Insensitivity to Losses: A Core Feature in Patients With Anorexia Nervosa?

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ABSTRACT

BACKGROUND: Patients with anorexia nervosa (AN) demonstrate aberrations in choice behavior, including impairments in laboratory measures of decision making. Although a wealth of studies suggest that these aberrations arise from alterations in value processing, it remains unclear by which core component of value processing this is mediated.

METHODS: We fit trial-by-trial data of patients with AN (n = 60 first cohort, n = 216 second cohort) and healthy control participants (n = 55) performing the Iowa Gambling Task to a computational model based on prospect utility theory. We determined, per participant, the best-fit model parameters and compared these between the groups.

RESULTS: Analyses revealed a decreased estimate of model parameter $\lambda$ in patients with AN, indicative of an attenuation of loss-averse behavior in the Iowa Gambling Task. In comparison, measures of reward sensitivity, value-based learning, and exploration versus exploitation were unaltered in patients with AN. A measurement in a second independent cohort replicated the finding that loss aversion, typically observed in healthy individuals, is reduced in patients with AN.

CONCLUSIONS: We show that patients with AN, in contrast to healthy control participants, demonstrate reduced loss-averse behavior. This finding provides important fundamental insights into the decision-making capacity of patients with AN, suggesting alterations in the mechanisms involved in value processing related to negative feedback.

Keywords: Anorexia nervosa, Computational modeling, Decision making, Eating disorders, Iowa Gambling Task, Value

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IGT data by means of computational trial-by-trial analyses (22). One study systematically compared a wide range of reinforcement learning models in their ability to explain choice behavior in the IGT and demonstrated that a model based on prospect utility theory was superior in this aspect (23). This theory (24–26) states that people are not perfectly rational decision makers, in the sense that under uncertainty, the subjective experience of reward is not linearly proportional to the actual received reward. Rather, subjective reward is thought to be concave to the actual reward (and convex for losses), so that winning $200 has a lower impact on behavior than winning $100 twice. Furthermore, the prospect utility value function is asymmetric for negative and positive values, so that, for most people, losses weigh heavier than gains in terms of their impact on choice behavior. In other words, most people are loss averse. Although this modeling approach provides important fundamental insights into the computational mechanisms subserving IGT performance, the majority of studies, especially those related to AN (21), do not use this possibility.

Here, we used computational trial-by-trial analysis of IGT data of a large cohort of patients with AN and healthy control participants to elucidate the basic computational processes that underlie the impaired performance of patients with AN in the IGT.

**Figure 1.** Iowa Gambling Task and computational model. (A) Task design. (B) Example data of a participant who starts with an exploratory approach but chooses a more exploitative approach in a later stage of the session. (C) Random effects model selection revealed that a model based on prospect utility theory was the best descriptor of the data (see also Table 2). (D) Visual depiction of the computational model. In each round, the participant chooses a card on the basis of a value representation of each of the decks. (E) Interpretation of model parameter values.
the IGT. By fitting the data to a large set of reinforcement learning models, we confirm that prospect utility is the best descriptor of behavior in the IGT. After comparing the computational model coefficients between patients and control participants, we demonstrate that patients with AN, in contrast to healthy control participants, show a reduction in loss-averse behavior.

**METHODS AND MATERIALS**

**Participants**

For this study, 115 participants were included, of whom 60 were diagnosed with AN and were symptomatic at the time of testing; the other 55 were healthy control participants (Table 1). Clinical information about this cohort and diagnostic criteria are presented in Elzakkers et al. (27,28). In brief, the criteria for participation in the study were adults (aged 18 years or older) with the presence of AN (binge-purge or restrictive subtypes; patients diagnosed with other specified feeding or eating disorder were excluded) according to the DSM-IV. This was established by eating disorder experts with ample experience in the treatment and diagnostic assessment of people with eating disorders and was confirmed by the Eating Disorder Examination. The only exclusion criterion for this study was an IQ below 70. On average, the patients had an age at onset of 17.8 years (SD = 4.9) and an illness duration of 8.6 years (SD = 8.1). Regarding diagnoses, 49% were diagnosed with the restrictive subtype and 51% with the binge-purge subtype. Most of the patients (74%) had previous treatment for their eating disorder, and nearly half of the patients (46%) had a hospital admission in the past. More than half (53%) had one comorbid Axis I disorder, and 31% had two or more comorbid Axis I disorders, of which a comorbid depressive disorder was most common (48.4%). Axis I comorbidity was established with the Structured Clinical Interview for Axis I Disorders. More than half (58%) of the patients received medication as part of their treatment; medication status for control participants is unknown. The second cohort included 216 adult participants, all of whom were diagnosed with AN and were symptomatic at the time of testing. For this cohort, a Structured Clinical Interview for Axis I Disorders was not conducted. All participants were recruited at the Altrecht Clinic for Eating Disorders Rintveld, a specialized center for eating disorders in Zeist, The Netherlands.

