Title

Brain reward response in adolescents and young adults with anorexia nervosa is moderated by changes in body weight and sweetness perception.

Journal

International Journal of Eating Disorders, 55(12)

Authors

Frank, Guido

Shott, Megan

Pryor, Tamara

et al.

Publication Date

2022-12-01

DOI

10.1002/eat.23814

Peer reviewed

HHS Public Access

Author manuscript

Int J Eat Disord. Author manuscript; available in PMC 2024 November 05.

Published in final edited form as:

Int J Eat Disord. 2022 December ; 55(12): 1799–1810. doi:10.1002/eat.23814.

Brain Reward Response in Adolescents and Young Adults with Anorexia Nervosa is Moderated by Changes in Body Weight and Sweetness Perception

Guido K.W. Frank, M.D.[a,b], **Megan E. Shott, B.S.**[a], **Tamara Pryor, Ph.D.**[c], **Skylar Swindle, B.S.**[a], **Joel Stoddard, M.D.**[d]

[a]University of California at San Diego, Department of Psychiatry, San Diego, California, USA

[b]Rady Children's Hospital San Diego, Medical Behavior Unit, San Diego, California, USA

[c]Eating Disorder Care, Denver, Colorado, USA

[d]University of Colorado, Anschutz Medical Campus, Department of Psychiatry, Aurora, Colorado, USA

Abstract

Objective: Anorexia nervosa (AN) is a severe psychiatric illness with complex etiology. Recently, we found elevated striatal brain response to sweet taste stimuli in adolescents and young adults with AN. Here we tested the hypothesis that nutritional rehabilitation normalizes prediction error activation, a measure for dopamine-related reward circuit response, to salient caloric taste stimuli in AN.

Method: Twenty-eight individuals with AN (age=16±2 years; body mass index, BMI=16±1) who previously underwent brain imaging while performing a taste prediction error task using sucrose as salient caloric stimulus, participated in a second brain imaging scan (BMI=18±1) after intensive specialized eating disorder treatment (41±15 days). Thirty-one healthy controls (age=16±3 years; BMI=21±2) were also studied on two occasions.

Corresponding Author: Guido K.W. Frank, M.D., Professor, University of California San Diego, Department of Psychiatry, UC San Diego Health Eating Disorders Center for Treatment and Research, 4510 Executive Drive, Suite 315, San Diego, CA 92121, Phone: 858-246-5073, gfrank@health.ucsd.edu.

Co-Author Details:

Megan E Shott: University of California at San Diego, mshott@health.ucsd.edu

Tamara L Pryor: ED Care Denver, tpryor@eatingdisorder.care

Skylar Swindle: University of California at San Diego, sswindle@health.ucsd.edu

Joel Stoddard: University of Colorado, Anschutz Medical Campus: joel.stoddard@cuanschutz.edu

Author Contributions Statement

Guido Frank contributed to the Conceptualization, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Supervision, Validation, Visualization, and Writing – original draft. Megan Shott contributed to the Data Curation, Investigation, Project Administration, Visualization, and Writing – review and editing. Skylar Swindle contributed to the Writing – review & editing. Tamara Pryor contributed to the Resources and Writing – review and editing. Joel Stoddard contributed to the Formal Analysis and Writing – review & editing.

Disclosures

None of the authors report any financial relationships with commercial interests.

IRB Statement

This study was approved by the Colorado Multiple Institutional Review Board. All participants gave written informed consent prior to completing any study procedures.

Results: At baseline, individuals with AN demonstrated an elevated salience response in bilateral caudate head and nucleus accumbens, and right ventral striatum. At the second scan, elevated response was only found in the right nucleus accumbens. A moderator analysis indicated that greater increase in BMI and greater decrease in sweetness perception predicted lesser prediction error response at the second scan in AN.

Conclusion: Consistent with the previously reported monetary stimulus-response, elevated taste prediction error response in AN was largely absent after weight restoration. This study indicates that changes in BMI and sweet taste perception are independent moderators of change of brain salience response in adolescents and young adults with AN. The study points toward dynamic changes in the brain reward circuitry in AN and highlights the importance of nutrition and weight restoration in that process.

Keywords

anorexia nervosa; adolescent; recovery; reward; taste

Introduction

Anorexia nervosa is the third most common chronic illness among adolescent females and is associated with high mortality.[1-3] The illness shows a complex interplay between neurobiological, psychological and environmental factors[4] and it is an often chronic disorder with frequent relapse, high treatment costs, and disease burden.[5]

Little is known about the pathophysiology or biomarkers that characterize brain function in anorexia nervosa and how neurobiology, illness behaviors, and recovery interact.[6] Food avoidance and the ability to withstand hunger in anorexia nervosa have led to the hypothesis that brain reward pathways could be altered in the disorder. [7-9] Those circuits have been extensively studied in animal and human brain research,[10,11] and behavioral and neuroimaging studies may help elucidate altered brain reward function in anorexia nervosa.[12,13] Recent studies in adolescents and young adults with anorexia nervosa suggested a preference for delayed rewards and reduced sensitivity to loss.[14,15] Others found that reward conditioning was moderated by cognitive bias,[16] and individuals with anorexia nervosa learned faster in the context of punishment, which was associated with medial frontal cortex activation.[17] Our group has focused on studying the reward prediction error response in anorexia nervosa. The prediction error construct tests brain function associated with the difference between an expectation and outcome, which yields the so-called prediction error, a dopamine-associated signal that reinforces new associations.[18,19] The direction of the prediction error may indicate a better (positive) or worse (negative) outcome than expected. The absolute value reflects the degree of deviation of the outcome from the expectation and has been conceptualized as a motivational salience signal.[20,21] The prediction error model is important for anorexia nervosa as it lends itself to a model where conditioned fear of eating and weight gain recruits the sensitized dopamine-related striatal circuits to override hunger cues and respond to food with dread and avoidance.[8,22]

We have been studying the prediction error model because the dopamine system adapts in opposite directions to extremes of food intake and could be linked to brain pathology

across the eating disorder spectrum.[23-26] Enhanced neuronal dopamine response occurs following food restriction,[10,27] which could be specifically relevant for the pathophysiology of anorexia nervosa.[13,28-30] Consistent with that model, we found previously in adolescents and young adults with anorexia nervosa elevated prediction error signal in a taste as well as a monetary paradigm when acutely underweight.[31,32] The monetary paradigm indicated elevated stimulus response before but not after treatment in anorexia nervosa compared to controls; however, the factors that are mechanistically involved in the change of brain response have been elusive.[32]

Hypotheses.

