Eating disorders are severe psychiatric disorders; however, disease models that cross subtypes and integrate behavior and neurobiologic factors are lacking.

OBJECTIVE To assess brain response during unexpected receipt or omission of a salient sweet stimulus across a large sample of individuals with eating disorders and healthy controls and test for evidence of whether this brain response is associated with the ventral striatal-hypothalamic circuitry, which has been associated with food intake control, and whether salient stimulus response and eating disorder related behaviors are associated.

DESIGN, SETTING, AND PARTICIPANTS In this cross-sectional functional brain imaging study, young adults across the eating disorder spectrum were matched with healthy controls at a university brain imaging facility and eating disorder treatment program. During a sucrose taste classic conditioning paradigm, violations of learned associations between conditioned visual and unconditioned taste stimuli evoked the dopamine-related prediction error. Dynamic effective connectivity during expected sweet taste receipt was studied to investigate hierarchical brain activation between food intake relevant brain regions. The study was conducted from June 2014 to November 2019. Data were analyzed from December 2019 to February 2020.

MAIN OUTCOMES AND MEASURES Prediction error brain reward response across insula and striatum; dynamic effective connectivity between hypothalamus and ventral striatum; and demographic and behavior variables and their correlations with prediction error brain response and connectivity edge coefficients.

RESULTS Of 317 female participants (197 with eating disorders and 120 healthy controls), the mean (SD) age was 23.8 (5.6) years and mean (SD) body mass index was 20.8 (5.4). Prediction error response was elevated in participants with anorexia nervosa (Wilks λ, 0.843; P = .001) and in participants with eating disorders inversely correlated with body mass index (left nucleus accumbens: r = −0.291; 95% CI, −0.413 to −0.167; P < .001; right dorsal anterior insula: r = −0.228; 95% CI, −0.366 to −0.089; P = .001), eating disorder inventory–3 binge eating tendency (left nucleus accumbens: r = −0.207; 95% CI, −0.333 to −0.073; P = .004; right dorsal anterior insula: r = −0.220; 95% CI, −0.354 to −0.073; P = .002), and trait anxiety (left nucleus accumbens: r = −0.148; 95% CI, −0.288 to −0.003; P = .04; right dorsal anterior insula: r = −0.221; 95% CI, −0.357 to −0.076; P = .002). Ventral striatal to hypothalamic directed connectivity was positively correlated with ventral striatal prediction error in eating disorders (r = 0.189; 95% CI, 0.045–0.324; P = .01) and negatively correlated with feeling out of control after eating (right side: r = −0.328; 95% CI, −0.480 to −0.164; P < .001; left side: r = −0.297; 95% CI, −0.439 to −0.142; P = .001).

CONCLUSIONS AND RELEVANCE The results of this cross-sectional imaging study support that body mass index modulates prediction error and food intake control circuitry in the brain. Once altered, this circuitry may reinforce eating disorder behaviors when paired with behavioral traits associated with overeating or undereating.
Eating disorders are severe psychiatric disorders with high mortality.\(^1\) Anorexia nervosa (AN) is characterized by severe underweight with intermittent binge eating or purging episodes; individuals with bulimia nervosa (BN) are at normal to high weight and regularly binge and purge. Binge-eating disorder (BED) is associated with binge-eating episodes and frequently elevated body weight.\(^2\) Eating disorders that do not meet full criteria for those diagnoses have been recognized as specific subgroups within the other specified feeding and eating disorders (OSFED) category of the DSM-5. Food restriction, episodic binge eating, or purging vary across the diagnostic groups, whereas body dissatisfaction and drive for thinness are typically elevated across all eating disorders, as are anxious traits and sensitivity to salient stimuli. Identifying how those behaviors are associated with particular biologic mechanisms could help create a better understanding of the underlying eating disorder pathophysiologic factors and development of specific treatments.\(^3\) To adopt a dimensional conceptualization of eating disorder specific behaviors and neurobiologic factors, we recruited individuals across the eating disorder spectrum and applied the prediction error construct from the National Institute of Mental Health Research Domain Criteria (RDoC) project.\(^4\)

