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Title:

The effect of stress on delay discounting in bulimia nervosa and alcohol use disorder: a functional magnetic resonance imaging study.

Running title:

The effect of stress on delay discounting in BN and AUD.

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Abstract

Background:

Stress could induce neurobiological changes in patients with bulimia nervosa (BN) and alcohol use disorder (AUD) that increase delay discounting (DD), making the short-term benefits of coping through eating or drinking outweigh long-term negative consequences. Therefore, this study explores differences in DD between patients (BN or AUD) and healthy controls (HC), the impact of stress on food and alcohol DD, and the associated changes in brain activity.

Methods:

A total of 102 female participants (AUD: 27, BN: 25, HC: 50; age range: 18-38 years) underwent repeated fMRI scanning while performing three DD tasks (DDT). Initially, all participants performed a monetary DDT. Then, participants performed a food or alcohol DDT before and after stress induction with the Montreal Imaging Stress Task (MIST). Specifically, patients with BN completed a food DDT, patients with AUD completed an alcohol DDT and HC were randomly allocated to either DDT.

Results:

No differences were found in the DD of money, food or alcohol between patients and controls before stress. However, stress increased the DD of alcohol in patients with AUD, but not in HC. Stress also increased the DD of food in HC, but not in patients with BN. Furthermore, stress caused patients with AUD to display a lower activity of the right supplementary motor area while discounting alcohol. Stress also caused HC to display a lower activity of the middle/super frontal cortex and a higher activity of the motor cortex while discounting food, but caused patients with BN to display a higher activity of the occipital cortex.

Conclusion:

The results suggest that stress induces neurobiological changes in patients with AUD which cause them to prefer more immediately available alcohol. However, the results observed in patients with BN suggest a more complex relation between stress and food.

Main Text

1. Introduction

Both bulimia nervosa (BN) and alcohol use disorder (AUD) are characterized by binge behavior (e.g., binge eating [BE] and binge drinking [BD]) where large amounts of a substance (e.g., food or alcohol respectively) are consumed within a short period of time (1). Though treatments for BN and AUD exist, large numbers of patients are not able to abstain from BE and BD after treatment (2,3). More effective interventions are therefore needed, but in order to develop them, a better understanding of what triggers binge behavior is required. To explore these triggers, most studies have investigated BN and AUD separately. However, studying these disorders together could provide more information by identifying common and unique triggers for BE and BD.

One factor that is thought to play a role in both disorders is stress. Most theoretical models hypothesize that BE and BD can be a way for patients to cope with stress (4,5). Indeed, studies in a laboratory setting report that inducing stress causes individuals who binge eat or binge drink to consume more food or alcohol than they would without stress (6,7). However, it remains unclear why the short-term benefits of coping with stress would outweigh more long-term negative consequences and potential relapse. One possible explanation for this could be that stress causes a disturbance in delay discounting (DD). DD is the process whereby rewards decrease in value the more delayed they are, meaning that individuals usually prefer more immediately available rewards over delayed ones (8). It could therefore be hypothesized that stress induces neurobiological changes in patients that increase DD, making them see the short-term benefits of coping through eating or drinking alcohol as more valuable than the long-term benefits of remission. However, it is unclear whether stress causes these behavioral and neurobiological changes in DD.

From a behavioral standpoint, DD involves both a reward processing and an impulsive-like component (9,10). On the one hand, DD is subsumed under the positive valence systems of the

Research Domain Criteria (RDoC), where it regarded as a moderator of reward valuation (9). On the other hand, DD is described as a distinct construct of impulsive-like behavior, because it reduces the significance of negative consequences in the distant future, making it more likely for individuals to engage in behaviors that provide immediate gratification (10). DD behavior can be investigated with a DD task (DDT) (8). In the DDT, participants need to choose between a smaller sooner and a larger later reward. Based on the decisions a participant makes, a DD rate can be calculated where higher values represent a stronger preference for more immediate rewards (8). Previous studies show that patients with BN and AUD prefer more immediately available monetary rewards over delayed ones (11,12). However, when it comes to disorder-specific food and alcohol DD, only a few studies have been published and their results have been mixed (13,14). We could identify one study that investigates alcohol DD in AUD, which finds higher discounting rates compared to healthy controls (HC) (13). We could also identify one study that investigates food DD in BN, but this study finds lower discounting rates (14). Even less is known when it comes to stress. Studies in healthy volunteers find that acute stress increases DD for money and makes individuals choose more based on subjective value, but no studies have explored the impact of stress on DD in patients with BN or AUD (15–18). Therefore, it remains unclear whether patients with BN and AUD inherently prefer more immediately available food and alcohol and whether this preference increases under stress. It is a first aim of this study to fill this gap and explore the following behavioral hypotheses:

1. Patients with BN and AUD display higher DD rates than HC for money.
2. Patients with BN and AUD display higher DD rates than HC for food and alcohol respectively.
3. Patients with BN and AUD, but not HC, display higher DD rates for food and alcohol when stressed.

Moreover, from a neurobiological standpoint, it is thought that DD is processed in five subsequent steps involving specific brain regions at each step (Figure 1) (19). Important steps are step III and IV, corresponding to the attribution of subjective value to the sooner and delayed rewards and the comparison between them. The attribution of subjective value is thought to be performed by the

anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), middle frontal gyrus (MFG), orbitofrontal cortex (OFC), insula, nucleus accumbens (NAc) and caudate nucleus (CN) (19). The comparison between the subjective values is thought to be performed by a dual system, consisting of a beta (β) system that is impulsive, reflexive, and focused on the immediate reward and a delta (δ) system which is controlled and considers immediate as well as delayed rewards (19,20). The β system is thought to be represented in the ACC and OFC while the δ system is encoded in the dorsomedial prefrontal cortex (DMPFC) and dorsolateral prefrontal cortex (DLPFC) (19,20). When it comes to the functioning of these brain regions during a DDT, no studies have compared current patients with BN and HC. However, a study in remitted patients finds a lower activity of the CN during a monetary DDT after fasting, but a higher activity after eating (21). More studies have been performed in patients with an AUD. Here, studies report that patients display a greater deactivation of the superior frontal gyrus (SFG) and PCC when making impulsive monetary choices, but a greater activation of the DLPFC, (pre)cuneus, insula and OFC when choosing the delayed option (22–24). Nevertheless, though these studies indicate that DD for money could be processed differently in patients with BN and AUD, they have not explored whether this is also the case for food or alcohol and whether this is impacted by stress. It is a second aim of this study to fill this gap and explore the following neurobiological hypothesis:

4. Differences in DD between HC and patients with BN or AUD are associated with brain activity changes in regions involved in the attribution and comparison of subjective value (i.e., the ACC, PCC, MFG, OFC, insula, DMPFC, DLPFC, NAc, and CN).

2. Methods

2.1. Participants

A total of 102 female right-handed participants were included in the study (AUD: 27, BN:25, HC:50) after removing 4 participants (BN:3, HC:1) due to artefacts and incidental findings. Recruitment ran from September 2019 to February 2022 (eMethods 1). The full in- and exclusion criteria can be found in the supplement (eMethods 2). Importantly, patients needed to meet the criteria for BN or AUD of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) with a maximum illness duration of 5 years (1). This maximum illness duration was set as the role of impulsive-like behaviors is thought to be largest in the first years after the onset of BN and AUD (5,25). Participants with AUD also needed to display a pattern of repetitive BD according to the criteria of the National Institute on Alcohol Abuse and Alcoholism (i.e., drinking 4 units of alcohol within 2 hours for women) (26). All participants gave their written consent, and the study was approved by the local ethical committee.

