1 second,
145 separating the rewarded and the punished trials. Additional nuisance regressors in all four models
146 were the event of stimulus presentation (lasting 0 seconds), six realignment parameters, six principal
147 noise components from the CompCor analysis, and one regressor for each motion or intensity outlier
148 volume.

149

150 *Second level analysis*

151 To verify that the task elicited the expected activation patterns, we first conducted whole-
152 brain one-sample t-tests on the regression weights of the parametric modulators of the first level
153 GLMs. To test for group differences, we then conducted independent samples t-tests on activation
154 regressors and parametric modulators. We also implemented a whole-brain 2x2 mixed factorial
155 ANOVA with group (AN/HC) as between- and feedback (punished/rewarded) as within-subjects
156 factors on the 1st level coefficients from our follow-up GLM using GLMFlex
157 (<http://mrtools.mgh.harvard.edu>), which allows for the estimation of partitioned errors terms.

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

163

164 **Results**

165 ***Sample Characteristics***

166 There were no significant differences in age, IQ, or handedness score between the pairwise
167 matched groups of AN and HC. However, as expected, AN had lower body mass index (BMI), higher
168 eating disorder symptom and depression scores (Table 1). Differences in the Behavioral Inhibition
169 Scale (BIS) or Junior Temperament and Character Inventory subscale ‘harm avoidance’ (HA) were not
170 significant in the sample with neuroimaging data. However, in a larger sample with questionnaire
171 data, that included the one used for the present study, AN patients had a significantly higher BIS and
172 HA (SM 2.1).

173 ***Behavioral and Modeling Data***

174 The results of the ANOVA on behavioral measures and on trial independent model
175 parameters (and of the Mann-Whitney test on ω) are summarized in Table 2. There were no group
176 differences for the number of correct answers and contingency reversals, for the total win and the
177 number of misses. The LME and the subject-specific model parameters (inverse log-decision noise
178 $\log(\beta)$, *tonic log-volatility* ω and *log-meta-volatility* $\log(\theta)$) also did not differ between the groups.

179 The results of the 2(HC/AN) \times 2(rewarded/punished) \times 2(correct/wrong) mixed model on the
180 trial dependent model parameters and the reaction times are summarized in Table 3 (see also Table
181 S5). The expected main effects and interactions of feedback and response on the learning rate, the
182 prediction error and the expected value were reproduced [(44, 48); SM 2.3]. Most importantly, a
183 group \times feedback interaction indicating a higher learning rate on punished trials in AN was found
184 [F(1,8262.6)=6.6, p=0.010; Figure 2]. This effect was not influenced by age (SM 2.3, Table S4). Further
185 explorative analyses indicated that increased learning rate after punishment in AN might be related
186 to eating disorder symptoms, but is not driven by HA or extreme underweight (SM 2.3, Table S6).

187 ***Imaging Data***

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

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

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

207 **Discussion**

208 We used computational modelling in combination with fMRI to provide insight into the
209 neural mechanisms underlying decision-making and feedback learning in young, acutely ill AN
210 patients. Bayesian Model Comparison (Methods) demonstrated better fit between a recently
211 developed HGF model (29) and the behavioral data for both the AN and HC groups than more
212 classical reinforcement learning models (30). However, AN patients were characterized by an
213 increased learning rate on punished trials; possibly indicating hypersensitivity to punishment which
214 has been observed clinically and empirically in AN (10, 12, 35). This finding suggests that when AN
215 patients experience negative feedback, they question their beliefs to a greater degree than HC. On a
216 neural level, time-dependent parameters of feedback learning correlated with BOLD activity in the
217 same brain regions in both groups. In particular, consistent with previous model-based fMRI studies
218 of decision-making and feedback-learning in healthy participants (31, 41), we found a significant
219 correlation between learning rate and BOLD activation in the pMFC, a region involved in outcome
220 evaluation and initiating adaptive adjustments accordingly (31, 38, 50). Most importantly, mirroring
221 the behavioral group difference, BOLD activation was increased in this region in AN after
222 punishment.