Here we followed up on the adolescent and young adult participants from the large taste prediction error study who had shown elevated brain response in striatal regions including bilateral caudate head and nucleus accumbens.[32] We hypothesized that elevated prediction error response in those regions would normalize with weight restoration, comparable to the results of the monetary task study.[32] This would support stimulus-independent changes of prediction error-related brain salience response during treatment. Second, we hypothesized that studying a larger sample compared to the monetary paradigm investigation would allow finding direct evidence that nutritional rehabilitation and specifically an increase in body mass index (BMI) as a measure of height-adjusted body weight moderates the normalization of brain function in anorexia nervosa. Such an interaction would support mechanisms found in basic science studies, which have not been shown in adolescents or adults with anorexia nervosa before.[24]

Methods

We recruited adolescents and young adults with anorexia nervosa studied previously at the beginning of intensive treatment.[31] Twenty-eight girls and young women with anorexia nervosa and thirty-one healthy comparison individuals participated; age range in both groups was 11 to 21 years (Table 1.). The anorexia nervosa group was recruited from partial hospitalization treatment, where closely supervised meal plans mitigated confounding brain effects of acute starvation or dehydration.[33] Treatment involved a highly structured program aimed at weight restoration over 5 weeks, including parent-training in meal support according to the family-based treatment model.[34] Patients completed meals or used supplement for calculated caloric needs to achieve weight goals. We required a minimum of two weeks in treatment between scans one and two for patients with anorexia nervosa to be included in the study. Healthy control participants were recruited through local advertisements. Each participant underwent functional MRI (fMRI) twice: individuals with anorexia nervosa before weight restoration and at discharge to a lower level of care, and healthy controls during the early follicular phase, two menstrual cycles apart, to reduce sex hormone effects on brain reward function. Reasons for individuals with anorexia nervosa not to participate in scan two after having performed scan one were early treatment dropout, discharge due to medical instability, no interest in a second scan, or inability to schedule a scan at treatment end due to time constraints and scanner availability (see Supplement for details). Participants with anorexia nervosa were amenorrheic. Individuals with anorexia nervosa were of the restricting type, and all fell below the 10th body

mass index (BMI, kg/m^2) percentile for age on scan one. Participants ages 18–21 years were administered the Structured Clinical Interview for DSM-5 (doctoral-level interviewer, anorexia nervosa n=6; healthy controls n=7). Those under age 18 completed the Mini-International-Neuropsychiatric Interview.[35] Participants were right-handed without a history of head trauma, neurological disease, major medical illness, psychosis, or substance use disorders. Of the healthy control group, 19 individuals were White, 6 Black, 3 Asian, and 3 of Central American ethnicity. The anorexia nervosa sample consisted of 23 White, 1 Black, 1 Asian, and 3 individuals of Central American background. A Chi-square test comparing race/ethnicity across groups was non-significant (Pearson Chi-Square=4.812, p=0.186). Six healthy controls and three anorexia nervosa participants took oral contraceptives. Oral contraception use was not significantly different across groups (Chi Square=0.850, p=0.357). Sixteen participants with anorexia nervosa took antidepressants at scan one and twenty at scan two, four took atypical antipsychotics at scan one, and five at scan two. Seven participants with anorexia nervosa had major depressive disorder, seven had OCD, and seventeen had an anxiety disorder. The Colorado Multiple Institutional Review Board approved the study. All participants and parents provided written informed assent or consent.

Self-Assessments

Participants completed the Eating Disorder Inventory-3 (to measure cognitive and behavioral characteristics of eating disorders), [36,37] the Temperament and Character Inventory (to measure personality and temperament),[38] the Spielberger State-Trait Anxiety Scale-Y (to measure state and trait anxiety),[39] and the Childhood Depression Inventory (to assess the cognitive, behavioral, affective, and somatic symptoms of depression),[40] and task-stimulus sweetness and pleasantness perception were measured on a 9-point Likert scale to assess changes with treatment. The assessments were used to compare the current sample with our previously described larger sample from which this study group is derived.[31]

Brain Imaging Methods

fMRI Image Acquisition.—Between 0700 and 0800 hours, participants with anorexia nervosa ate their meal plan breakfast and healthy controls ate a quality- and calorie-matched breakfast (Table 1.). Brain imaging was performed between 0800 and 0900 hours (3T GE Signa or Siemens Skyra 3T scanner), three-plane scout scan (16 seconds), sagittally acquired, spoiled gradient sequence T1-weighted (172 slices, thickness=1mm, TI=450ms, TR=8ms, TE=4ms, flip angle=12°, FOV=22cm, scan matrix=64×64), and T2*-weighted echo planar scans for blood-oxygen-level-dependent (BOLD) functional activity (3.4×3.4×2.6mm voxels, TR=2100ms, TE=30ms, flip angle=70°, 28 axial slices, thickness=2.6mm, gap=1.4mm).

Taste Reward Task.—The design was adapted from O'Doherty et al.[31] Participants learned to associate three unconditioned taste stimuli (US: 1 molar sucrose solution, no solution, or artificial saliva) with paired conditioned visual stimuli (CS). Each CS was probabilistically associated with its US such that 20% of sucrose and no solution CS trials were unexpectedly followed by no solution and sucrose US, respectively. Taste stimuli were applied using a customized-programmable syringe pump (J-Kem Scientific, St Louis, MO,

USA) and E-Prime Software (Psychological Software Tools, Pittsburgh, PA, USA).[41] The CS visual stimuli differed and were randomized between study days.

FMRI Analysis.—Image preprocessing and analysis were performed using SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/). Images were realigned to the first volume, normalized to the Montreal Neurological Institute template and smoothed at 6mm full-width-at-half-maximum Gaussian kernel. Subjects with head motion greater than one voxel were removed from the analysis. Data were preprocessed with slice time correction and modeled with a hemodynamic response convolved function using the general linear model, including temporal and dispersion derivatives. A 128-second high-pass filter (removing low-frequency BOLD signal fluctuations), motion parameters (as first-level analysis regressors), and SPM's FAST (pre-whitening attenuation of autocorrelation effects) were applied.

Prediction Error Analysis.: Each participant's prediction error signal was modeled based on trial sequence (event-related design) and regressed with brain activation across all trials.[32,42,43] The predicted value ($\widehat{V}$) at any time (t) within a trial is calculated as a linear product of weights (w_i) and the presence of a conditioned visual stimulus (CS) at time t, coded in a stimulus representation vector $x_i(t)$ where each stimulus x_i is represented separately at each moment in time:

$$V(t) = \sum_i W_i x_i(t)$$

The predicted stimulus value at time t is updated by comparing the predicted value at time t+1 to that observed at time t, leading to the prediction error δ(t):

$$\delta(t) = r(t) + \gamma \widehat{V}(t+1) - \widehat{V}(t)$$

where r(t) is the reward at time t. The parameter γ is a discount factor, which determines the extent to which rewards arriving sooner are more important than rewards that arrive later during the task, with γ=0.99. The weights w_i relate to how likely a particular unconditioned reward stimulus (US) follows the associated CS and are updated on each trial according to the correlation between prediction error and stimulus representation:

$$\Delta w_i = \alpha \sum_t x_i(t)\delta(t)$$

where α is a learning rate. A slow α=0.2 was applied.[32] Initial reward values were 1 for Sucrose Receipt and 0 for No Sucrose. Trial-to-trial prediction error was regressed with brain activation across all trials within each subject. Prediction error calculated for each trial was modeled as an absolute (reflecting degree of deviation of the outcome from the expectation) without separating positive or negative prediction error trials. Model prediction error values were then regressed against fMRI data for each subject, to identify brain regions correlating with the model-predicted time series.[44]

Region of Interest (ROI) Data Extraction.: We extracted parameter estimates from predefined regions of interest bilaterally using the automated anatomical labeling Atlas, AAL, to compare results with our previous studies and assess change over time.[31,32,45] Mean parameter estimates across all voxels from eight predefined anatomical regions of interest (ROIs) were extracted, bilateral caudate head, ventral striatum, nucleus accumbens, inferior, medial, and middle orbitofrontal cortex, and dorsal and ventral anterior insula.

Statistical Analysis

SPSS 28 software was used for statistical analyses (IBM, Armonk, N.Y.). Data were tested for normality with the Shapiro-Wilk test and rank-transformed when non-normally distributed. Demographic and behavioral data were analyzed using Student's t-test. Changes in demographic and behavioral values between scans one and two were assessed using paired sample t-tests. MANCOVA and correlation analyses were used to test the effects of potential confounding categorical or continuous variables such as scanner, comorbidity, medication or birth control use, or age. Variables that affected the primary outcome variable brain response were included in group-comparisons. First scan (before weight restoration) data were analyzed using MANCOVA to confirm similar results as in our previous analysis in the larger sample.[31]

For the main analysis in this study, repeated measures MANCOVA was used and analyzed using a full factorial design, including group, scan order, and brain region interactions. Partial η^2 was calculated for effect size in addition to power calculations.