Brain reward circuits have been repeatedly implicated in eating disorders, and altered reward learning may play a particularly important role.\(^5\) In reward learning, the difference between an expectation and outcome yields a prediction error, a dopamine-associated signal that reinforces new associations.\(^6,7\) The direction of the prediction error is indicated by its sign, which indicates a better (positive) or worse (negative) outcome than expected. The absolute value reflects the degree of deviation from the outcome of the expected and is related to surprise or conceptualized as a motivational salience signal.\(^8,9\) The dopamine system adapts in opposite directions to extremes of food intake.\(^10-13\) Food restriction enhances dopamine circuit activity\(^14,15\) and excessive food intake downregulates dopamine circuit activity,\(^12\) which could be relevant for eating disorder pathophysiologic factors.\(^16-19\) Studies in AN found elevated prediction error response to taste and monetary stimuli compared with healthy controls but a lower response in small studies in individuals with BN and individuals with overweight.\(^20-23\) Those studies suggested that the prediction error signal is inversely correlated with eating disorder behaviors from restrictive to loss of control food intake (binge eating).\(^24\) Furthermore, prediction error response was positively correlated in adolescent AN with ventral striatum-hypothalamus directed effective connectivity, a circuitry that has been associated with food intake control.\(^23\)

For consistency with the RDoC approach, we studied a large group of individuals with eating disorders, varying on a spectrum of restrictive undereating to loss-of-control overeating. To validate previous results, we also recruited a healthy control group. First, we hypothesized that we would find inverse correlations between prediction error response and eating disorder behavior from undereating to overeating, as reflected in body mass index (BMI) and binge eating severity. This hypothesis would support basic and translational science research by externally validating a core behavioral dimension via its associations with reward-responsiveness. Second, we hypothesized that effective connectivity would be directed from the ventral striatum to the hypothalamus in the eating disorder sample. This hypothesis would support a potential trait mechanism across eating disorders to attempt to control eating drive.\(^21\) Third, we hypothesized that associations between biological and behavioral data may help develop a model to explain how traits, eating disorder behaviors, and neurobiologic factors interact and reinforce the often chronic nature of eating disorders.\(^25\)

### Methods

#### Participants

The Colorado Multiple institutional review board approved the study. All participants provided written informed consent. We recruited 197 women with an eating disorder: 69 AN restricting subtype, 22 AN binge-eating/purging subtype, 17 OSFED atypical AN subtype, 17 OSFED purging disorder subtype, 56 BN, 3 OSFED binge-eating subtype, and 13 binge eating disorder (BED). Participants with eating disorders were recruited from eating disorder partial hospitalization specialty care (EDCare Denver or Children's Hospital Colorado) within the first 2 weeks of treatment, to mitigate effects of acute starvation or dehydration.\(^26\) Following RDoC instructions, we recruited any interested patient with eating disorders who was admitted to treatment. In addition, we recruited 120 women as healthy controls (HCs) through local advertisements. The study was conducted from June 2014 to November 2019. Data were analyzed from December 2019 to February 2020. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cross-sectional studies.

Participants were right-handed without history of head trauma, neurological disease, major medical illness, bipolar disorder, psychosis, or current (past 3 months) substance use disorder. The healthy controls were studied during the first 10 days of the menstrual cycle to reduce potential hormonal
variations. For eating disorders, treatment stage was the primary variable we controlled for, but we recorded days from last menstrual cycle as a proxy to test for hormonal variation.