**Task**

A computerized version of the original IGT (18) was used to assess decision-making ability, and participants did not play for actual money. The IGT simulates real-life decision making under uncertain circumstances with a conflict between immediate reward and delayed punishment, so that participants need to make advantageous choices. Participants are instructed to maximize their (virtual) profit by choosing 1 card at a time from 1 of 4 card decks (Figure 1A, B). After each choice (100 choices in total) a specific amount of money is awarded, while at certain times participants also lose a fixed amount of money, resulting in a net loss. Decks A and B are considered disadvantageous because they contain high gains but also high losses, disclosing a net value of $−250 per 10 cards. These decks have the same overall net loss but differ in frequency and degree of punishment. With smaller gains but also smaller losses, decks C and D are considered to be advantageous in the long run, disclosing a net value of +$250 per 10 cards. These two decks also display the same overall net loss while differing in frequency and degree of punishment. Traditionally, decision making is examined by dividing the 100 trials into 5 blocks of 20 card choices, also referred to as the learning effect during the task. For each block, a net score is calculated by the difference in number of choices between the advantageous and disadvantageous decks: C + D - (A + B). An impairment in decision-making ability is characterized by a lack of improvement of performance over time.

**Modeling Analysis**

In the modeling analysis, we tested 8 different reinforcement learning models (Figure 1C), all as described in Ahn et al. (23) [see also (29,30) for a comparison of IGT models]. All these models assume that participants make decisions by a process that is reiterated on every trial (Figure 1D) and comprises 1) a utility function that transforms the gains or losses from that trial into a net subjective value or utility, 2) updating the value representations of the decks on the basis of this subjective value, and 3) making a choice among the 4 decks by comparing their expected values. In each of these 3 steps, 2 different types

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Table 1. Demographics of Participants

<table>
<thead>
<tr>
<th>Group Size, n</th>
<th>Patients With AN</th>
<th>Healthy Control Participants</th>
<th>p Value</th>
<th>Patients With AN</th>
<th>p Value (vs. First Cohort Patients With AN)</th>
<th>p Value (vs. First Cohort Control Participants)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group Size, n</td>
<td>60</td>
<td>55</td>
<td>216</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women in Group, %</td>
<td>100</td>
<td>100</td>
<td></td>
<td>96</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body Mass Index, kg/m²</td>
<td>15.41 (1.90)</td>
<td>21.74 (2.81)</td>
<td>16.42 (2.40)</td>
<td>22.25 (7.27)</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Age, Years</td>
<td>27.28 (9.93)</td>
<td>24.47 (8.31)</td>
<td>.0001</td>
<td>&lt;.0001</td>
<td>p = .0001</td>
<td>p &lt; .0001</td>
</tr>
<tr>
<td>Level of Education*</td>
<td>6.84 (0.37)</td>
<td>6.84 (0.37)</td>
<td>.0001</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values indicate mean (SD) except where noted. The p values denote significance in an unpaired t test.

AN, anorexia nervosa; n/a, not available.

*Level of education is an arbitrary measure ranging from 1 (primary school not finished) to 7 (university).
of equations were tested, so that all possible combinations of equations resulted in a total of $2^3 = 8$ models. For the utility function, an equation based on prospect utility theory (which assumes that the subjective gain is not linearly proportional to the actual payoff) was tested as well as an equation based on expected utility theory (which assumes that the subjective gain is linearly proportional to the actual payoff). For the value updating function, a delta learning rule was tested (i.e., the Rescorla–Wagner model, which only updates the chosen deck based on reward prediction error) as well as a decay reinforcement learning rule (which also discounts the value of a deck when it is not chosen). For the choice function, a softmax equation was used, one based on the assumption that choice stochasticity (i.e., the explore/exploit trade-off parameter) was stable within a session (trial-independent choice rule) and one based on the assumption that choice stochasticity may change over a session (trial-dependent choice rule; e.g., a participant could start with an exploratory approach but become more deterministic in a later stage of the task).