Pearson correlation analysis tested associations between weight change and behavior variables, and the results were multiple comparisons controlled using False Discovery Rate.[46]

Moderator analysis (PROCESS) was used to test the effects of variables that changed during treatment (moderators) from scan one to two on change in brain prediction error response between scan one (X) and scan two (Y). The primary hypothesis was that increase in BMI, reflective of treatment that is geared toward increasing food intake and resulting in weight gain, would moderate brain response change in regions elevated at scan one. Other factors that might be related to sweet taste prediction error response and could change during treatment were also explored. The analysis included scanner as covariate and results were bootstrapped (default setting 5000 samples).

Results

Demographic and Behavioral Variables

Demographic values and scan one prediction error values in this sample were consistent with the larger scan one data set (Table 1.). The anorexia nervosa group had significantly lower BMI and scored higher on eating disorder behaviors, anxiety, and depression measures. BMI range on admission in healthy controls was 17.2 to 25.1 and in the anorexia nervosa group 14.1 to 17.7. From scan one to two, both groups gained significantly in BMI, but weight gain was higher in the anorexia nervosa group. From scan one to two, sweetness perception ratings of participants with anorexia nervosa decreased significantly for the 1 molar sucrose

solution applied during brain scanning and were significantly lower at scan two compared to controls. In addition, drive for thinness was significantly lower at scan two, although still highly elevated compared to healthy controls. Number of days between scans was higher in healthy controls (51±14) compared to participants with anorexia nervosa (4±15, range 14-64; p=0.009). This was due to healthy controls being studied during the first ten days of the menstrual cycle to keep hormonal variation low, while participants with anorexia nervosa were studied at end of treatment. The range of days between scan day 1 and scan day 2 was 58 days for healthy controls (minimum 19 days, maximum 77 days) and 50 days for the anorexia nervosa group (minimum 14 days and maximum 64 days).

Analysis of Cofactors and Covariates

A MANCOVA to test the effects of cofactors or covariates indicated a significant effect for scanner in the healthy control (Wilk's Lambda=0.447, p=0.009) but not for the anorexia nervosa group (Wilk's Lambda=0.600, p=0.648). Imaging data were non-normally distributed before transformation but normally distributed after rank transformation as previously (Kolmogorov-Smirnov Statistic p≥0.1 for all regions). There were no significant effects in either group for age (healthy controls: Wilk's Lambda=0.594, p=0.066; anorexia nervosa: Wilk's Lambda=0.689, p=0.770), sweetness perception (healthy controls: Wilk's Lambda=0.536, p=0.779; anorexia nervosa: Wilk's Lambda=0.334, p=0.976). In the anorexia nervosa group, there were no significant effects for major depressive disorder (Wilk's Lambda=0.383, p=0.745), obsessive-compulsive disorder (Wilk's Lambda=0.362, p=0.714), generalized anxiety disorder (Wilk's Lambda=0.578, p=0.616), antidepressant (Wilk's Lambda=0.902, p=0.973) or antipsychotic use (Wilk's Lambda=0.670, p=0.745).

Correlation Analysis

BMI change from scan one to two was not significantly correlated with any behavioral measures in either group. Specifically, BMI change was not significantly correlated with change in sweetness perception in healthy controls (r=−0.024, p=0.896) or individuals with anorexia nervosa (r=−0.013, p=0.947). In healthy controls, BMI values at scan one and two were positively correlated with scan one prediction error response in the right dorsal anterior insula (BMI scan one: r= 0.510, p=0.004, CI95%= 0.275 to 0.706; BMI scan two: r=0.452, p=0.012, CI95%= 0.239 to 0.655), left ventral anterior insula (BMI scan one: r=0.387, p=0.035, CI95%= 0.077 to 0.640; BMI scan two: r=0.386, p=0.035, CI95%= 0.121 to 0.631). Scan two prediction error response did not significantly correlate with BMI or change in BMI in healthy controls.

In the anorexia nervosa group, right middle orbitofrontal cortex prediction error at scan one was negatively correlated with BMI change (r=−0.385, p=0.05) but the result did not remain significant after multiple comparison correction. There was no significant correlation between number of days between scans and prediction error brain response at scan time one or two in either group, and there was no significant correlation between number of days between scans and increase in BMI in the anorexia nervosa group (r=0.258, p=0.185).

Brain Response Group Contrast

The MANCOVA for scan one prediction error data revealed similar results as the previous study in the larger sample with significant group differences in bilateral caudate head and nucleus accumbens (Supplemental Table 1.).

The repeated measures ANCOVA for prediction error response across the 16 ROIs studied indicated a significant group effect for regional brain response with very large effect size (Wilk's lambda=0.589, F=1.957, p=0.044, partial $\eta 2$=0.411, power=0.880).

Scan by group response was non-significant, but effect size was large (Wilk's lambda=0.717, F=1.105, p=0.381, partial $\eta 2$=0.283, power=0.584).

Post hoc univariate analyses (Table 2., Figure 1.) indicated significantly higher prediction error brain response in anorexia nervosa at scan one for bilateral caudate head (R: p=0.001, CI95% for difference= −22.909 to −6.432; L: p=001, CI95% for difference= −23.023 to −6.583) and bilateral nucleus accumbens (R: p<0.001, CI95% for difference= −23.880 to −7.722; L: p=002, CI95% for difference= −22.098 to −5.457), and in anorexia nervosa at scan two for right nucleus accumbens (p=0.048, CI95% for difference= −17.724 to −0.098). There was no significant effect of scan within each group, although prediction error response tended to be lower in anorexia nervosa but higher in controls at scan two.

Moderator Analysis

In the healthy control group, tests for the moderating effects of BMI on regional prediction error response change were not significant (Supplemental Table 3.). No other potential moderating factors in healthy controls were explored as no other taste-related variables including sweetness perception or pleasantness ratings changed between scans. In participants with anorexia nervosa (Table 3., Supplemental Table 3.), BMI increase had a negative moderating effect (negative interaction) on this correlation in the right ventral striatum and right nucleus accumbens. Sweetness perception, which decreased significantly between scan times in the adolescents and young adults with anorexia nervosa, had significant moderator effects (negative interaction) on prediction error response correlation between scans one and two in the right caudate head, left ventral striatum, and left nucleus accumbens. BMI change and change in sweetness perception were not related, and a moderator analysis with two moderators, BMI change and change in sweetness perception, was conducted. That analysis (Table 3.; Figure 2.) showed significant moderator effects on right caudate head, bilateral ventral striatum, bilateral nucleus accumbens, and left dorsal anterior insula. To account for potential scanner effects, brain scanner was included in all moderator analyses as covariate. False discovery rate correction on the combined interaction p-values for regions that were elevated at scan one compared to controls was significant for bilateral caudate nucleus accumbens, ventral striatum, and right caudate head. Exploratory analyses using days between scans or drive for thinness were also conducted for their moderating effects on prediction error response change in anorexia nervosa but were not significant.

Discussion

This study indicates that elevated taste prediction error response in adolescents and young adults with anorexia nervosa is primarily seen before weight restoration and is consistent with previous studies using monetary stimuli. The study further lends support to the hypothesis that both BMI increase and sweetness taste-perception decrease are independent moderators of adjustment of the prediction error signal in anorexia nervosa during treatment. These results support animal studies that have tied food intake and changes in body weight mechanistically to the dopamine-related prediction error response.