Assessments
Psychiatric diagnoses were assessed using the Structured Clinical Interview for DSM-5 by a doctoral-level interviewer. Participants completed the Eating Disorder Inventory-3 (EDI-3) for drive for thinness (intense fear of weight gain), bulimia (tendency to engage in binge eating), body dissatisfaction (discontentment with size of body regions), Revised Sensitivity to Punishment and Reward Questionnaire, State-Trait Depression Inventory-II; participants blindly rated sugar solutions for sweetness and pleasantness using a 9-point Likert scale. A subset of participants (eating disorder, n = 128, HC, n = 84) completed the Eating Expectancy Inventory for eating leads to feeling out of control.

Brain Imaging Methods
Functional Magnetic Resonance Imaging
Between 7:00 AM and 9:00 AM on the study day, participants with eating disorders ate their meal-plan breakfast and HC ate a quality-matched and calorie-matched breakfast (Table 1). Brain imaging was performed between 8:00 AM and 9:00 AM using the 3-T Signa (General Electric Company) or Skyra 3-T scanner (Siemens) (eMethods 1 in the Supplement). A scanner covariate was included in the multivariate analysis of covariance model for group contrast.

Taste Reward Task
The design of this study was adapted from O’Doherty et al (eMethods 2 and eFigure 2 in the Supplement). Participants learned to associate 3 unconditioned taste stimuli (1 molar sucrose solution, no solution, or artificial saliva) with paired conditioned visual stimuli. Each conditioned visual stimulus was probabilistically associated with its unconditioned taste stimulus such that 20% of sucrose and no solution conditioned visual stimuli trials were unexpectedly followed by no solution or sucrose unconditioned taste stimuli, respectively.

Functional Magnetic Resonance Imaging Analysis
Image preprocessing and analysis were performed using Statistical Parametric Mapping, version 12 (Wellcome Trust Centre for Neuroimaging). Images were realigned to the first volume, normalized to the Montreal Neurological Institute template, smoothed at 6-mm full width at half maximum gaussian kernel. 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 blood oxygen level dependent signal fluctuations), motion parameters (as first-level analysis regressors), and the SPM FAST (prewhitening attenuation of autocorrelation effects) were applied.

Prediction Error Analysis
Each participant’s prediction error signal was modeled based on trial sequence (absolute of positive and negative prediction error) and regressed with brain activation across all trials (eMethods 3 in the Supplement). We extracted mean parameter estimates across all voxels from 5 predefined anatomical regions of interest (ROIs) bilaterally, based on ROIs that differentiated groups previously: bilateral dorsal anterior insula (automated anatomical labeling Atlas), ventral anterior insula, caudate head, ventral striatum, and nucleus accumbens.

Effective Connectivity Analysis
We extracted ROI functional activation for trials of expected receipt of 1 molar sucrose solution (n = 80). The Tetrad-V was used to infer effective connectivity with independent multilsample greedy equivalence search and linear non-gaussian orientation, fixed structure search algorithms. We extracted edge coefficients for ventral striatum-hypothalamus (hypothalamus ROI, SPM12 WFU PickAtlas extension) connectivity to test for correlations with behavior or PE values based on our previous studies (eMethods 4 in the Supplement).

Statistical Analysis
Statistical analysis was performed with SPSS 27 software (IBM). Data were tested for normality with Shapiro-Wilk test and ranked and normalized using Rankit procedure if nonnormally distributed. Demographic and behavior data were analyzed using analysis of variance, and post hoc analyses were Bonferroni corrected. Multivariate analysis of covariance and correlation analyses were used to test effect sizes of potential confounding categorical or continuous variables such as comorbidity, medication use, or age. Variables associated with the primary outcome variable brain response were included in a group-comparison multivariate analysis of covariance and estimated marginal means post hoc comparisons Bonferroni corrected. Partial n2 was calculated for effect size in addition to power calculations. Pearson correlation analysis was used to test associations between behavior and brain activation, CIs were calculated using bootstrap (10000 samples) and results were multiple comparisons controlled using false discovery rate. All P values were 2-tailed, and a P value less than .05 was considered statistically significant.