2.2. Procedure

The course of the magnetic resonance imaging (MRI) scan can be seen in Figure 2. Participants were instructed not to eat or drink in the six hours leading up to the scan and needed to refrain from using substances in the 24 hours before the scan. The participants came in 45 minutes early to familiarize themselves with the tasks of the study in a practice session. Immediately before scanning, a photoplethysmography (PPG) sensor was placed on the left index finger to measure heart rate. The scan itself was divided into four main parts. First, all participants performed a monetary DDT (DDT1). Second, the participants performed a disorder-specific (e.g., food or alcohol) DDT (DDT2). This meant that patients with BN completed a DDT with food while patients with AUD completed one with alcohol. The HC were randomly allocated to either the food (HC_{food}) or alcohol ($HC_{alcohol}$) DDT as a comparison for the patients with BN and AUD respectively. Third, stress was induced with the Montreal Imaging Stress Task (MIST) (31). Fourth, the participants repeated the food or alcohol DDT

post-MIST (DDT3). The DDT1, DDT2 and STRESS blocks were separated by other MRI sequences not analyzed in this manuscript (see Figure 2) Further information on the study procedure can be found in the supplement (eMethods 3).

2.3. Measures

2.3.1 Baseline measures

The Structured Clinical Interview for DSM-5 (SCID-5-S) was used to confirm the diagnosis of BN or AUD and to screen for other psychiatric disorders (27). BN and AUD severity were assessed with the Eating Disorder Examination Questionnaire (EDE-Q) and the Alcohol Use Disorders Identification Test (AUDIT) respectively (28,29).

2.3.2. Delay Discounting Tasks

The DDTs were adapted from a food DDT that was used in a previous study (29). In each of DDTs, the participants chose between an amount of money, food or alcohol that was immediately available and a larger amount of the same reward that was available after a delay. The immediate rewards were 5 euro, around 250 kcal of food or 1 unit of alcohol, while the delayed rewards where multiples (2-5x) of the immediate reward. The type of food and alcohol used in the DDT was picked by each participant from a list of possible food items and alcoholic beverages in the practice session (eMethods 4). Each of the multiples was paired with one out of 10 delays for each decision, resulting in 40 trials per DDT. These delays were the deciles of a maximally tolerated delay level plus ten percent that was determined in the practice session (eMethods 5). The delays for the DDT with money were expressed in weeks, while the delays for the DDTs with food and alcohol were expressed in minutes. Each trial started with an inter-stimulus interval (ISI) that varied between 3.5 and 5 seconds. Afterwards, the participants were shown the immediate and delayed options and had 6 seconds to make their choice with a button box. Then, a red arrowhead appeared beneath their chosen option for the remainder of the 6 seconds before the next trial started. The ISI as well

as the magnitude, delay and position of the delayed reward were determined pseudorandomly for each trial. The total duration of every DDT was 6 minutes and 50 seconds.

2.3.3. Montreal Imaging Stress Task

The MIST is a task that uses mental arithmetic, failure and negative social evaluation to induce stress in participants (31). It typically consists of a rest condition (i.e., only the interface), a control condition (i.e., only mental arithmetic) and an experimental condition (i.e., mental arithmetic with the stress components). As the purpose of using the MIST in this study was to induce stress, the participants only completed the experimental condition in the scanner. During this condition, participants were given mathematical problems and needed to respond before a certain amount of time expired. The participants saw their own performance and a fictive average performance of all previously included subjects. The participants were instructed to beat this average, but the task adapted the difficulty of the mathematical problems so that the participants performed poorly. In addition, negative feedback was given to the participants emphasizing their poor performance and urging them to perform better. The difficulty level for each participant in the scanner was established in the practice session (eMethods 6) (32). The total duration of MIST in the scanner was 6 minutes.

2.3.4. Subjective stress

The participants rated their stress levels at the beginning of the scan, before each task (DDT1, DDT2, STRESS, DDT3) and at the end of the scan with a visual analogue scale (VAS). The VAS had ten levels ranging from 0 (not stressed at all) to 10 (never experienced such stress before).

2.3.5. Heart rate

PPG data were gathered at 500 Hz with the wireless pulse oximeter of the MR system. These were then preprocessed with SCANPHYSLOG_Tools (33). First, peaks were identified in the pulse

waveforms. Second, the data were divided into 1-minute long epochs and the heart rate for each epoch was calculated. Third, implausible heart rates below 30 or above 200 were filtered out.

2.4. MR sequences

Scanning was performed on a 3T Achieva dStream Philips MRI scanner with a 32-channel receiver head coil. T2*-weighted echo-planar images were acquired during every DDT (275 volumes, 46 slices, TR=1.5s, TE=33ms, flip angle=80°, voxel size=2.14x2.14x3mm, MB=2). A high-resolution T1-weighted image was acquired during the MIST using a 3D turbo field echo sequence (208 slices, TR=5.9ms, TE=2.7ms, flip angle=8°, voxel size=0.8x0.8x0.8mm).

2.5. Data analysis

The data were analyzed and reported in accordance with the guidelines of Frank et al. (2018) (34). A checklist can be found as an appendix to this manuscript.

2.5.1 Delay Discounting

For every DDT, a k-value (i.e., a DD rate) was estimated by fitting the choice data to a hyperbolic discounting model (eMethods 7) (30). These k-values were logarithmically transformed due to their non-normal distribution. The log(k)-values at each DDT were compared between groups with robust linear regression models. These models included the log(k)-values as the outcome and included group as the main effect (BN, AUD, HC for the monetary DDT; BN, HC_{food} for the food DDT; AUD, $HC_{alcohol}$ for the alcohol DDT). The impact of stress was evaluated within groups with robust linear mixed models. These models included random intercepts for the participants, the log(k)-values of the disorder-specific DDT as the outcome as well as group (BN, HC_{food} for the food DDT; AUD, $HC_{alcohol}$ for the alcohol DDT) and time (before, after the MIST) as main and interaction effects. All models included age and BMI as covariates.

178 2.5.2 Subjective and physiological stress response

179 The impact of the MIST on subjective stress ratings and heart rate was evaluated with robust linear
180 mixed models, similarly to the models described above but included the subjective stress ratings or
181 heart rate as outcome. For subjective stress, only the data pre- and post-MIST were used. For heart
182 rate, only the data from the six minutes pre-MIST (i.e., during a resting-state arterial spin labeling
183 sequence) and six minutes during the MIST were used.