This study confirmed in a subsample from our previous report elevated prediction error response in anorexia nervosa before weight restoration. However, after weight restoration, there was indication of partial normalization in anorexia nervosa and comparable to our study using monetary stimuli.[32] The multivariate test indicated significant regional group differences, and post hoc tests showed that for scan one the anorexia nervosa group had elevated prediction error response in caudate nucleus, nucleus accumbens, and the left ventral striatum, consistent with the results in the large sample previously reported on.[31] For scan two, regional prediction error data acquired after intensive treatment, the anorexia group had higher brain response in the right nucleus accumbens only. Post hoc tests within group did not show significant differences for regional prediction error salience response between scans.

The primary result of this study is that we find evidence that changes in BMI and sweetness perception in anorexia nervosa have direct effects on changes in dopamine-related brain salience response. Prediction error at scans one and two in the anorexia nervosa group were strongly positively correlated; however, the higher the BMI increase was during treatment, and the more sweetness perception decreased between the two scans, the lower prediction error response was at scan point two. Adding both moderators in one model had the strongest effects and those were significant in the bilateral ventral striatum, nucleus accumbens, and right caudate head. Such direct effects have not been shown before in anorexia nervosa. Animal research has indicated direct effects of food restriction or excessive food intake on dopamine-related brain reward function.[24,28] Studies on substance use and obesity in humans have indicated pathophysiologies that are overlapping and involve dopaminergic circuits.[42,47] While decreases in brain salience response in the anorexia nervosa group were not significant from scan one to two, this study suggests that changes in brain response in adolescents and young adults with anorexia nervosa during treatment are directly moderated by nutritional rehabilitation.

An increase in BMI in anorexia nervosa during specialized eating disorder treatment is reflective of increased food intake, restriction of exercise, increased variety of food, and potentially other factors. Depending on a patient's behavior before treatment, one or more factors contribute to the BMI increase during treatment, and specific individual effects cannot be determined from this study. Several studies have suggested that dopamine-related circuits are involved in the pathophysiology of anorexia nervosa in adults and there is an emerging literature that indicates elevated salience response in adolescents as well.[31,32] Whether increased food intake and associated weight gain desensitize central dopamine

receptors or whether for instance neuroreceptor distribution is downregulated is unclear. The available neurotransmitter receptor literature is small and inconsistent and derived from adult samples. Dopamine metabolites in cerebrospinal fluid were found to be reduced when ill but elevated after recovery from anorexia nervosa, suggesting dynamic changes with weight recovery.[48] Positron emission tomography studies showed normal dopamine D2 receptor distribution when ill, but elevated receptor binding potential after long-term recovery, also supporting adaptations to food intake.[49,50] Whether those results reflect the changes in the pathophysiology described in this study is unclear and indicate the need for novel and innovative research that can identify dopamine and other neurotransmitter function in vivo in anorexia nervosa.

Sweetness perception in adolescents and young adults with anorexia nervosa decreased with nutritional rehabilitation, while pleasantness was similar across time points. There is an indication that taste sensitivity in anorexia nervosa is altered, although the literature is not consistent and the available studies have largely been done in adults.[51] Some studies found negative associations between sweet taste sensitivity and food intake.[52] We hypothesize that increased food exposure and intake desensitized sweet taste perception in the anorexia nervosa group during treatment, and lower sweet taste sensitivity might contribute to reduced prediction error salience signal at scan two. Whether altering taste sensitivity in anorexia nervosa during the ill state has any therapeutic benefits remains to be studied.

Our hypothesis for change in brain activation was based on biological changes with changes in food intake and focused on BMI and taste perception changes. However, psychological changes as drivers of change in brain prediction error response cannot be excluded. Drive for thinness significantly improved during treatment in the individuals with AN; however, an exploratory analysis did not show any significant effects for drive for thinness moderating changes in brain response.

Limitations.

Although the sample size was relatively large compared to other neurobiological repeated functional imaging research in adolescents and young adults with anorexia nervosa, it was still modest, and participants had various comorbidities. Those factors likely contributed to the lack of significant multivariate group by regional brain response by scan time point differences, as well as lack of correlations between brain response and behavior variables. The scan one effect sizes for group contrasts were large and the right nucleus accumbens group difference at scan two was in the moderate to large effect size range. The ROIs were selected a priori and independent of any prior analysis. They were selected for involvement in reward and salience processing. To avoid selection bias, we did not solely focus on regions that were significant between groups at scan one in the larger sample. An exploratory analysis of only the caudate head and nucleus accumbens regions was significant for group main effect and group by scan interaction. The significant group effect for the sixteen-region comparison suggests that there are regional differences between the two groups; however, the lack of significance for the group by scan interaction was likely due to the orbitofrontal and insular regions not showing group differences at either time point. Despite non-significance of the group by scan interaction, the large effect

size of this interaction suggests that future research may identify more regionally specific treatment effects between the groups that we may not have detected here. The elevated right nucleus accumbens response after weight restoration could indicate long lasting biological vulnerabilities. Behavioral data could not predict BMI change or regional brain response and the effects of those variables remain unclear. While the effects from comorbid conditions cannot be excluded, the analyses did not indicate significant effects from such conditions or age. The ROI-based approach of this study was decidedly narrow to be in line with our previous studies. A whole brain analysis may have provided different results and will be explored in future studies. Participants were evenly distributed across scanners (Supplemental Table 2.), but while significant scanner effects were detected in the healthy control group, such effects in anorexia nervosa could not be excluded, and scanner was included in all image analyses for healthy controls and the anorexia nervosa participants. The study sample included about 20% of individuals between the ages of 18 and 21 years. This resulted from NIH's previous definition of that age group as children. Age was not significantly related to brain response and brain development continues to age 21. Thus, we do not have an indication that including those individuals biased or confounded the results. Race or ethnicity was not significantly different across groups, but most participants were White and whether results can be generalized to other populations needs further study. The moderator analysis indicated significant independent negative interaction effects from changes in BMI and sweet taste perception on change in brain response from scan one to scan two. Treatment for anorexia nervosa is geared toward BMI increase via increased food variety and intake, as well as energy expenditure restriction. We, therefore, believe it is likely those factors contributed to the moderating effects, but specific individual or patient-specific factors cannot be determined from the study. Future studies may therefore identify other factors as moderators of prediction error change during treatment.

In summary, in this study, we find the first direct evidence that in anorexia nervosa changes in prediction error salience response during specialized eating disorder treatment are moderated by an increase in BMI and a decrease in sweetness perception. The study highlights the need to normalize food intake to normalize brain function and this is consistent with basic research. The independent moderator effects of BMI and sweet taste perception are intriguing, raising the question of whether lower sweet taste sensitivity and maybe flavor intensity, in general, could aid in normalizing food intake in anorexia nervosa. The study also indicates that normalization of brain response is a protracted process that may not be completed after high-intensity treatment. The relapse rate in anorexia nervosa is highest within the first twelve months after treatment and we hypothesize that extended altered brain reward circuit function could have a significant role.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We would like to thank all the individuals who have participated in this study.