223 Our finding of increased pMFC activation after punishment in AN converges with recent
224 evidence attributing a role of this region to the pathophysiology of the disorder. For example
225 adolescent AN patients exhibited an elevated neural response to punishment in the “cognitive” zone
226 of the dACC relative to HC in a monetary guessing task. (21). Conversely, Zastrow et al. (24) found
227 decreased pMFC activation specifically on “shift” trials of a target detection task in AN. Altered pMFC
228 activity has also been reported during temporal reward discounting (19, 51) and during inhibitory
229 processing (52). Moreover, a recent resting-state functional connectivity study (53), found reduced
230 connectivity between pMFC and the executive control network in adolescent AN. While these studies
231 suggest altered pMFC functioning in AN, the direction of group differences vary and the possible
232 interpretations range from altered conflict monitoring, excessive cognitive control and increased
233 neural efficiency. Structurally, volume reductions in the ACC (including portions of the pMFC) in
234 acutely ill AN have been related to deficits in perceptual organization and conceptual reasoning,
235 while the degree of normalization during treatment was linked to clinical outcome (54). Using SPECT,
236 reduced regional cerebral blood flow in the dACC extending into the pre-SMA was observed during
237 the acute phase of the illness and after weight recovery (55). Our study gives additional support for

238 functional pmFC alterations in acutely ill AN using a novel approach that had been applied
239 successfully in other disorders before (42–44). Taken together, our behavioral and imaging findings
240 suggest that the elevated pmFC response in AN may help to explain the abnormally rapid learning
241 rate following punishment.

242 Restrictive food choice and extreme resistance to treatment are just two examples of altered
243 decision-making in AN. While previous laboratory investigations (14, 15) were relatively limited in
244 their ability to isolate specific alterations, a recent cognitive modelling study of IGT performance
245 found a “recency bias” in AN captured by a learning/memory parameter (58). Although the model
246 did not uncover a group difference in a feedback sensitivity parameter, the finding that patients
247 tended to base their decisions on recent experience is commensurate with our finding of increased
248 learning rate in AN. The current evidence of altered decision-making in response to negative
249 feedback is in line with notion of altered reinforcement learning in AN (1–5, 8) and, considered in
250 light of similar recent findings (13), is suggestive of a particular sensitivity to punishment. Decision-
251 making may be intact, however, in paradigms that don’t include negative feedback, at least in
252 adolescents (19, 59). Nonetheless, these findings were made in predominately restrictive AN and
253 future studies are needed to clarify potential subtype differences in reward and punishment
254 sensitivity (10, 11). Furthermore, given the presumption that AN is characterized by altered general
255 reward-related decision-making (4, 8, 19) and the lack of group differences in this respect in both the
256 current study and other recent ones (21, 51), future research is also needed to clarify under which
257 conditions the neural substrates of reward processing are aberrant in AN.

258 While our study was not designed to clarify whether altered decision-making causes AN or is
259 a temporary effect of acute illness, correlation between punishment sensitivity and attachment
260 insecurity has been reported (60). This suggests that, together with attachment style, a decision-
261 making strategy geared toward loss avoidance may develop early in life. Speculatively, oversensitivity
262 to negative feedback may contribute to the onset of AN. For example, negative comments from
263 peers regarding physical appearance might be given exaggerated importance as an effect of an
264 increased learning rate, and consequently, predispose (future) AN patients to change their
265 nutritional habits and activity levels to lose weight (61). Indeed, it has been found that increased HA
266 persists after recovery in AN, raising the possibility that such a trait exists premorbidly (62, 63).

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

269 tryptophan intake because of food restriction (63–65) has been suggested for acute AN (62). In
270 healthy participants (66), it was found that acute tryptophan depletion (ATD), a method for
271 transiently reducing cerebral 5-HT levels, was associated with increased BOLD responses in a region
272 of the dorsomedial PFC overlapping the pmFC during a probabilistic reversal learning task, especially
273 after punishment. Given the role of 5-HT in altered neural mechanisms during feedback learning and
274 evidence suggesting normal or even increased 5-HT levels in recovered AN (62, 67), future studies in
275 weight-recovered AN targeting the pmFC during feedback learning are of great interest.

276 At a more qualitative level, our model-based approach suggests that learning and decision-
277 making activate the same brain regions similarly in both AN and HC. This finding fits neatly with our
278 model comparison: by using different computational models of feedback learning, we found that the
279 behavior of both groups was better explained by the Bayesian HGF model than Rescorla-Wagner
280 models (either with fixed or flexible learning rate) suggesting that, equally to controls, AN patients
281 place differential importance on prediction errors depending on their perception of environmental
282 volatility. Note that for other psychiatric disorders such as binge eating disorder (57), schizophrenia
283 (68) or alcoholism (69), Bayesian Model Selection indicated that patients' behavior was guided by
284 different (typically less efficient) decision-making strategies. For example, in adolescent ADHD,
285 patients choice behavior was better explained by a Rescorla-Wagner model with constant learning
286 rate whereas for HC the HGF provided a better fit (56). Previous computational modeling studies in
287 AN (16, 70) used a temporal difference model with a fixed learning rate (28) to derive prediction
288 error measures in passive taste reward learning tasks, but model parameters and model comparison
289 data were not reported in these studies.