184

185 2.5.3 Functional MRI data

186 The fMRI data of each DDT were initially preprocessed with fmriprep, version 21.0.1., after which
187 they were smoothed with an 8 mm full width at half maximum (FWHM) Gaussian kernel in SPM12
188 (eMethods 8) (35). These smoothed images were then used in a first-level analysis in SPM12
189 (eMethods 9). On the one hand, this analysis included boxcar regressors which separately modeled
190 the decision and feedback stages. The decision stages started with the presentation of the rewards
191 and ended when the participants submitted their choice through the response box. The feedback
192 stages followed immediately after and ended 6 seconds after the initial presentation of the rewards.
193 These boxcar regressors were convolved with the canonical hemodynamic response function. On the
194 other hand, the first-level analysis included 3 rotation, 3 translation, 6 derivatives, 5 wCompCor, 5
195 cCompCor and 5 cosine variables as nuisance regressors (36–38). More information on the nuisance
196 regressors can be found in the supplement (eMethods 8). From the first-level analysis, contrast
197 images were calculated for the decision stages.
198 These contrast images were used in a second-level analysis in SPM12. First, whole-brain analyses
199 compared brain activity at each DDT between groups. This was done with an ANOVA design (group:
200 BN, AUD, HC) for the monetary DDT and a t-test design for the food (group: BN, HC_{food}) or alcohol
201 (group: AUD, $HC_{alcohol}$) DDTs. Secondly, whole-brain analyses investigated the impact of stress on
202 brain activity during the food or alcohol DDT within groups. This was done with a full factorial design
203 which included group (BN, HC_{food} for the food DDT; AUD, $HC_{alcohol}$ for the alcohol DDT) and time

(before, after the MIST) as main and interaction effects. All designs included age and BMI as covariates of no interest. The statistical contrasts were tested for significance using cluster-level inference with an uncorrected cluster-defining threshold of $p<0.001$ and a family-wise error (FWE) corrected cluster threshold of $p<0.05$. Third, underlying contrast values of the significant clusters were extracted with the MarsBaR toolbox and related to relevant participant characteristics. As advised by the guidelines of Frank et al. (2018), the contrast values were related to the log(k)-values, AUDIT and EDE-Q scores, BE and BD frequency, illness duration, age, BMI, presence of comorbidities and use of contraceptives (34). An exploration of the effect of ethnicity, menstrual cycle or history of anorexia nervosa was not possible due to a lack of observations. The analyses were performed with robust regression models which included the contrast values as the outcome and included a patient characteristic as predictor. As the whole-brain analysis included age and BMI as covariates, these variables were also entered as covariates in the robust regression models. Because of this reason, the relation between the contrast values and age or BMI were investigated with one model which included both age and BMI as predictors.

3. Results

3.1. Sample characteristics

The characteristics of the patients with BN (n=25) and AUD (n=27) and their respective controls (HC_{food}, n=25 and $HC_{alcohol}$, n=25) can be seen in Table 1. There were no significant differences in age, BMI or years of education between the patients and their control groups. The characteristics of the pooled HC group (n=50) can be found in the supplement (eTable 1). Here, there was a significant difference in BMI between the patients with BN (mean=25.5; SD=5.8; CI=23.2-28.0) and the pooled HC (mean=22.3; SD=2.2; CI=21.7-23.0).

3.2. Behavioral and functional MRI data

The results for the different DDTs can be found in Table 2 and Table 3. The results for the fMRI data can be seen in Figure 3 and Figure 4.

3.2.1 Delay discounting of money

There were no significant differences between the log(k)-values of the different groups, nor were there any differences in brain activity.

3.2.2 Delay discounting of food and alcohol before stress

Food (pre-MIST): There were no significant differences between the log(k)-values of the patients with BN and HC_{food}. However, the patients with BN displayed a weaker deactivation of the left posterior insula (MNI: x=-47, y=-12, z=8; k=213, t_{46}=4.31; p_{FWE}=0.005) and right posterior insula (MNI: x=36, y=-21, z=2; k=131, t_{46}=4.27; p_{FWE}=0.039) than the HC_{food}. Furthermore, in patients with BN, BMI was negatively associated with brain activity in the left posterior insula (β=-0.046, SE=0.220, p=0.049) and right posterior insula (β=-0.040, SE=0.012, p=0.004). In other words, the weaker deactivation of the left and right posterior insula was more pronounced in patients with a lower BMI.

Alcohol (pre-MIST): There were no significant differences between the log(k)-values of the patients with AUD and the $HC_{alcohol}$, nor were there any differences in brain activity.

3.2.3. Subjective and physiological stress response

There was a significant increase in subjective stress ratings for all groups post-MIST compared to pre-MIST (HC: β=3.369, SE=0.270, p<0.001; BN: β=4.654, SE=0.381, p<0.001; AUD: β=4.335, SE=0.367, p<0.001), but this was more pronounced in patients (BN: β=1.30, SE=0.467, p=0.007; AUD: β=0.967, SE=0.456, p=0.036). There was also a significant increase in heart rate during the MIST compared to before the MIST in all groups (HC: β=10.084, SE=0.613, p<0.001; BN: β=10.416,

SE=0.857, p<0.001; AUD: β=8.077, SE=0.872, p<0.001), but this did not differ significantly between the groups.

3.2.4. Delay discounting of food and alcohol after stress

Food (within-group, pre- vs post-MIST):

Compared to before the MIST, there were significantly higher log(k)-values after the MIST in HC_{food} (β=0.060, SE=0.028, p=0.039), but not in patients with BN (β=0.020, SE=0.028, p=0.478). This means that the HC_{food} chose the immediately available food options more often after the induction of stress. When it comes to brain activity, the HC_{food} group displayed a higher activity after the MIST in the left postcentral gyrus (MNI: x=-26, y=-60, z=60; t_{48}=5.07;p_{FWE}<0.001), right postcentral gyrus (MNI: x=0, y=36, z=54; t_{48}=4.49;p_{FWE}=0.009), left supplementary motor area (MNI: x=-11, y=7, z=38; t_{48}=5.15,p_{FWE}=0.003) and right supplementary motor area (SMA) (MNI: x=17, y=-10, z=72; t_{48}=4.82;p_{FWE}=0.040), but a lower activity of the medial MFG/SFG (MNI: x=2, y=63, z=18; t_{48}=6.70;p_{FWE}<0.001) and PCC (MNI: x=4, y=-45, z=38; t_{48}=5.97;p_{FWE}<0.001). Furthermore, the patients with BN showed a higher activity after the MIST of the left inferior occipital, superior occipital, lingual and fusiform gyrus (MNI: x=-30, y=-66, z=-6; k=556; t_{48}=5.13;p_{FWE}=<0.001) and right lingual and fusiform gyrus (MNI: x=24, y=-79, z=-6; k=137, t_{48}=4.19;p_{FWE}=0.021).

Food (between-group, post-MIST):

Comparing brain activity between groups after the MIST, the patients with BN displayed a weaker deactivation of the ACC (MNI: x=-2, y=22, z=-4; k=203; T_{46}=4.78,p_{FWE}=0.008) than the HC_{food}. Furthermore, a lower activity of the ACC was associated with higher log(k)-values in HC_{food} (β=-0.733, SE=0.356, p=0.048) and with a higher BMI (β=-0.083, SE=0.029, p=0.009) in patients with BN. This means that a lower activity of the ACC was related to a higher preference for more immediately available food in the HC_{food}.

Alcohol (within-group, pre- vs post-MIST): Compared to pre-MIST, there were significantly higher log(k)-values post-MIST in patients with AUD (β=0.073, SE=0.19, p=0.004), but not in $HC_{alcohol}$

(β=0.006, SE=0.019, p=0.761). In other words, the patients with AUD chose the immediately available alcohol more often after the induction of stress. When it comes to brain activity, the AUD group displayed a lower activity after the MIST of the right SMA (MNI: x=13, y=5, z=56; k=123, t_{48}=5.23; p_{FWE}=0.007).