The study was supported by NIMH grants MH096777 and MH103436.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. Golden NH, Katzman DK, Kreipe RE, et al. Eating disorders in adolescents: position paper of the Society for Adolescent Medicine. J Adolesc Health. Dec 2003;33(6):496–503. doi:S1054139X03003264 [pii] [PubMed: 14642712]
2. Sullivan PF. Mortality in anorexia nervosa. Am J Psychiatry. Jul 1995;152(7):1073–4. [PubMed: 7793446]
3. Rosling AM, Sparen P, Norring C, von Knorring AL. Mortality of eating disorders: a follow-up study of treatment in a specialist unit 1974-2000. Research Support, Non-U.S. Gov't. Int J Eat Disord. May 2011;44(4):304–10. doi:10.1002/eat.20827 [PubMed: 21472749]
4. Bulik CM. Exploring the gene-environment nexus in eating disorders. J Psychiatry Neurosci. Sep 2005;30(5):335–9. [PubMed: 16151538]
5. Attia E. Anorexia nervosa: current status and future directions. Annu Rev Med. 2010;61:425–35. doi:10.1146/annurev.med.050208.200745 [PubMed: 19719398]
6. Bulik CM, Berkman ND, Brownley KA, Sedway JA, Lohr KN. Anorexia nervosa treatment: A systematic review of randomized controlled trials. Int J Eat Disord. Mar 16 2007;
7. Frank GKW, Shott ME, DeGuzman MC. The neurobiology of eating disorders. Child Adolesc Psychiatr Clin N Am. Oct 2019;28(4):629–640. doi:10.1016/j.chc.2019.05.007 [PubMed: 31443880]
8. Frank GKW. From desire to dread-A neurocircuitry based model for food avoidance in anorexia nervosa. J Clin Med. May 21 2021;10(11)doi:10.3390/jcm10112228
9. Faure A, Richard JM, Berridge KC. Desire and dread from the nucleus accumbens: cortical glutamate and subcortical GABA differentially generate motivation and hedonic impact in the rat. PLoS One. Jun 18 2010;5(6):e11223. doi:10.1371/journal.pone.0011223 [PubMed: 20585461]
10. Kelley AE. Ventral striatal control of appetitive motivation: role in ingestive behavior and reward-related learning. Neurosci Biobehav Rev. Jan 2004;27(8):765–76. doi:10.1016/j.neubiorev.2003.11.015 [PubMed: 15019426]
11. Morales I, Berridge KC. 'Liking' and 'wanting' in eating and food reward: Brain mechanisms and clinical implications. Physiol Behav. Aug 23 2020:113152. doi:10.1016/j.physbeh.2020.113152 [PubMed: 32846152]
12. Kaye WH, Wierenga CE, Bailer UF, Simmons AN, Wagner A, Bischoff-Grethe A. Does a shared neurobiology for foods and drugs of abuse contribute to extremes of food ingestion in anorexia and bulimia nervosa? Biol Psychiatry. May 01 2013;73(9):836–42. doi:10.1016/j.biopsych.2013.01.002 [PubMed: 23380716]
13. Monteleone AM, Castellini G, Volpe U, et al. Neuroendocrinology and brain imaging of reward in eating disorders: A possible key to the treatment of anorexia nervosa and bulimia nervosa. Prog Neuropsychopharmacol Biol Psychiatry. Jan 03 2018;80(Pt B):132–142. doi:10.1016/j.pnpbp.2017.02.020 [PubMed: 28259721]
14. Verharen JPH, Danner UN, Schroder S, Aarts E, van Elburg AA, Adan RAH. Insensitivity to losses: A core feature in patients with anorexia nervosa? Biol Psychiatry Cogn Neurosci Neuroimaging. Nov 2019;4(11):995–1003. doi:10.1016/j.bpsc.2019.05.001 [PubMed: 31262707]
15. Bernardoni F, Bernhardt N, Pooseh S, et al. Metabolic state and value-based decision-making in acute and recovered female patients with anorexia nervosa. J Psychiatry Neurosci. Jul 1 2020;45(4):253–261. doi:10.1503/jpn.190031 [PubMed: 32129584]
16. Vogel V, Dittrich M, Horndasch S, et al. Pavlovian-to-instrumental transfer in anorexia nervosa: A pilot study on conditioned learning and instrumental responding to low- and high-calorie food stimuli. Eur J Neurosci. Apr 2020;51(8):1794–1805. doi:10.1111/ejn.14592 [PubMed: 31606905]

17. Bernardoni F, Geisler D, King JA, et al. Altered medial frontal feedback learning signals in anorexia nervosa. Biol Psychiatry. Feb 1 2018;83(3):235–243. doi:10.1016/j.biopsych.2017.07.024 [PubMed: 29025688]
18. Schultz W. Dopamine reward prediction error coding. Dialogues Clin Neurosci. Mar 2016;18(1):23–32. [PubMed: 27069377]
19. O'Doherty JP, Cockburn J, Pauli WM. Learning, reward, and decision making. Annu Rev Psychol. Jan 3 2017;68:73–100. doi:10.1146/annurev-psych-010416-044216 [PubMed: 27687119]
20. Fouragnan E, Queirazza F, Retzler C, Mullinger KJ, Philiastides MG. Spatiotemporal neural characterization of prediction error valence and surprise during reward learning in humans. Sci Rep. Jul 6 2017;7(1):4762. doi:10.1038/s41598-017-04507-w [PubMed: 28684734]
21. D'Ardenne K, Lohrenz T, Bartley KA, Montague PR. Computational heterogeneity in the human mesencephalic dopamine system. Cogn Affect Behav Neurosci. Dec 2013;13(4):747–56. doi:10.3758/s13415-013-0191-5 [PubMed: 23943512]
22. Castro DC, Cole SL, Berridge KC. Lateral hypothalamus, nucleus accumbens, and ventral pallidum roles in eating and hunger: interactions between homeostatic and reward circuitry. Front Syst Neurosci. 2015;9:90. doi:10.3389/fnsys.2015.00090 [PubMed: 26124708]
23. Carr KD. Chronic food restriction: enhancing effects on drug reward and striatal cell signaling. Physiol Behav. Aug 15 2007;91(5):459–72. doi:10.1016/j.physbeh.2006.09.021 [PubMed: 17081571]
24. Johnson PM, Kenny PJ. Dopamine D2 receptors in addiction-like reward dysfunction and compulsive eating in obese rats. Nat Neurosci. May 2010;13(5):635–41. doi:10.1038/nn.2519 [PubMed: 20348917]
25. Volkow ND. Addiction Reviews. Introduction. Ann N Y Acad Sci. Oct 2008;1141:xi–xii. doi:10.1196/annals.1441.034 [PubMed: 18991948]
26. Brooks SJ, Rask-Andersen M, Benedict C, Schioth HB. A debate on current eating disorder diagnoses in light of neurobiological findings: is it time for a spectrum model? BMC Psychiatry. Jul 06 2012;12:76. doi:10.1186/1471-244X-12-76 [PubMed: 22770364]
27. Oinio V, Backstrom P, Uhari-Vaananen J, Raasmaja A, Piepponen P, Kiianmaa K. Dopaminergic modulation of reward-guided decision making in alcohol-preferring AA rats. Behav Brain Res. May 30 2017;326:87–95. doi:10.1016/j.bbr.2017.03.007 [PubMed: 28274654]
28. Carr KD, Tsimberg Y, Berman Y, Yamamoto N. Evidence of increased dopamine receptor signaling in food-restricted rats. Neuroscience. 2003;119(4):1157–67. [PubMed: 12831870]
29. Carr KD, Cabeza de Vaca S, Sun Y, Chau LS. Reward-potentiating effects of D-1 dopamine receptor agonist and AMPAR GluR1 antagonist in nucleus accumbens shell and their modulation by food restriction. Psychopharmacology (Berl). Mar 2009;202(4):731–43. doi:10.1007/s00213-008-1355-9 [PubMed: 18841347]
30. Frank GKW, DeGuzman MC, Shott ME. Motivation to eat and not to eat - The psycho-biological conflict in anorexia nervosa. Physiol Behav. Jul 1 2019;206:185–190. doi:10.1016/j.physbeh.2019.04.007 [PubMed: 30980856]
31. Frank GKW, DeGuzman MC, Shott ME, Laudenslager ML, Rossi B, Pryor T. Association of brain reward learning response with harm avoidance, weight gain, and hypothalamic effective connectivity in adolescent anorexia nervosa. JAMA Psychiatry. Oct 1 2018;75(10):1071–1080. doi:10.1001/jamapsychiatry.2018.2151 [PubMed: 30027213]
32. DeGuzman M, Shott ME, Yang TT, Riederer J, Frank GKW. Association of elevated reward prediction error response with weight gain in adolescent anorexia nervosa. Am J Psychiatry. Jun 01 2017;174(6):557–565. doi:10.1176/appi.ajp.2016.16060671 [PubMed: 28231717]
33. Frank GKW, Favaro A, Marsh R, Ehrlich S, Lawson EA. Toward valid and reliable brain imaging results in eating disorders. Int J Eat Disord. Mar 2018;51(3):250–261. doi:10.1002/eat.22829 [PubMed: 29405338]
34. Lock J, Le Grange D, Agras WS, Moye A, Bryson SW, Jo B. Randomized clinical trial comparing family-based treatment with adolescent-focused individual therapy for adolescents with anorexia nervosa. Arch Gen Psychiatry. Oct 2010;67(10):1025–32. doi:10.1001/archgenpsychiatry.2010.128 [PubMed: 20921118]