Results
Demographic and Behavioral Variables
Of 317 female participants (197 with eating disorders and 120 healthy controls), the mean (SD) age was 23.8 (5.6) years and mean (SD) BMI (calculated as weight in kilograms divided by height in meters squared) was 20.8 (5.4). eTable 1 in the Supplement provides demographic and behavioral data for all groups. To increase power for comparison with HC, we combined restrictive and binge-eating/purging AN subgroups (AN, severe food restriction), OSFED atypical AN and purging disorder subgroups (OSFEDr, intermediate restrictive eating, normal BMI), and OSFED binge-eating and BED

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Table 1. Participant Demographic and Behavioral Characteristics

| Variable                          | Mean (SD) | HC (n = 120) | AN (n = 91) | OSFEDr (n = 34) | BN (n = 56) | BED (n = 16) | MANOVA analysis |
|----------------------------------|-----------|--------------|-------------|----------------|-------------|--------------|----------------|
|                                  |           |              |             |                |             |              | Partial η²     | F          | P value   | Post hoc differences |
| Age, y                           |           | 25.15 (4.95) | 21.85 (5.82) | 22.10 (5.92)   | 23.52 (4.65) | 28.60 (7.39) | 0.104          | F = 9.1    | <0.001    | HC, BED>AN (P < .01); HC>OSFEDr (P < .05); BED>OSFEDr (P < .01); BED>BN (P < .05) |
| BMI                              |           | 21.49 (1.64) | 16.39 (1.05) | 20.66 (3.09)   | 23.21 (7.06) | 32.92 (9.52) | 0.672          | F = 159.5   | <0.001    | HC, OSFEDr, BN, BED>AN (P < .01); BN>OSFEDr (P < .01); BED>HC, OSFEDr, BN (P < .001) |
| High lifetime BMI                |           | 22.40 (1.92) | 20.83 (2.27) | 25.27 (5.35)   | 27.32 (8.56) | 34.84 (10.59) | 0.362          | F = 41.6    | <0.001    | HC, OSFEDr, BN, BED>AN (P < .01); BED>HC, OSFEDr (P < .001); BED>BN (P < .01); BED>HC (P < .001) |
| Low lifetime BMI                 |           | 19.94 (1.54) | 14.78 (1.62) | 17.49 (3.37)   | 18.75 (4.22) | 24.05 (6.82) | 0.517          | F = 77.7    | <0.001    | HC, OSFEDr, BN, BED>AN (P < .01); HC, BED>OSFEDr, BN (P < .001); BN, BED>HC (P < .001) |
| Novelty seeking                  |           | 18.91 (5.54) | 15.52 (6.53) | 16.53 (5.75)   | 18.89 (6.81) | 20.75 (3.61) | 0.076          | F = 6.4     | <0.001    | HC>AN (P < .01); BN>AN (P < .01); BED>AN (P < .02) |
| Harm avoidance                   |           | 10.74 (5.23) | 21.85 (7.63) | 23.94 (6.86)   | 23.96 (6.49) | 17.56 (7.23) | 0.402          | F = 52.5    | <0.001    | AN, OSFEDr, BN>HC (P < .01); BED>HC (P < .01); OSFEDr, BN>BED (P < .05) |
| Depression                       |           | 1.64 (2.07)  | 27.65 (11.81) | 32.27 (11.90)  | 28.75 (11.36) | 17.00 (12.33) | 0.634          | F = 128.2   | <0.001    | AN, OSFEDr, BN, BED>HC (P < .01); AN, BN+BED (P < .01); OSFEDr>BED (P < .001) |