Alcohol (between-group, post-MIST): Comparing brain activity between groups after the MIST, no significant differences were found between patients with AUD and $HC_{alcohol}$. However, a lower activity of the right SMA was associated with higher log(k)-values (β=-0.682, SE=0.190, p=0.003) in patients with AUD. This indicates that a lower activity of the right SMA was related to a higher preference for more immediately available alcohol in the patients with AUD.

4. Discussion

This study investigates four hypotheses. First, that patients with BN or AUD have higher DD rates for money than HC. Second, that patients with BN or AUD have higher DD rates for food or alcohol than HC. Third, that patients with BN and AUD, but not HC, display higher DD rates for food or alcohol when stressed. Fourth, that these behavioral differences are related to brain activity changes in regions involved in the attribution and comparison of subjective value.

When it comes to behavior, this study could not find any differences in the DD of money, food or alcohol between HC and patients with BN or AUD. However, it does find that stress increases the preference for more immediately available food in HC, but not in patients with BN. It also finds that stress increases the preference for more immediately available alcohol in patients with AUD, but not in HC. When it comes to brain activity, the results show that patients with BN display a weaker deactivation of the left and right posterior insula while DD food than HC. They also show that stress causes HC to display a lower activity of the frontal cortex and a higher activity of the motor cortex while DD food, but causes patients with BN to display a higher activity of the occipital cortex. Furthermore, the results show that stress causes patients with AUD to display a lower activity of the right SMA while DD alcohol.

The lack of a difference between patients and controls in the DD of money, food, and alcohol is unexpected as such a difference has been found in previous studies (11,12,14). These negative findings could be due to a relatively small sample size. Though this study meets the sample size requirements of guidelines and includes a similar number of participants as previous studies, the sample size is still limited (11,12,34). Future studies should therefore explore behavioral differences in food or alcohol DD with a larger number of participants.

The finding that stress causes patients with AUD, but not HC, to prefer more immediately available alcohol is in accordance with our hypotheses. It expands our knowledge from previous studies which show that stress can increase the value of alcohol and make individuals prefer alcohol over other commodities such as money (39,40). Together, these results suggest that stress causes patients to see immediately available alcohol as more valuable than any other type of reward. This is important as it could be the reason why stress causes patients to drink more alcohol and why stress is an important predictor of relapse (7,41). Unexpectedly, this higher preference for more immediately available alcohol is related to a lower activity of the right SMA in the current study, which is involved in step V (response) of the neural processing of DD. Indeed, the SMA is known for its role in regulating goal-directed motor activity, but is also important for cognitive and inhibitory control (42,43). The lower activity of the SMA after stress could therefore reflect a loss of control over alcohol in the patients with AUD. Future studies should explore whether this relation between stress and alcohol DD is predictive of treatment outcome and whether it can be impacted by interventions.

The absence of a difference in food DD between HC and patients with BN raises the question what the weaker deactivation of the posterior insula in patients with BN signifies. In general, the insula is important in step II (consequences of approach) of the neural processing of DD. Furthermore, previous studies show that the insula plays a role in the neural processing of food rewards, especially in the encoding of the intensity and the aversity of food (44–46). For example, lesions to the posterior insula cause food to be perceived as less intense or unpleasant (47,48). Taken together, the findings of the current study suggest that the patients with BN experienced choosing

the food items as more intense or aversive. One reason why this study would find such a result is that the patients were asked to select an item of food with which they could have a BE episode. Indeed, previous studies report that food items consumed during a BE epiosde can be 'forbidden' outside of a BE episode (49). This could make the patients in the current study more inclined to restrict their food intake. If so, this would be in line with a previous study reporting that patients with BN have lower DD rates for food than HC, meaning that they prefer the delayed food option over the immediately available one (14).

This study does not find that stress causes patients with BN to prefer more immediately available food. Though previous studies have found that stress causes individuals who BE to eat more, most of these studies have been performed in patients with binge eating disorder who do not display compensatory behaviors such as fasting (6). To our knowledge, there is only one study that investigates the impact of stress on food intake in patients with BN and it reports no effect (50). This suggests that the acute kind of stress which is typically induced in a laboratory or neuroimaging setting does not make patients with BN lose control. Indeed, a previous study finds that such acute stress does not reduce inhibitory control in patients with BN (51). However, studies in daily life do find that negative emotions such as stress increase before a BE episode in patients with BN (52,53). They also find that some emotions are more related to BE than others (i.e., guilt versus nervousness) and that not acute stress, but the pileup of stress is predictive of BE (54,55). Together, these findings suggest that the relation between negative emotions and BE in patients with BN could be dependent on the underlying emotions and their dynamics. Future neuroimaging studies should explore this by investigating the effect of different negative emotions with different designs (e.g., longer or repeated stress induction).

Though this study finds no impact of stress on food DD in patients with BN, it does find that stress changes how food DD is processed in patients. Namely, patients display a higher activity of the occipital cortex after stress, which is involved in step I (object representations) of the neural processing of DD. This is in line with a study showing that patients with BN display a higher activity of

359 the occipital cortex when viewing images of food after stress (56). Indeed, previous studies report
360 that stress can lead to a higher activity of the occipital cortex and that this could be a sign of
361 hypervigilance or amplified sensory processing (57,58). Therefore, these results suggest that stress
362 makes patients with BN process food differently, but the results do not explain how. Future studies
363 should explore how stress changes the sensory processing of food in patients with BN and how this
364 is related to certain cognitions about food.
365 In contrast to the patients with BN, this study does find that stress increases the preference for
366 immediately available food in HC. In addition, the HC also displayed a lower activity of the PCC and
367 medial MFG/SFG after stress. These regions play an important role in step III (subjective value) of the
368 neural processing of DD. A decrease in their activity could indicate that the delayed food option has
369 less value to the HC after stress. If so, this could be the reason why the HC were more likely to
370 choose the immediately available food option and this would explain why a lower activity in the
371 frontal cortex after stress was related to higher log(k)-values.
372 This study has several limitations. First, the relatively small sample size could have limited the power
373 to detect differences between patients and HC. Second, the order of the different DDTs has not been
374 randomized within a session or separated across sessions. The decision to place the monetary DDT
375 before the food or alcohol DDT is based on previous studies reporting that exposure to cues can
376 impact reward processing in patients (59). Also, the tasks have not been split across sessions to limit
377 within-person variability. Third, as participant have not been randomized between a stress and
378 control condition, it could be that some effects in this study are due to fatigue or the repeated use of
379 the DDT. Fourth, most patients in this study are young Caucasian women with a short illness
380 duration. This limits the generalizability of the results to all patients with BN or AUD. Future studies
381 should aim to replicate the findings in other samples. Fifth, like most studies investigating the
382 neurobiological reward system in BE and BD, this study looks at voxel-wise brain activity (60).
383 However, reward processing is more than a simple hyper- and hypoactivation of brain areas (60).
384 Future studies should also explore connectivity or perform multi-variate analyses to examine

385 neurobiological differences in DD. This study also has several strengths. In contrast to most studies
386 investigating the reward system in BE and BD, it not only uses monetary rewards, but also food and
387 alcohol (60). Furthermore, it is the first study to investigate DD in both patients with BN and AUD.

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Data availability statement:
The data and scripts that support the findings of this study are available upon request.