35. Sheehan DV, Sheehan KH, Shytle RD, et al. Reliability and validity of the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID). J Clin Psychiatry. Mar 2010;71(3):313–26. doi:10.4088/JCP.09m05305whi [PubMed: 20331933]
36. Cumella E. Review of the Eating Disorder Inventory-3. Journal of Personality Assessment. 2006;81(1):116–117.
37. Garner D. Eating Disorder Inventory™-3 (EDI™-3). Psychological Assessment Resources, Inc.; 2004.
38. Cloninger CR, Przybeck TR, Svrakic DM, Wetzel RD. The Temperament and Character Inventory (TCI): A Guide to its Development and Use. St. Louis, MO: Center for Psychobiology of Personality, Washington University; 1994.
39. Spielberger CD. Manual for the State-Trate Anxiety Inventory. Consulting Psychologists Press, Inc.; 1983.
40. Kovacs M. The Children's Depression, Inventory (CDI). Psychopharmacol Bull. 1985;21(4):995–8. [PubMed: 4089116]
41. Frank G, Kaye W, Carter C, et al. The evaluation of brain activity in response to taste stimuli--a pilot study and method for central taste activation as assessed by event related fMRI. J Neurosci Methods. 2003;131(1-2):99–105. [PubMed: 14659829]
42. Frank GK, Reynolds JR, Shott ME, et al. Anorexia nervosa and obesity are associated with opposite brain reward response. Neuropsychopharmacology. Aug 2012;37(9):2031–46. doi:10.1038/npp.2012.51 [PubMed: 22549118]
43. O'Doherty JP, Dayan P, Friston K, Critchley H, Dolan RJ. Temporal difference models and reward-related learning in the human brain. Neuron. Apr 24 2003;38(2):329–37. [PubMed: 12718865]
44. O'Doherty JP, Hampton A, Kim H. Model-based fMRI and its application to reward learning and decision making. Ann N Y Acad Sci. May 2007;1104:35–53. doi:10.1196/annals.1390.022 [PubMed: 17416921]
45. Tzourio-Mazoyer N, Landeau B, Papathanassiou D, et al. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage. 2002;15:273–289. [PubMed: 11771995]
46. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Statist Soc B. 1995;57(289–300)
47. Volkow ND, Wang GJ, Fowler JS, Telang F. Overlapping neuronal circuits in addiction and obesity: evidence of systems pathology. Philos Trans R Soc Lond B Biol Sci. Oct 12 2008;363(1507):3191–200. doi:10.1098/rstb.2008.0107 [PubMed: 18640912]
48. Kaye WH, Frank GK, McConaha C. Altered dopamine activity after recovery from restricting-type anorexia nervosa. Neuropsychopharmacology. Oct 1999;21(4):503–6. doi:10.1016/S0893-133X(99)00053-6 [PubMed: 10481833]
49. Broft A, Slifstein M, Osborne J, et al. Striatal dopamine type 2 receptor availability in anorexia nervosa. Psychiatry Res. Sep 30 2015;233(3):380–7. doi:10.1016/j.pscychresns.2015.06.013 [PubMed: 26272038]
50. Frank GK, Bailer UF, Henry SE, et al. Increased dopamine D2/D3 receptor binding after recovery from anorexia nervosa measured by positron emission tomography and [11c]raclopride. Biol Psychiatry. Dec 01 2005;58(11):908–12. doi:10.1016/j.biopsych.2005.05.003 [PubMed: 15992780]
51. Kinnaird E, Stewart C, Tchanturia K. Taste sensitivity in anorexia nervosa: A systematic review. Int J Eat Disord. Aug 2018;51(8):771–784. doi:10.1002/eat.22886 [PubMed: 29984498]
52. Tan SY, Tucker RM. Sweet Taste as a Predictor of Dietary Intake: A Systematic Review. Nutrients. Jan 5 2019;11(1)doi:10.3390/nu11010094

Public Significance Statement

Anorexia nervosa is a severe psychiatric illness. Biological factors that integrate neurobiology and behavior could become important targets to improve treatment outcome. This study highlights the importance of weight normalization and taste perception on the normalization of brain function, and food type or taste specific interventions could help in the recovery process. Furthermore, the study suggests that food and non-food related reward processing adapts to illness state in anorexia nervosa.

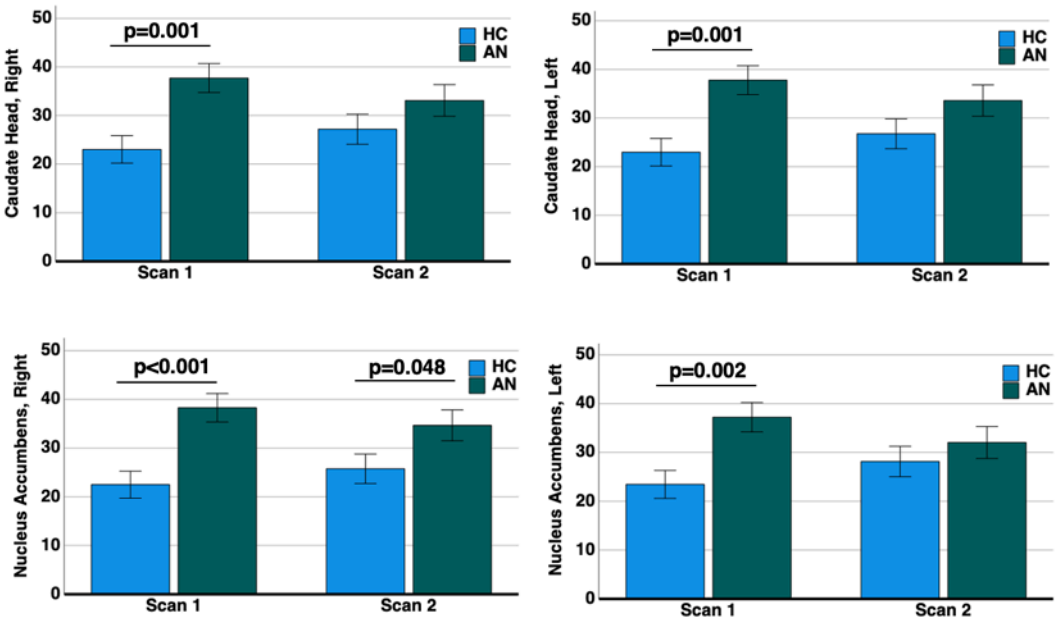

Figure 1.