| Drive for thinness               |           | 1.98 (2.96)  | 19.07 (7.44) | 21.73 (6.77)   | 22.05 (5.38) | 18.44 (6.74) | 0.611          | F = 121.6   | <0.001    | AN, OSFEDr, BN, BED>HC (P < .01) |
| Bulimia                          |           | 0.76 (1.03)  | 5.59 (7.09)  | 7.18 (6.91)    | 18.18 (7.68) | 19.44 (7.33) | 0.548          | F = 93.9    | <0.001    | AN, OSFEDr, BN, BED>HC (P < .01); BN, BED>AN, OSFEDr (P < .001) |
| Body dissatisfaction             |           | 4.22 (4.96)  | 24.72 (10.27) | 31.61 (9.03)   | 29.98 (9.04) | 27.50 (7.91) | 0.602          | F = 116.3   | <0.001    | AN, OSFEDr, BN, BED>HC (P < .01); OSFEDr>AN (P < .01); BN+BED (P < .05) |
| Intolerance of uncertainty      |           | 48.92 (11.78) | 83.76 (18.87) | 82.79 (24.39)  | 87.66 (22.13) | 72.75 (20.99) | 0.427          | F = 58.0    | <0.001    | AN, OSFEDr, BN, BED>HC (P < .01) |
| Reward sensitivity               |           | 5.07 (3.35)  | 7.19 (4.02)  | 7.48 (2.51)    | 8.11 (3.52)  | 8.50 (3.27)  | 0.129          | F = 11.5    | <0.001    | AN, BN+HC (P < .01); OSFEDr, BED>HC (P < .01) |
| Punishment sensitivity           |           | 4.75 (3.29)  | 12.21 (4.41) | 13.03 (4.43)   | 13.32 (3.70) | 10.31 (4.22) | 0.437          | F = 60.4    | <0.001    | AN, OSFEDr, BN, BED>HC (P < .01) |
| State anxiety                    |           | 25.95 (6.35) | 55.16 (12.35) | 58.38 (12.75)  | 55.46 (13.08) | 42.20 (14.83) | 0.565          | F = 100.9   | <0.001    | AN, OSFEDr, BN, BED>HC (P < .01); AN, BN+BED (P < .05); OSFEDr>BED (P < .01) |
| Trait anxiety                    |           | 27.35 (5.65) | 56.20 (11.97) | 59.29 (11.26)  | 61.05 (11.27) | 46.31 (13.80) | 0.576          | F = 105.4   | <0.001    | AN, OSFEDr, BN, BED>HC (P < .01); OSFEDr>BED (P < .01); OSFEDr>BN+BED (P < .01) |
| Eating leads to feeling out of control | 5.19 (2.41) | 19.14 (5.79) | 22.30 (5.20) | 24.05 (4.19) | 23.14 (3.89) | 0.689 | F = 114.8 | <0.001 | AN, OSFEDr, BN, BED>HC (P < .01); OSFEDr>AN (P < .05); BN+AN (P < .001) |
| Sucrose pleasantness             |           | 5.01 (2.27)  | 4.23 (2.44)  | 3.50 (2.14)    | 4.54 (2.60)  | 5.44 (2.61)  | 0.046          | F = 4.2     | .003      | HC(OSFEDr) (P < .01); BED(OSFEDr) (P < .05) |
| Sucrose sweetness                |           | 7.98 (0.87)  | 8.19 (0.98)  | 7.56 (1.46)    | 8.29 (0.89)  | 8.19 (0.98)  | 0.044          | F = 3.2     | .01       | AN, BN<OSFEDr (P < .05) |
| Binge frequency (weekly)         |           | 0            | 1.80 (7.26)  | 0.25 (1.09)    | 14.50 (15.69) | 4.38 (2.51)  | 0.615          | F = 96.5    | <0.001    | BN>HC, AN, OSFEDr; BED (P < .001) |
| Purge frequency (weekly)         |           | 0            | 3.05 (10.22) | 3.67 (6.28)    | 16.02 (17.27) | 0            | 0.426          | F = 43.4    | <0.001    | BN>HC, AN, OSFEDr, BED (P < .001) |
| Breakfast calories, kcal         |           | 605 (133)    | 584 (153)    | 605 (180)      | 596 (185)    | 623 (112)    | 0.005          | F = 0.4     | .80       | NA |