Ethical standards:
The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

6. Table and figure legends

Table 1. Sample characteristics

Table 2. log(k)-values of the different delay discounting tasks

Table 3. Table 3. Differences in delay discounting

Figure 1. Neural processing of delay discounting. First, sensory information is transformed into object representations. Second, the object representations are used to establish the consequences of choosing the sooner or delayed reward. Third, the consequences are attributed a subjective value. Fourth, the subjective value between the sooner and delayed reward is compared by a dual system. Fifth, information on the decision is used to produce motor responses to acquire the reward. Regions: 1, insula; 2, superior temporal gyrus; 3, angular gyrus; 4, parietal cortex; 5, occipital cortex; 6 lingual gyrus; 7 thalamus; 8 cingulate cortex; 9 amygdala; 10, hippocampus; 11, middle frontal gyrus; 12, dorsolateral prefrontal cortex; 12, posterior cingulate gyrus; 13, anterior cingulate gyrus; 14, anterior cingulate gyrus; 15, ventromedial prefrontal cortex; 16, orbitofrontal cortex; 17, caudate nucleus; 18, nucleus accumbens; 19, precentral gyrus; 20, putamen.

Figure 2. Study design. Participants fasted in the six hours prior to the MRI scan. They came in 45 minutes early to practice the tasks. The scan was divided into four main parts. First, all participants performed a monetary delay discounting task (DDT1). Second, Patients with BN completed a DDT with food while patients with AUD completed one with alcohol. The HC were randomly allocated to either the food or alcohol DDT (DDT2 pre-stress). Third, stress was induced with the Montreal Imaging Stress Task (MIST; STRESS). Fourth, the participants repeated the food or alcohol DDT (DDT3 post-stress). During the scan, participants reported on their stress level. Their heart rate was measured with a photoplethysmography sensor. Abbreviations: AUD, alcohol use disorder; ASL, arterial spin labeling; BN, bulimia nervosa; DDT, delay discounting task; DWI, diffusion-weighted imaging; HC, healthy control, rsfMRI, resting-state functional magnetic resonance imaging.

Figure 3. Whole-brain between-group and within-group differences during the delay discounting tasks. A) During the food DDT before the MIST (pre-stress), the patients with BN showed a weaker deactivation of the left insula and right insula compared to HC_{FOOD} B) During the food DDT after the MIST (post-stress), the patients with BN displayed a weaker deactivation of the ACC compared to HC_{FOOD} C) After the MIST compared to before the MIST, patients with BN displayed a higher activity of the left occipital cortex and right occipital cortex. The HC_{FOOD} had a higher activity of the left and right postcentral gyrus, left and right supplementary motor area, but a lower activity of the middle and superior frontal gyrus and PCC. The patients with AUD displayed a lower activity of the right supplementary motor area. Abbreviations: AUD, alcohol use disorder; BN, bulimia nervosa; DDT, delay discounting task; HC_{FOOD}, healthy controls who performed the food delay discounting task; MIST, Montreal Imaging Stress Task.

Figure 4. Associations between brain activity during the delay discounting tasks and the behavioral measures. A) In patients with AUD, after stress, brain activity in the right supplementary motor area during the alcohol DDT was negatively associated with log(k)-values (β=-0.679, SE=0.201, p=0.004). B) In HC_{FOOD}, after stress, brain activity in the ACC/vmPFC during the food DDT was negatively associated with log(k)-values (β=0.733, SE=0.356, p=0.048). Abbreviations: AUD, alcohol use disorder; DDT, delay discounting task; β = estimate; HC_{FOOD}, healthy controls who performed the food DDT; MIST, Montreal Imaging Stress Task.

Table 1. Sample characteristics

	AUD (n=27)		HC				BN (n=25)	
			$HC_{alcohol}$ (n=25)		HC_{food} (n=25)			
	Mean (SD)	95% CI	Mean (SD)	95% CI	Mean (SD)	95% CI	Mean (SD)	95% CI
Age	21.7 (4.6)	19.9-23.5	21.0 (1.9)	20.2-21.7	22.2 (3.0)	21.0-23.4	23.0 (4.5)	21.2-24.8
BMI	22.4 (2.1)	21.6-23.3	22.1 (1.6)	21.5-22.8	22.5 (2.7)	21.4-23.6	25.5 (5.8)	23.2-28.0
Illness Duration (years)	3.0 (1.2)	2.5-3.4	0 (0)	0-0	0 (0)	0-0	2.4 (1.5)	1.8-3.0
Education (years)	14.6 (1.8)	13.9-15.3	14.7 (1.2)	14.2-15.2	15.6 (1.9)	14.8-16.4	15.0 (2.0)	14.2-15.9
AUDIT	13.9 (4.4)	12.2-15.7	3.6 (2.1)	2.7-4.4	3.5 (2.1)	2.7-4.4	4.1 (3.6)	2.6-5.6
EDE-Q								
Restraint	0.8 (1.0)	0.4-1.2	0.3 (0.6)	0.1-0.6	0.5 (0.8)	0.2-0.9	3.0 (1.5)	2.3-3.6
Shape Concern	1.7 (1.5)	1.1-2.3	0.9 (0.8)	0.5-1.2	1.1 (1.1)	0.6-1.5	4.3 (1.4)	3.8-4.9
Weight Concern	1.3 (1.4)	0.7-1.8	0.8 (0.9)	0.4-1.2	0.7 (1.0)	0.3-1.2	4.1 (1.3)	3.6-4.7
Eating Concern	0.5 (0.9)	0.2-0.8	0.2 (0.2)	0.1-0.3	0.3 (0.5)	0.1-0.5	2.9 (1.6)	2.3-3.6
Total	1.2 (1.1)	0.7-1.6	0.6 (0.5)	0.4-0.8	0.7 (0.8)	0.4-1.1	3.7 (1.2)	3.2-4.2
Eating disorder symptoms (days/4 weeks)								
Binge eating	0 (0)	0-0	0 (0)	0-0	0 (0)	0-0	10.1 (8.5)	6.6-13.6
Fasting	0 (0)	0-0	0 (0)	0-0	0 (0)	0-0	6.6 (7.8)	3.3-9.8
Vomiting	0 (0)	0-0	0 (0)	0-0	0 (0)	0-0	4.3 (8.9)	0.6-8.0
Laxative use	0 (0)	0-0	0 (0)	0-0	0 (0)	0-0	0.6 (5.6)	0-2.0
Diuretic use	0 (0)	0-0	0 (0)	0-0	0 (0)	0-0	1.1 (5.6)	0-3.4
Compensatory exercise	0 (0)	0-0	0 (0)	0-0	0 (0)	0-0	6.1 (6.4)	3.4-8.7
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Binge drinking frequency								
Never	0 (0%)	0-0%	12 (48%)	32-69%	14 (56%)	40-76%	13 (52%)	36-73%
Annually	0 (0%)	0-0%	1 (4%)	0-25%	2 (8%)	0-28%	4 (16%)	0-37%
Semi-annually	0 (0%)	0-0%	3 (12%)	0-33%	3 (12%)	0-32%	1 (4%)	0-25%
Three-monthly	3 (11%)	0-32%	5 (20%)	4-41%	4 (16%)	0-36%	4 (16%)	0-37%
Monthly	6 (22%)	7-43%	3 (12%)	0-33%	2 (8%)	0-28%	2 (8%)	0-29%
Biweekly	12 (44%)	30-66%	1 (5%)	0-25%	0 (0%)	0-0%	0 (0%)	0-0%
Weekly	3 (11%)	0-32%	0 (0%)	0-0%	0 (0%)	0-0%	1 (4%)	0-25%
>Weekly	3 (11%)	0-32%	0 (0%)	0-0%	0 (0%)	0-0%	0 (0%)	0-0%
Therapy (BN/AUD)								
Past	0 (0%)	0-0%	0 (0%)	0-0%	0 (0%)	0-0%	10 (40%)	20-60%
Present[a]	0 (0%)	0-0%	0 (0%)	0-0%	0 (0%)	0-0%	4 (16%)	1-31%
Previous AN	0 (0%)	0-0%	0 (0%)	0-0%	0 (0%)	0-0%	6 (24%)	6-42%
Ethnicity								
Caucasian	26 (96%)	93-100%	25 (100%)	100-100%	23 (92%)	88-100%	24 (96%)	92-100%
Latino	1 (4%)	0-10%	0 (0%)	0-0%	0 (0%)	0-0%	0 (0%)	0-0%
Asian	0 (0%)	0-0%	0 (0%)	0-0%	1 (4%)	0-16%	0 (0%)	0-0%
Mixed	0 (0%)	0-0%	0 (0%)	0-0%	1 (4%)	0-16%	0 (0%)	0-0%
Middle-Eastern	0 (0%)	0-0%	0 (0%)	0-0%	0 (0%)	0-0%	1 (4%)	0-11%
Contraceptive use	21(78%)	61-94%	22 (88%)	75-100%	24 (96%)	88-100%	19 (76%)	58-94%
Amenorrhea	0 (0%)	0-0%	0 (0%)	0-0%	0 (0%)	0-0%	1 (4%)	0-12%
SSRI	3 (11%)	0-24%	0 (0%)	0-0	0 (0%)	0-0%	4 (16%)	1-31%
Comorbidities								
MDD	1 (4%)	0-18%	0 (0%)	0-0%	0 (0%)	0-0%	1 (4%)	0-25%
PD	1 (4%)	0-18%	0 (0%)	0-0%	0 (0%)	0-0%	1 (4%)	0-25%
SAD	1 (4%)	0-18%	0 (0%)	0-0%	0 (0%)	0-0%	1 (4%)	0-25%
PTSD	1 (4%)	0-18%	0 (0%)	0-0%	0 (0%)	0-0%	0 (0%)	0-0%