Bar graphs for the group by condition analysis of prediction error brain response across groups for caudate head and nucleus accumbens (rank transformed data).

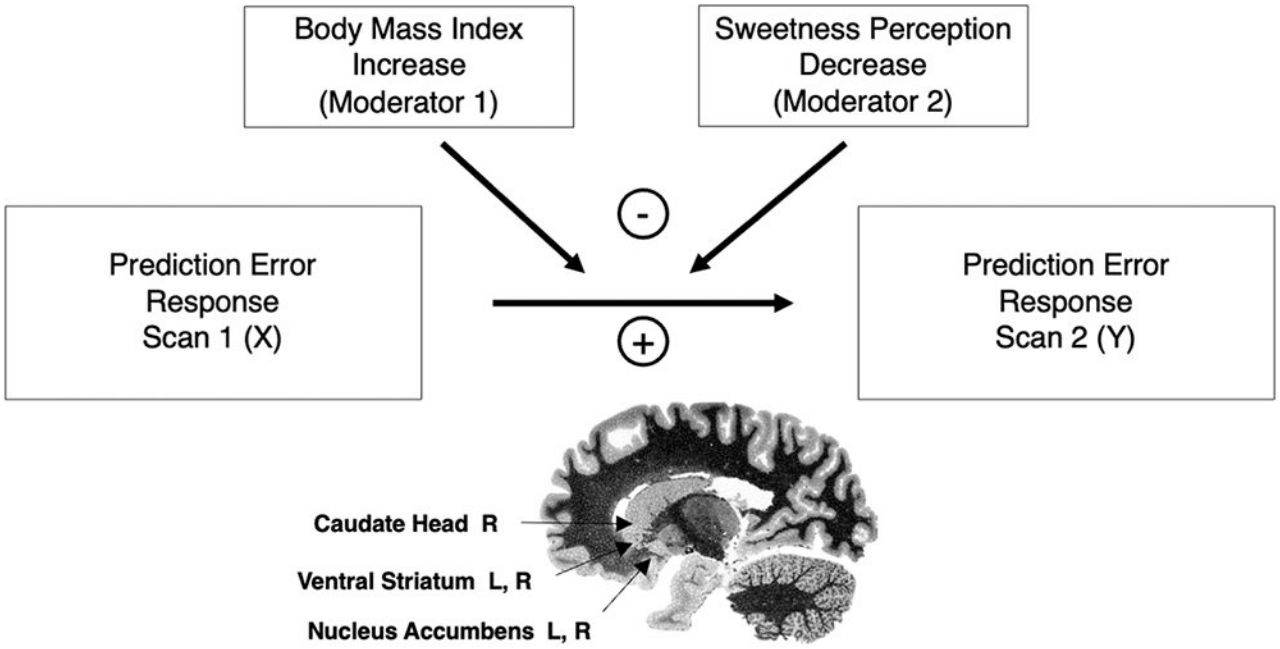

Figure 2.

BMI increase and sweetness perception decrease are independent moderators of change in brain response from scan one to two.

Table 1.

Demographic and behavior data at scan times one and two across study groups. HC: healthy control; AN: anorexia nervosa, restricting subtype; BMI: body mass index; MDD: major depressive disorder; OCD: obsessive compulsive disorder; [a] Temperament and Character Inventory; [b] Beck Depression Inventory – 2; [c] Eating Disorders Inventory; [d] State-Trait Anxiety Inventory; *p < 0.05, **p < 0.01, ***p < 0.001, indicates significant change from scan one to scan two (paired samples t-test).

	Scan 1						Scan 2					
	HC (n = 31)		AN (n = 28)				HC (n = 31)		AN (n = 28)			
	Mean	SD	Mean	SD	t	p	Mean	SD	Mean	SD	t	p
Age (years)	15.78	2.89	16.11	2.43	−0.47	0.320	15.92***	2.87	16.22***	2.44	−0.43	0.335
BMI (kg/m^2)	20.96	2.25	15.99	0.96	11.18	<0.001	21.24**	2.37	18.13***	1.40	6.20	<0.001
Age-adjusted BMI percentile	60.48	23.46	3.56	3.52	12.46	<0.001	61.34	23.94	22.54***	14.95	7.07	<0.001
Novelty seeking[a]	20.65	5.94	16.04	6.30	2.88	0.003	21.32	5.99	16.86	7.60	2.52	0.007
Harm avoidance[a]	11.74	4.94	22.04	7.84	−5.96	<0.001	11.77	5.31	22.14	7.27	−6.30	<0.001
Depression[b]	3.33	2.93	16.15	9.12	−6.87	<0.001	3.63	6.76	15.33	10.51	−4.94	<0.001
Drive for thinness[c]	2.06	2.82	19.61	7.84	−11.21	<0.001	2.10	2.84	17.75***	8.79	−9.01	<0.001
Bulimia[c]	1.35	2.01	2.21	3.73	−1.09	0.142	1.19	1.64	1.32	2.63	−0.23	0.411
Body dissatisfaction[c]	3.48	3.75	24.50	10.38	−10.13	<0.001	3.52	4.47	25.18	11.90	−9.08	<0.001
State anxiety[d]	27.68	6.34	47.82	15.07	−6.57	<0.001	28.71	9.79	46.79	12.16	−6.32	<0.001
Trait anxiety[d]	29.23	7.59	50.29	15.98	−6.36	<0.001	28.65	5.65	50.14	12.43	−8.40	<0.001
Sucrose pleasantness	5.13	2.45	4.46	2.20	1.09	0.140	4.65	2.74	4.36	2.11	0.46	0.326
Sucrose sweetness	7.94	1.09	7.61	1.34	1.03	0.153	7.61	1.05	6.75*	1.58	2.44	0.009
Breakfast calories (kcal)	603.4	146.5	632.5	141.7	−0.77	0.221	607.8	152.4	586.2	187.1	0.49	0.314
BMI change							0.28	0.46	2.14	1.03	−8.81	<0.001
Age-adjusted BMI percentile change							0.86	3.31	18.98	12.88	−6.83	<0.001
	N	%	N	%			N	%	N	%		
Oral contraceptive use	6	19.4	3	10.7			6	19.4	3	10.7		
Antidepressant use	0	0.0	16	57.1			0	0.0	20	71.4		
Antipsychotic use	0	0.0	4	14.3			0	0.0	5	17.9		
MDD	0	0.0	7	25.0								
OCD	0	0.0	7	25.0								

	Scan 1						Scan 2					
	HC (n = 31)		AN (n = 28)				HC (n = 31)		AN (n = 28)			
	Mean	SD	Mean	SD	t	p	Mean	SD	Mean	SD	t	p
Anxiety Disorder	0	0.0	17	60.7								

Table 2.

Repeated measures analysis of covariance on prediction error response across scans one and two with significant group effect (Wilk's lambda=0.589, F=1.957, p=0.044, partial η2=0.411, power=0.880, estimated marginal means, rank transformed, including scanner as covariate).