(continued)
Table 1. Participant Demographic and Behavioral Characteristics (continued)

| Variable                                      | HC (n = 120) | AN (n = 91) | OSFEDr (n = 34) | BN (n = 56) | BED (n = 16) | Partial η² Statistic | P value | Posthoc differences |
|-----------------------------------------------|--------------|-------------|------------------|-------------|--------------|----------------------|---------|---------------------|
| Antidepressant use, No. (%)                   | 0            | 24 (70.6)   | 33 (58.9)        | 7 (43.8)    | NA           | χ² = 6.1 .10          |         | NA                  |
| Antipsychotic use, No. (%)                    | 0            | 6 (17.6)    | 7 (12.5)         | 0           | NA           | χ² = 3.3 .35          |         | NA                  |
| OCD, No. (%)                                  | 0            | 8 (23.5)    | 8 (14.3)         | 2 (12.5)    | NA           | χ² = 3.2 .36          |         | NA                  |
| PTSD, No. (%)                                 | 0            | 12 (35.3)   | 19 (33.9)        | 4 (25.0)    | NA           | χ² = 5.8 .12          |         | NA                  |
| Anxiety disorder, No. (%)                     | 0            | 21 (61.8)   | 42 (75.0)        | 6 (37.5)    | NA           | χ² = 7.9 .047         |         | NA                  |

Eating Disorder Inventory-3. (EDI-3 drive for thinness was significant for AN vs HC, BN and BED; harm avoidance, depression, drive for thinness, body dissatisfaction, bulimia, eating leads to feeling out of control, intolerance of uncertainty, reward and punishment sensitivity, and state and trait anxiety were higher in eating disorder groups vs HC. Sucrose pleasantness was lower in OSFEDr vs HC and AN. Frequency of weekly binge eating and purging episodes was higher in BN vs remaining groups. Breakfast calories were similar across groups.

Correlations between behavior data were consistent with previous research (Table 2 in the Supplement). EDI-3 body dissatisfaction and EDI-3 drive for thinness were significantly positively correlated with scores for harm avoidance (body dissatisfaction $r = 0.345$; 95% CI, 0.222-0.456; $P < .001$), drive for thinness $r = 0.357$; 95% CI, 0.210-0.482; $P < .001$), depression (body dissatisfaction $r = 0.436$; 95% CI, 0.294-0.562; $P < .001$), drive for thinness $r = 0.378$; 95% CI, 0.237-0.508; $P < .001$), intolerance of uncertainty (body dissatisfaction $r = 0.274$; 95% CI, 0.138-0.396; $P < .001$) drive for thinness $r = 0.400$; 95% CI, 0.274-0.507; $P < .001$), sensitivity to punishment (body dissatisfaction $r = 0.335$; 95% CI, 0.201-0.459; $P < .001$), drive for thinness $r = 0.354$; 95% CI, 0.201-0.492; $P < .001$), and trait anxiety (body dissatisfaction $r = 0.448$; 95% CI, 0.322-0.566; $P < .001$), drive for thinness $r = 0.480$; 95% CI, 0.333-0.598; $P < .001$). EDI-3 bulimia was significantly positively correlated with BMI ($r = 0.516$; $P < .001$).

Forty-five HC and 40 participants with eating disorders took oral contraceptives ($χ^2 = 16.329$; $P < .001$). Use of antidepressant or antipsychotic medication, or comorbidity with major depression, obsessive-compulsive disorder, or posttraumatic stress disorder were not differentially distributed between eating disorder groups, but comorbid anxiety disorder was ($χ^2 = 7.935$; $P = .047$).

Brain Response–Behavior Correlations

In the HC group, correlations between age, BMI, or behavior and brain imaging values were not significant or were not found after multiple comparison correction.