[a] Patients were in different treatment modalities (i.e., ambulatory psychologist, psychiatrist, dietician or outpatient treatment program). Abbreviations: AN, anorexia nervosa; AUD, alcohol use disorder; AUDIT, alcohol use disorders identification test; BMI, body mass index; BN, bulimia nervosa; CI, confidence interval; EDE-Q, Eating Disorder Examination Questionnaire; MDD, major depressive disorder; n, number; PD, panic disorder; PTSD, post-traumatic stress disorder; SAD, social anxiety disorder; SD, standard deviation; SSRI, Selective serotonin reuptake inhibitors.

Table 2. log(k)-values of the different delay discounting tasks

Variable	AUD (n=27)	HC (n=50)	BN (n=25)
DD money	-0.46 (0.53)	-0.58 (0.44)	-0.40 (0.55)

Variable	AUD (n=27)	$HC_{alcohol}$ (n=25)	HC_{food} (n=25)	BN (n=25)
DD food/alcohol before MIST	-0.28 (0.60)	0.07 (0.67)	-0.54 (0.41)	-0.62 (0.34)
DD food/alcohol after MIST	-0.21 (0.61)	0.07 (0.68)	-0.46 (0.53)	-0.56 (0.42)

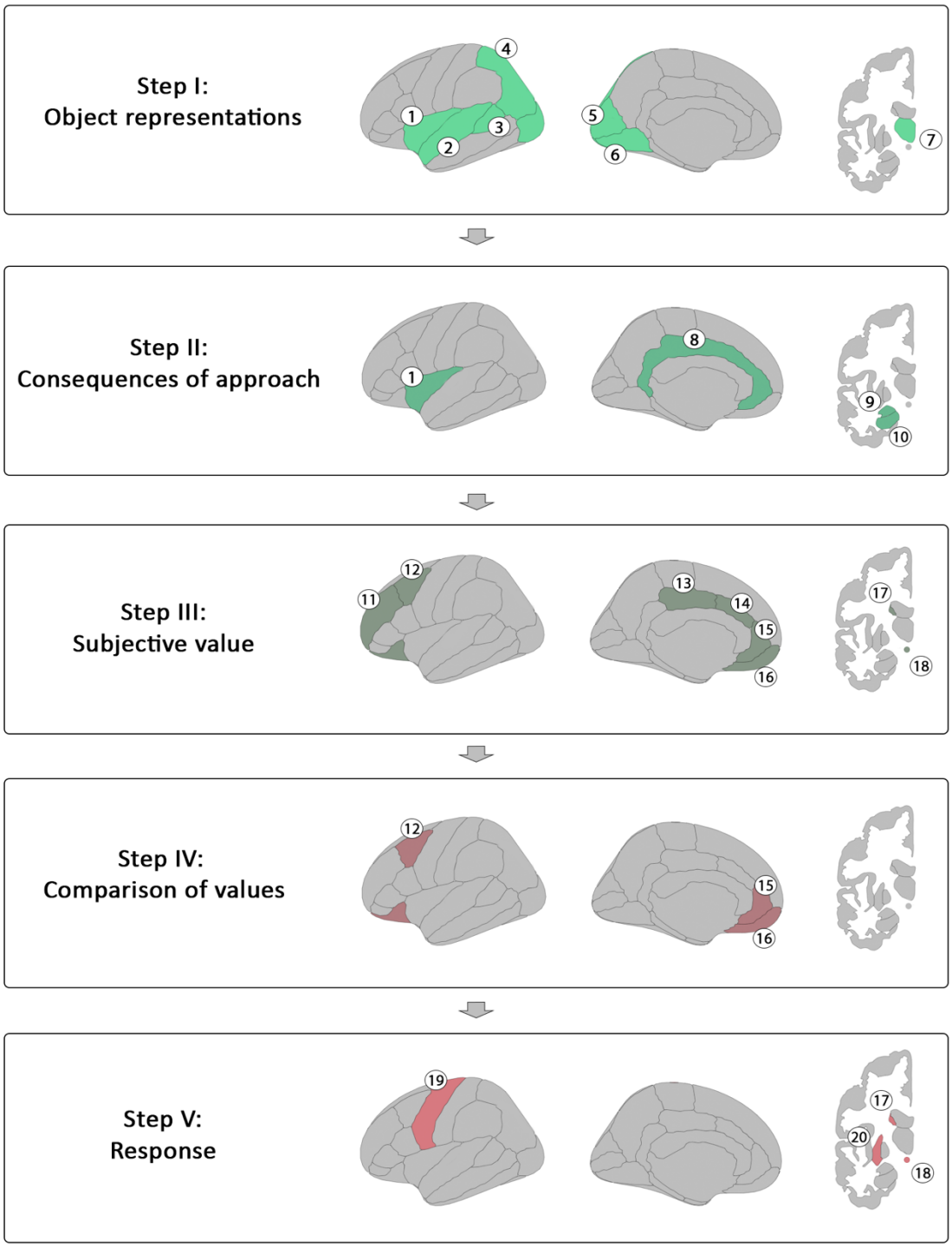
Variables are represented as mean (standard deviation). Abbreviations: AUD, alcohol use disorder; BN, bulimia nervosa; DD, delay discounting; HC, healthy control; $HC_{alcohol}$, healthy controls who performed the alcohol delay discounting task; HCfood; MIST, Montreal imaging stress task.