290 Our study has to be seen in the light of the following limitations: First, we focused on young
291 (mostly adolescent) patients with acute AN. While this has the advantage of minimizing secondary
292 effects of prolonged malnutrition on cognition, it provides no indication whether parameters such as
293 the learning rate can be seen as biological markers. Therefore, studies measuring patients
294 longitudinally after weight restoration or complete recovery are needed. However, although patients
295 were in a state of undernutrition, they did not show reduced performance and the behavioral results
296 were not driven by particularly underweight patients (SM 2.3, Table S6). Second, although we
297 compared three computational models of behavior and identified one with best fit for both groups
298 (suggesting that the general strategies employed in AN are normal), there may be better models that
299 lead to different conclusions. Third, although our sample size was large relative to most fMRI studies

300 in AN and the employed task had a comparable number of trials as in similar clinical studies (21), the
301 power of our study to detect all relevant between-group effects (e.g. reward-related) may be limited
302 and future studies with more observations in larger samples are needed. Fourth, the group
303 difference in self-reported HA was not significant in the present study, presumably because of lack of
304 statistical power (SM 2.1), and the expected correlation between HA and learning rate after
305 punishment was not found (SM 2.3). Therefore, alternative explanations of increased learning rate in
306 AN including impaired memory (58) and uncertainty regarding present beliefs are also plausible.
307 However, an increased learning rate specifically after punishments indicates that an exaggerated
308 importance is placed to negative feedback, despite uncertainty due to the probabilistic nature of
309 contingencies.

310 Computational approaches focusing on learning mechanisms appear to be particularly
311 promising with respect to the detection of basic mechanisms contributing to the development and
312 maintenance of mental disorders. Altered decision-making has been linked to treatment outcome in
313 AN (71) and quantification of individual differences in learning mechanisms have the potential to
314 guide the development of new therapeutic strategies that directly aim at the modification of such
315 behavior patterns. Given the present results in patients with acute AN, a stronger focus on increasing
316 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 \times feedback interaction (significant also after Bonferroni correction across the four tested models $p(\text{corrected}) = 0.40$) 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.

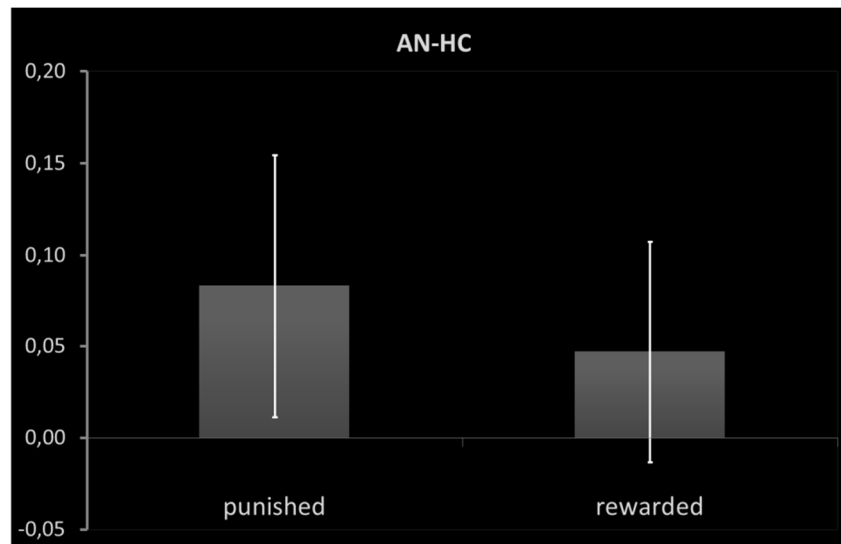


Figure 3. a: Correlation of BOLD activity after feedback with learning rate α . Learning rate was computed within a Hierarchical Gaussian Filter and the expected pattern of activation in the pmFC (31, 41) across all participants (whole-brain one-sample t-test) was reproduced. **b: Increased BOLD activity 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 examined using one-way ANCOVAs controlling for IQ. Means and standard deviations (SD) are given.

	AN		HC		test statistics	
	Mean	SD	Mean	SD	T	p
Demographic variables						
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						
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 ($U=612.5$, $p(2\text{-tailed})=0.089$).

	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
<i>tonic log-volatility</i> [ω]	-1.15	.59	-1.62	1.54	2.86	.095
Log <i>meta-volatility</i> [$\log(\theta)$]	-5.87	1.38	-6.01	.64	.313	.578
Observational model parameter					F	p
Log <i>decision-noise</i> [$-\log(\beta)$]	-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 2x2x2 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