The eating disorder group showed significant correlations between BMI (left nucleus accumbens: $r = −0.291$; 95% CI, −0.431 to −0.167; $P < .001$), left ventral anterior insula: $r = −0.208$; 95% CI, −0.339 to −0.070; $P = .004$), binge-eating frequency (left nucleus accumbens: $r = −0.183$; 95% CI, −0.312 to −0.055; $P = .01$), left ventral anterior insula: $r = −0.084$; 95% CI, −0.212 to −0.047; $P = .26$), EDI-3 bulimia (left nucleus accumbens: $r = −0.207$; 95% CI, −0.333 to −0.073;
Analysis of the combined sample did not improve results with prediction error response in any group. Exploratory correlations were not found after controlling for BMI. Number of days since last menstrual cycle was not significantly correlated with prediction error response in any group. Exploratory analysis of the combined sample did not improve results (eMethods 5 in the Supplement).

**Effective Connectivity**

Effective connectivity was directed in HC from hypothalamus to ventral striatum. In the eating disorder sample, effective connectivity was directed from ventral striatum to hypothalamus (Figure 1). eFigure 4 in the Supplement shows individual graphs for AN and BN groups.

Extracted effective connectivity edge coefficients from right ventral striatum to hypothalamus in eating disorder correlated significantly with right-sided ventral striatum prediction error response ($r = 0.189; 95\% CI, 0.045–0.324; P = .01$). Left-sided correlation was also positive but nonsignificant ($r = 0.104; 95\% CI, −0.030 to 95\% CI 0.231; P = .15$). Edge coefficients correlated in eating disorders significantly in 3 ways: first, bilaterally negatively with eating leads to feeling out of control (right sided: $r = –0.328; 95\% CI, –0.480 to –0.164$; $P < .001$; left sided: $r = –0.297; 95\% CI, –0.439 to –0.142$; $P = .001$), intolerance of uncertainty (right sided: $r = –0.213; 95\% CI, –0.355 to –0.047; P = .004$; left sided: $r = –0.221; 95\% CI, –0.354 to –0.080; P = .003$), and sensitivity to punishment (right sided: $r = –0.163; 95\% CI, –0.295 to –0.011; P = .03$; left sided: $r = –0.166; 95\% CI, –0.307 to –0.007; P = .03$), second, on the right side negatively with bulimia ($r = –0.162; 95\% CI, –0.291 to –0.005; P = .03$), and body dissatisfaction ($r = –0.147; 95\% CI, –0.279 to –0.001; P = .047$); and third, on the left side with drive for thinness ($r = –0.182; 95\% CI, –0.317 to –0.044; P = .01$), harm avoidance ($r = –0.183; 95\% CI, –0.334 to –0.029; P = .01$), and trait anxiety ($r = –0.151; 95\% CI, –0.278 to –0.007; P = .04$).

**Confounding Variables Assessment on Prediction Error Response**

Multivariate analysis of covariance in the combined eating disorder group indicated no significant effect sizes for antidepressants (Wilks λ, 0.930; $P = .21$), antipsychotics (Wilks λ, 0.923; $P = .145$), major depressive disorder (Wilks λ, 0.945; $P = .004$; left ventral anterior insula: $r = –0.143; 95\% CI, –0.282 to 0.047$; $P = .047$), trait anxiety (left nucleus accumbens: $r = –0.166; 95\% CI, –0.290 to –0.035$; $P = .01$), or body dissatisfaction ($r = –0.221; 95\% CI, –0.354 to –0.080; $P = .003$), and sensitivity to punishment ($r = –0.163; 95\% CI, –0.295 to –0.011; P = .03$), second, on the right side negatively with bulimia ($r = –0.162; 95\% CI, –0.291 to –0.005; P = .03$), and body dissatisfaction ($r = –0.147; 95\% CI, –0.279 to –0.001; P = .047$); and third, on the left side with drive for thinness ($r = –0.182; 95\% CI, –0.317 to –0.044; P = .01$), harm avoidance ($r = –0.183; 95\% CI, –0.334 to –0.029; P = .01$), and trait anxiety ($r = –0.151; 95\% CI, –0.278 to –0.007; P = .04$).
Prediction Error Group Contrasts