Table 3. Differences in delay discounting

Model	Effect	β	SE	p
DD money	Group (AUD vs HC)	0.134	0.122	0.271
	Group (BN vs HC)	0.137	0.135	0.311
DD alcohol before MIST	Group (AUD vs $HC_{alcohol}$)	-0.357	0.191	0.068
DD alcohol after MIST	Group (AUD vs $HC_{alcohol}$)	-0.253	0.184	0.174
DD alcohol after vs before MIST	Group (AUD)	0.073	0.019	<0.001*
	Group ($HC_{alcohol}$)	0.006	0.019	0.761
DD food before MIST	Group (BN vs HC_{food})	-0.061	0.121	0.613
DD food after MIST	Group (BN vs HC_{food})	-0.098	0.132	0.416
DD food after vs before MIST	Group (BN)	0.020	0.028	0.478
	Group (HC_{food})	0.060	0.028	0.039*

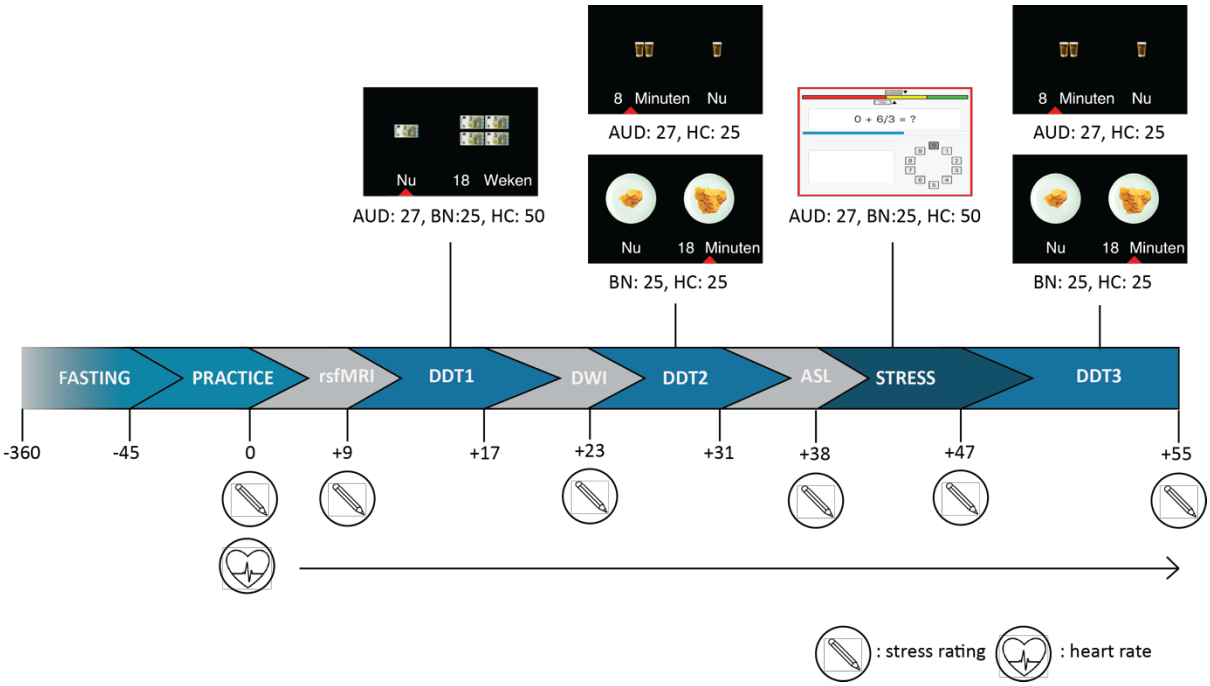
*significant result. Abbreviations: AUD, alcohol use disorder; β, estimate; BN, bulimia nervosa; CI, confidence interval; DD, delay discounting; HC, healthy control; $HC_{alcohol}$, healthy controls who performed the alcohol delay discounting task; HC_{food}, healthy controls who performed the food delay discounting task; MIST, Montreal imaging stress task; SE, standard error.

Figure 1. Neural processing of delay discounting.



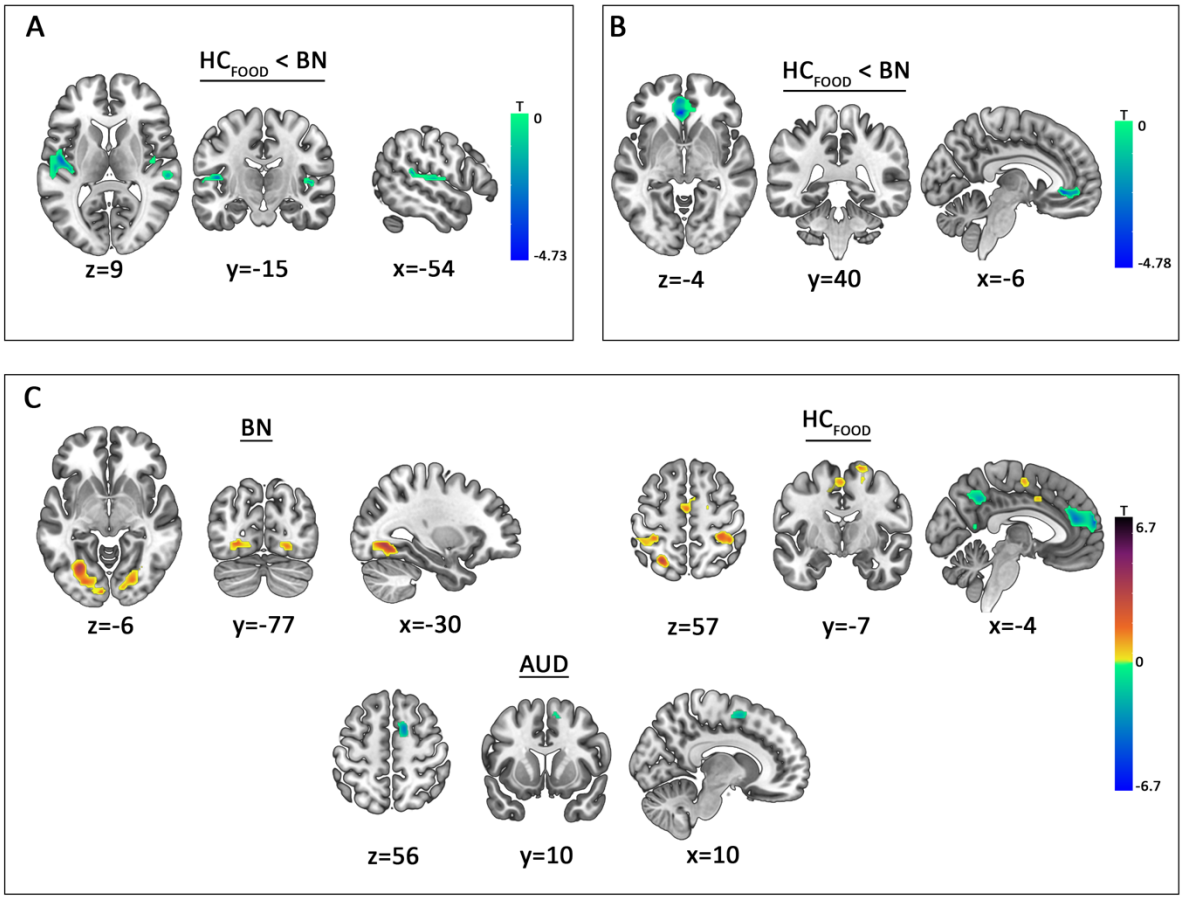
First, sensory information is transformed into object representations. Second, the object representations are used to establish the consequences of choosing the sooner or delayed reward. Third, the consequences are attributed a subjective value. Fourth, the subjective value between the sooner and delayed reward is compared by a dual system. Fifth, information on the decision is used to produce motor responses to acquire the reward. Regions: 1, insula; 2, superior temporal gyrus; 3, angular gyrus; 4, parietal cortex; 5, occipital cortex; 6 lingual gyrus; 7 thalamus; 8 cingulate cortex; 9 amygdala; 10, hippocampus; 11, middle frontal gyrus; 12, dorsolateral prefrontal cortex; 12, posterior cingulate gyrus; 13, anterior cingulate gyrus; 14, anterior cingulate gyrus; 15, ventromedial prefrontal cortex; 16, orbitofrontal cortex; 17, caudate nucleus; 18, nucleus accumbens; 19, precentral gyrus; 20, putamen.