The trial-by-trial data of participants were fit to each of these models, and random effects model selection (31) was performed using the individual log model evidence estimates with the function spm_BMS in the MATLAB toolbox (The MathWorks, Inc., Natick, MA) SPM12 (Wellcome Trust Centre for Neuroimaging, London, UK). This is a Bayesian model selection procedure, which estimates which of the models are more common in the population than the others (measured as the protected exceedance probability). The model that was the best descriptor of IGT performance was model 5 (highest protected exceedance probability) (Figure 1C and Table 2), which was the model based on prospect utility function, a delta learning rule, and a trial-dependent choice rule.

For a description of the winning model and parameter estimation methods, see Supplemental Methods and Materials.

Statistics

All outcome measures were tested for being normally distributed using the D’Agostino and Pearson omnibus normally test (threshold set at $p < .05$), after which the appropriate statistical test was performed. All computational analyses were performed with MATLAB 2014a, and the statistical tests were performed with GraphPad Prism 6.0 (GraphPad Software, San Diego, CA).

RESULTS

IGT Performance of Patients With AN Is Altered

In total, we compared IGT performance of 60 patients with AN with that of 55 healthy control participants (Figure 2A). In accordance with the literature, we observed reduced learning over the different trial blocks in patients with AN compared with control participants (Figure 2A, left panel). As a result, patients with AN received more negative feedback (i.e., losses) on the task than healthy control participants (Supplemental Figure S1). After classifying patients with AN into the restrictive and binge-purge subtypes, we observed visually comparable differences in the control group, although there was only a significant group $\times$ block interaction effect in the binge-purge subtype group compared with control participants (Figure 2A, right panels). However, a 2-way analysis of variance performed on the 2 AN subtypes separately revealed no significant differences between the 2 patient groups (group effect: $p = .83$; group $\times$ block interaction effect: $p = .15$).

Patients With AN Exhibit Decreased Loss Aversion

After fitting the model to the data and estimating the model parameter values, we observed a significant decrease in the estimate of loss aversion parameter $\lambda$ in patients with AN as compared with healthy control participants (Figure 2B and Supplemental Figure S2). Furthermore, we performed individual 1-sample statistical tests on the 2 groups to assess whether their $\lambda$ estimates were significantly higher than 1, which would be indicative of a stronger impact of losses than wins on behavior, as would be expected based on the literature (32,33). Indeed, the estimate of $\lambda$ for the control participants was significantly different from 1 (Wilcoxon signed-rank test, $p = .0002$), but this was not the case for patients with AN (1-sample $t$ test, $p = .8352$). This indicates that patients with AN were not loss averse, in contrast to healthy control participants. No significant differences were found between patients with AN and healthy control participants on the estimates of feedback sensitivity parameter $\alpha$, learning rate $\beta$, or stochasticity parameter $c$.

We observed no significant differences between the $\lambda$ estimates of the 2 different AN subtypes (Figure 2C). Furthermore,
a trend toward a significant correlation ($p = .05$) was observed between body mass index (BMI) and loss aversion parameter $\lambda$ in the AN group but not in the healthy control group, suggesting that the reduction in loss aversion in patients with AN (Figure 2D) was strongest for those with the lowest body weight.

Some studies have shown that symptoms of anxiety and depression, which are common comorbidities of AN (34), may affect performance in tasks such as the IGT (35). Therefore, we assessed different self-report measures of anxiety and depression and found, as expected, that patients with AN scored higher on these (Supplemental Figure S3). However, none of these measures correlated with the estimates of loss aversion parameter $\lambda$, suggesting that the differences in model fit between patients with AN and control participants was not driven by baseline differences in anxiety and depression.

To test whether the differences in model parameter values between patients with AN and control participants were sufficient to describe the observed changes in the classic measure of IGT performance (Figure 2A), we performed a posterior predictive check of the model (36). Thus, we simulated data for each participant individually, using only the participant’s model parameter estimates, and plotted the IGT performance of the simulated data over the different trial blocks. This procedure replicated the observed impairment in IGT performance (Figure 3), indicating that the differences in model parameter values were sufficient to explain differences in IGT performance in the group.