	Scan 1								Scan 2							
	HC (n = 31)		AN (n = 28)						HC (n = 31)		AN (n = 28)					
	Mean	SE	Mean	SE	Effect Size (η2)	Power	F	p	Mean	SE	Mean	SE	Effect Size (η2)	Power	F	p
Caudate Head, Right	23.04	2.83	37.71	2.98	0.19	0.94	12.73	<0.001	27.20	3.09	33.11	3.25	0.03	0.25	1.73	0.193
Caudate Head, Left	22.98	2.83	37.78	2.97	0.19	0.94	13.02	<0.001	26.76	3.07	33.59	3.23	0.04	0.33	2.35	0.131
Ventral Striatum, Right	25.57	2.99	34.90	3.14	0.08	0.56	4.63	0.036	29.79	3.14	30.24	3.30	0.00	0.05	0.01	0.922
Ventral Striatum, Left	26.38	3.02	34.01	3.18	0.05	0.40	3.03	0.087	29.94	3.14	30.07	3.30	0.00	0.05	0.00	0.978
Nucleus Accumbens, Right	22.50	2.78	38.30	2.92	0.22	0.97	15.35	<0.001	25.77	3.03	34.68	3.19	0.07	0.51	4.10	0.048
Nucleus Accumbens, Left	23.46	2.86	37.24	3.01	0.16	0.90	11.00	0.002	28.15	3.11	32.05	3.27	0.01	0.14	0.75	0.391
Inferior Orbitofrontal Cortex, Right	27.08	3.04	33.23	3.20	0.03	0.28	1.94	0.169	30.68	3.11	29.25	3.27	0.00	0.06	0.10	0.753
Inferior Orbitofrontal Cortex, Left	28.56	3.06	31.60	3.21	0.01	0.10	0.47	0.496	30.10	3.06	29.89	3.22	0.00	0.05	0.00	0.961
Medial Orbitofrontal Cortex, Right	30.82	3.13	29.09	3.29	0.00	0.07	0.15	0.704	29.32	3.14	30.76	3.30	0.00	0.06	0.10	0.753
Medial Orbitofrontal Cortex, Left	28.88	3.12	31.24	3.28	0.01	0.08	0.27	0.605	29.39	3.12	30.68	3.28	0.00	0.06	0.08	0.777
Middle Orbitofrontal Cortex, Right	27.98	3.10	32.24	3.27	0.02	0.15	0.90	0.348	29.49	3.06	30.57	3.21	0.00	0.06	0.06	0.809
Middle Orbitofrontal Cortex, Left	29.16	3.11	30.93	3.27	0.00	0.07	0.15	0.696	29.45	3.11	30.61	3.28	0.00	0.06	0.07	0.799
Dorsal Anterior Insula, Right	28.16	2.89	32.04	3.04	0.02	0.15	0.85	0.360	29.65	3.06	30.39	3.22	0.00	0.05	0.03	0.869
Dorsal Anterior Insula, Left	29.22	3.00	30.87	3.16	0.00	0.07	0.14	0.706	27.17	3.01	33.14	3.17	0.03	0.27	1.86	0.178
Ventral Anterior Insula, Right	27.13	2.99	33.18	3.15	0.03	0.28	1.94	0.170	28.53	3.12	31.63	3.28	0.01	0.10	0.47	0.497
Ventral Anterior Insula, Left	29.24	2.99	30.84	3.15	0.00	0.07	0.14	0.715	28.70	2.99	31.44	3.15	0.01	0.10	0.40	0.530

Table 3.

Moderator analysis in adolescents and young adults with anorexia nervosa for the effects of change of BMI and sweetness perception on the change of prediction error response from scan one to two. Regional prediction error at scan two (PE scan two) was predicted by regional prediction error at scan one (PE scan one), body mass index (BMI) change, sweetness perception (Sweet) change, and BMI and sweetness perception change were tested for their interaction on prediction error response between scan one and two. In addition, the interaction for BMI and sweetness perception combined was tested; coefficient, Coeff.; standard error, SE.

	Model Summary			Model Coefficients							Test of highest order unconditional interaction			
Region	**R^2**	**F**	**P**		**coeff**	**se**	**t**	**p**	**LLCI**	**ULCI**	**R^2-change**	**F**	**p**	**q**
Caudate Head, Right [PE Scan 2]	0.56	4.37	0.005	**[PE Scan 1]**	1.36	0.34	3.99	<0.001	0.65	2.06				
				BMI Change	1.87	0.69	2.71	0.013	0.44	3.30				
				BMI Change Interaction	−0.03	0.02	−1.53	0.142	−0.07	0.01				
				Sweet Change	0.62	0.35	1.80	0.087	−0.10	1.35				
				Sweet Change Interaction	−0.02	0.01	−2.15	0.044	−0.04	0.00				
				BMI + Sweet Change Int.							0.21	4.84	**0.0187**	**0.0281**
Caudate Head, Left [PE Scan 2]	0.39	2.24	0.080	**[PE Scan 1]**	0.83	0.40	2.09	0.049	0.01	1.66				
				BMI Change	0.97	0.85	1.13	0.269	−0.81	2.75				
				BMI Change Interaction	−0.02	0.02	−0.71	0.488	−0.07	0.03				
				Sweet Change	−0.03	0.38	−0.07	0.945	−0.81	0.76				
				Sweet Change Interaction	−0.01	0.01	−0.67	0.512	−0.03	0.01				
				BMI + Sweet Change Int.							0.03	0.53	0.5968	0.5968
Ventral Striatum, Right [PE Scan 2]	0.49	3.31	0.019	**[PE Scan 1]**	1.42	0.36	3.93	<0.001	0.67	2.17				
				BMI Change	1.69	0.65	2.61	0.017	0.34	3.04				
				BMI Change Interaction	−0.04	0.02	−2.29	0.032	−0.08	0.00				
				Sweet Change	0.61	0.35	1.76	0.093	−0.11	1.34				
				Sweet Change Interaction	−0.02	0.01	−1.83	0.081	−0.04	0.00				
				BMI + Sweet Change Int.							0.27	5.51	**0.0119**	**0.0238**
Ventral Striatum, Left [PE Scan 2]	0.53	3.97	0.008	**[PE Scan 1]**	1.39	0.32	4.38	<0.001	0.73	2.05				
				BMI Change	1.46	0.58	2.51	0.020	0.25	2.66				
				BMI Change Interaction	−0.03	0.02	−1.79	0.088	−0.07	0.01				
				Sweet Change	0.68	0.32	2.13	0.045	0.02	1.34				
				Sweet Change Interaction	−0.02	0.01	−2.45	0.023	−0.04	0.00				

Region	Model Summary			Model Coefficients							Test of highest order unconditional interaction			
	R^2	F	P		coeff	se	t	p	LLCI	ULCI	R^2-change	F	p	q
Nucleus Accumbens, Right [PE Scan 2]	0.60	5.28	0.002	**BMI + Sweet Change Int.**							0.27	6.15	**0.0079**	**0.0237**
				[PE Scan 1]	1.28	0.31	4.14	<0.001	0.64	1.93				
				BMI Change	2.19	0.57	3.84	0.001	1.00	3.38				
				BMI Change Interaction	−0.04	0.02	−2.57	0.018	−0.07	−0.01				
				Sweet Change	0.53	0.31	1.70	0.104	−0.12	1.17				
				Sweet Change Interaction	−0.02	0.01	−1.96	0.064	−0.03	0.00				
Nucleus Accumbens, Left [PE Scan 2]	0.53	3.94	0.009	**BMI + Sweet Change Int.**							0.27	7.14	**0.0043**	**0.0258**
				[PE Scan 1]	1.24	0.37	3.37	0.003	0.48	2.01				
				BMI Change	1.46	0.70	2.08	0.050	0.00	2.93				
				BMI Change Interaction	−0.02	0.02	−0.98	0.340	−0.06	0.02				
				Sweet Change	0.63	0.38	1.65	0.113	−0.16	1.41				
				Sweet Change Interaction	−0.02	0.01	−2.40	0.026	−0.04	0.00				
				BMI + Sweet Change Int.							0.17	3.73	**0.0410**	**0.0492**