Figure 2. Study design



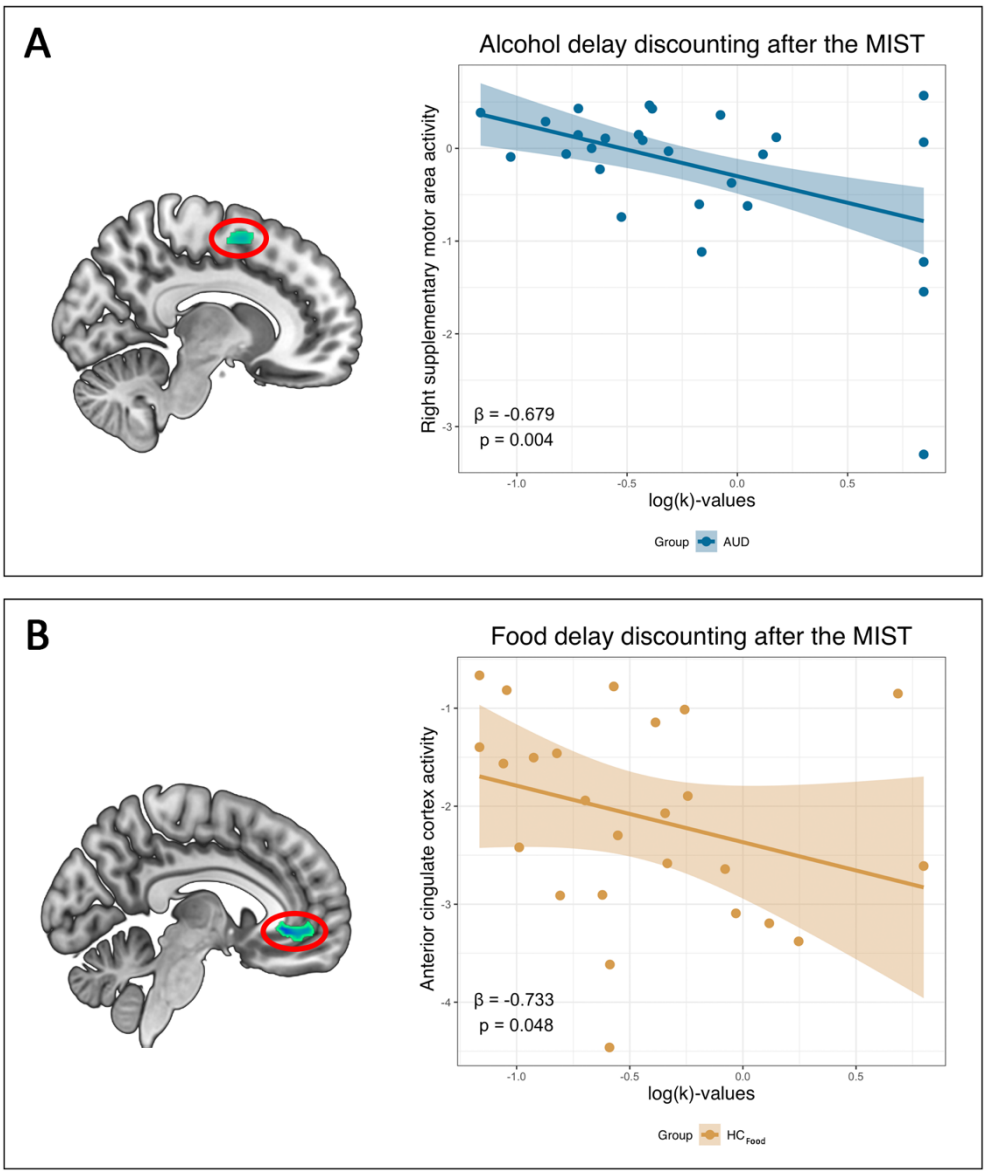
Participants fasted in the six hours prior to the MRI scan. They came in 45 minutes early to practice the tasks. The scan was divided into four main parts. First, all participants performed a monetary delay discounting task (DDT1). Second, Patients with BN completed a DDT with food while patients with AUD completed one with alcohol. The HC were randomly allocated to either the food or alcohol DDT (DDT2 pre-stress). Third, stress was induced with the Montreal Imaging Stress Task (MIST; STRESS). Fourth, the participants repeated the food or alcohol DDT (DDT3 post-stress). During the scan, participants reported on their stress level. Their heart rate was measured with a photoplethysmography sensor. Abbreviations: AUD, alcohol use disorder; ASL, arterial spin labeling; BN, bulimia nervosa; DDT, delay discounting task; DWI, diffusion-weighted imaging; HC, healthy control, rsfMRI, resting-state functional magnetic resonance imaging.

Figure 3. Whole-brain between-group and within-group differences during the delay discounting tasks.



A) During the food DDT before the MIST (pre-stress), the patients with BN showed a weaker deactivation of the left insula and right insula compared to HC_{FOOD} B) During the food DDT after the MIST (post-stress), the patients with BN displayed a weaker deactivation of the ACC compared to HC_{FOOD} C) After the MIST compared to before the MIST, patients with BN displayed a higher activity of the left occipital cortex and right occipital cortex. The HC_{FOOD} had a higher activity of the left and right postcentral gyrus, left and right supplementary motor area, but a lower activity of the middle and superior frontal gyrus and PCC. The patients with AUD displayed a lower activity of the right supplementary motor area. Abbreviations: AUD, alcohol use disorder; BN, bulimia nervosa; DDT, delay discounting task; HC_{FOOD}, healthy controls who performed the food delay discounting task; MIST, Montreal Imaging Stress Task.

Figure 4. Associations between brain activity during the delay discounting tasks and the behavioral measures.



A) In patients with AUD, after stress, brain activity in the right supplementary motor area during the alcohol DDT was negatively associated with log(k)-values (β=-0.679, SE=0.201, p=0.004). B) In HC_{FOOD}, after stress, brain activity in the ACC/vmPFC during the food DDT was negatively associated with log(k)-values(β=0.733, SE=0.356, p=0.048). Abbreviations: AUD, alcohol use disorder; DDT, delay discounting task; β = estimate; HC_{FOOD}, healthy controls who performed the food DDT; MIST, Montreal Imaging Stress Task.