**Replication in Second Cohort**

To replicate the observed effects, we tested an additional 216 patients on the IGT (142 patients with the restrictive subtype and 74 with the binge-purge subtype). Although this experiment lacked a formal healthy control group, assessing the absolute value estimate of loss aversion parameter $\lambda$ may provide insights into the IGT performance of this patient group (Supplemental Figure S4A, B). Again, we observed a $\lambda$ parameter value estimate that was close to 1 (yet different from 1; 1-sample $t$ test, $p = .0208$); this is considerably lower than what is known in healthy subject participants from the literature (23,37,38) and significantly lower than the control group from the first cohort ($p = .003$), but it is statistically indistinguishable from the first cohort of patients with AN ($p = .40$). Furthermore,
we again observed no significant differences in the estimates of $\lambda$ between the different AN subtypes ($p = .71$). In this cohort, no significant correlation was observed between the estimate of loss aversion parameter $\lambda$ and BMI (Supplemental Figure 1C).

**DISCUSSION**

In this study, we have assessed behavior in the IGT of patients with AN by employing computational trial-by-trial analyses. We replicated data from a vast body of literature (21) showing that patients with AN are impaired in IGT performance and subsequently demonstrated that this was driven by a reduction in loss-averse behavior. This reduction prevented participants from avoiding the disadvantageous decks, leading to a less steep learning curve in the classic measures of IGT performance. Although the classic form of the IGT (as used in this study) is not ideal to distinguish between loss aversion and risk aversion, we observed that feedback sensitivity parameter $\alpha$ was not different between patients with AN and control participants. This shows that the convex relationship between the actual monetary gain and the experienced subjective gain in the task was similar between the two groups, suggesting no general changes in decision making under uncertainty, including risk aversion. Therefore, it is likely that the observed effects are driven by a general reduction in sensitivity to monetary losses in the task.

It might be the case that this diminished loss aversion plays a role in the apparent insensitivity of patients with AN to the negative consequences of the disease itself, including the suppression of extreme hunger and social isolation. Surprisingly, patients with AN self-report increased sensitivity to punishment in questionnaires (17), suggesting suboptimal reflection of their own behavior. This mismatch between self-report measures and empirical measures may be of clinical relevance because it sheds light on the inability of patients with AN to assess their own actions in hindsight and reflect on their own well-being and body weight. Indeed, it has been suggested that diminished mental capacity may affect disease progression of AN and the ability of patients to recover (27).

Several studies have assessed the neural basis of loss aversion in human subjects. In accordance with reward prediction error theory (39,40), one seminal study demonstrated that in healthy subjects who were confronted with different gambling options, the functional magnetic resonance imaging blood oxygen level–dependent signal was reduced in the ventral striatum and ventromedial prefrontal cortex, the target regions of midbrain dopamine, when the potential losses of the gamble increased (41). In another study, blood oxygen level–dependent responses in the ventral striatum of patients with AN did not distinguish between positive and negative feedback in a gambling task (42). Given the existence of alterations in the dopamine system in patients with AN (43) and the role of dopamine in value-based learning (44,45), it is tempting to speculate that malfunction in the dopamine system underlies the observed reduction of loss aversion in patients with AN. To date, however, results with psychotropic medication targeting the dopamine system in patients with AN have been disappointing, although there is some evidence that treating patients with a dopamine D2 receptor antagonist has beneficial effects on weight restoration (46). Other brain structures involved in value computations or negative emotion processing could underlie the observed changes in loss aversion in patients with AN. For example, structural and neurophysiological changes in the prefrontal cortex and amygdala have been reported in patients with AN (47).

**Limitations and Considerations**

One possible concern of this study is the finding that we observed a trend toward a significant correlation between BMI and the estimate of loss aversion parameter $\lambda$ in patients with AN of the first cohort. Although BMI may merely reflect disease severity, a lower BMI also implies higher levels of starvation, and therefore hunger status may partially drive the observed effects on $\lambda$. Although very few studies have investigated the effects of hunger on performance in standardized decision-making tasks, it is generally assumed that a negative energy balance negatively affects cognitive performance (48). Studies that compared decision-making capacity between recovered and symptomatic patients with AN, however, demonstrate the persistence of cognitive deficits after recovery (6,49–51). One caveat of the IGT in particular is that with repeated measurements in the same subject, one may remember the reward contingencies of the decks from earlier sessions. This makes it challenging to repeat the IGT in patients on a short time frame, for example, directly after disease recovery. To overcome these caveats, the IGT could be modified so that it includes a reversal component, or ideally one would test a large cohort of children on the IGT and follow these participants throughout adolescence and adulthood to observe which of them develop AN.

One other limitation of this study is the fact that the patient and control groups of the first cohort differed in terms of their...
level of education (Table 1). Given the negative effect that AN can have on school performance, however, this does not necessarily imply differences in intelligence. Furthermore, paradoxically, a higher level of education is usually associated with worse IGT performance (52). Thus, if any effects were to be expected on the basis of education, this effect should be in the opposite direction of what was observed in this study. One other possible confounder is that patients with AN demonstrated higher levels of measures of anxiety and depression (Supplemental Figure S3). Although these measures did not directly correlate with loss aversion parameter \( \lambda \) in the IGT, there have been reports showing that decision making under uncertainty is affected in individuals with depression or anxiety (35) and that loss aversion is related to levels of stress hormones such as cortisol (53). The possibility that these factors at least partially confound the effects observed on IGT performance between patients with AN and control participants cannot be fully excluded. Finally, it is important to note that the participants included in our study consisted of adults, the majority of whom were in their 20s. Because differences in IGT performance have been observed between different age groups (54), it might be that our results do not directly apply to adolescent or older patients with AN. This would be an important topic for future research.

Finally, it is interesting to note that the overall estimates of choice stochasticity parameter \( c \) were negative for both the control and AN groups, indicating that the majority of participants chose more randomly as the session progressed. This is consistent with previous work showing that patients with AN have reduced aversion to uncertain outcomes (55). However, it is important to note that this effect was not statistically significant, and further research is needed to confirm these findings.

Comparison With Other Studies

A previous study also used a computational model based on prospect utility theory to fit a pooled set of IGT data of patients with AN gathered in 3 independent institutes (22). Besides the model parameters based on prospect utility theory, Chan et al.’s model included the decay reinforcement learning rule and trial-independent choice rule—a model that we also tested but that was not the best descriptor of IGT performance in our analysis (Table 2, model 8). Furthermore, data from their AN group were collected across 3 research institutes, while their control group comprised participants recruited at only 1 institute. Interestingly, the authors also observed a significant decrease in loss aversion when comparing patients and control subjects only from the institute that was used for recruitment of the control group, but this effect statistically disappeared after pooling the groups from the different institutes (22).

A recent study assessed IGT performance in a large cohort of 611 female individuals, approximately half of whom were patients with AN (55). Despite their large sample size, Gianunzio et al. did not observe any significant differences in the model parameters that were fitted to the data, although they used a model based on expected utility theory that we and others have shown to be a poor descriptor of behavior in the IGT (23). Furthermore, the authors did not describe what method they used to estimate the model parameters, nor did they provide a quantification of the fit of the model, making a comparison between our studies difficult (55).

Several other studies have demonstrated altered negative feedback learning in patients with AN, although not all these studies seem directly in accordance with our findings. For example, one study performed a probabilistic reversal learning task in patients with AN in a functional magnetic resonance imaging scanner (15) and observed an increased learning rate for negative feedback in patients with AN compared with healthy control subjects, although this effect was numerically modest. Negative feedback coincided with elevated levels of activity in the posterior medial prefrontal cortex in patients with AN compared with control subjects, while no differences were observed in hemodynamic responses to reward. Although the dissociable effect on punishment and not on reward is in accordance with our study, we would have expected a decrease, rather than an increase, in learning rate following punishment. Having said that, any comparisons between the 2 studies is challenging given that the task used in Bernardoni et al.’s study involved changes in reward contingencies throughout the session (15), and therefore performance may rely on neurocomputational mechanisms other than the IGT (15).

Conclusions

Although the neural underpinnings of AN are largely unknown, it has been proposed that the neurocognitive deficits associated with AN are a contributing factor in the progression of the disease and the inability of patients to recover. By using computational analysis of data of patients performing the IGT, we have shown that patients with AN exhibit reduced loss-averse behavior, in contrast to what is seen in healthy control participants. Our data are in line with previous work that shows alterations in negative feedback processing in patients with AN and points toward disruptions in the brain circuits involved in value processing. Together, these findings provide important fundamental insights into the decision-making capacity of patients with AN and may provide handles for the future search for therapies for AN.

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