Prediction error response significantly differentiated groups (Wilks $\lambda$, 0.843; $P = .001$). After Bonferroni correction, prediction error remained elevated in AN compared with HC, BN, and BED, which is consistent with previous studies. In eating disorders, prediction error response was inversely correlated with BMI and binge eating behaviors. Furthermore, ventral striatal prediction error response correlated with effective connectivity from the ventral striatum to the hypothalamus in eating disorders, indicating an association between prediction error responsiveness and strength of a circuitry that has been associated with food intake control.45

Discussion

This cross-sectional study in a large sample of women across the eating disorder diagnostic spectrum indicates elevated prediction error response in AN compared with HC, BN, and BED, which is consistent with previous studies. In eating disorders, prediction error response was inversely correlated with BMI and binge eating behaviors. Furthermore, ventral striatal prediction error response correlated with effective connectivity from the ventral striatum to the hypothalamus in eating disorders, indicating an association between prediction error responsiveness and strength of a circuitry that has been associated with food intake control.45

The results support basic science studies showing that prediction error response adapts to patterns of food intake.10-13 Regional prediction error response was higher the more re-
Table 3. Group Comparison for Regional Prediction Error Parameter Estimates

| Region of Interest | Post hoc | F | Power | P value | Post hoc | F | Power | P value | Post hoc | F | Power | P value |
|--------------------|----------|---------|--------|---------|----------|---------|--------|---------|----------|----------|---------|--------|---------|
| Right lateral hypothalamus | −0.026 (−0.237 to 0.194) | 0.039 (−0.310 to 0.136) | 0.067 (−0.431 to 0.133) | 0.123 (−0.683 to 0.014) | 0.130 (−0.542 to 0.023) | 0.675 (−2.330 to 0.069) | 0.122 (−0.618 to 0.016) | 0.130 (−0.421 to 0.090) | 0.011 (−0.446 to 0.023) | 0.130 (−0.542 to 0.023) | 0.128 (−0.407 to 0.090) | 0.011 (−0.446 to 0.023) |
| Left lateral hypothalamus | −0.030 (−0.208 to 0.147) | 0.048 (−0.280 to 0.128) | 0.130 (−0.660 to 0.009) | 0.130 (−0.542 to 0.023) | 0.276 (−1.060 to 0.353) | 0.009 (−0.446 to 0.023) | 0.130 (−0.542 to 0.023) | 0.276 (−1.060 to 0.353) | 0.009 (−0.446 to 0.023) | 0.130 (−0.542 to 0.023) | 0.276 (−1.060 to 0.353) | 0.009 (−0.446 to 0.023) |

MANCOVA: multivariate analysis of covariance. OSFEDr: other specified feeding disorder restricting subtype. BED: binge eating disorder. AN: anorexia nervosa. BN: bulimia nervosa. HC: healthy controls. Partial η²: partial eta-squared. Power: power of the test. Post hoc: post hoc analysis. MANCOVA model included obsessive-compulsive disorder score, scanner and age as factors or covariates. Post hoc comparisons were Bonferroni corrected.

Previously, prediction error was associated with harm avoidance in adolescent AN, which we did not find in adults across the eating disorder spectrum. It is possible that at an earlier age prediction error response affects anxiety and triggers eating disorder behaviors. However, during longer illness, such associations may be attenuated, after eating disorder behaviors have transformed to become a way of maintaining a sense of control.

Ventral striatal-hypothalamic effective connectivity during sugar tasting in opposite directions between HC and eating disorder groups, together with positive correlation with ventral striatum prediction error response, extends previous results in smaller eating disorder samples. Dopamine and prediction error signaling have been associated with energy homeostasis regulation, and a fear mediated dopamine circuit from the ventral striatum to the hypothalamus has been identified that inhibits food intake. A drive-mediated dopamine circuitry to suppress eating drive thus could be a trait common to all eating disorders, which is most effective in the context of sensitized dopamine circuits, reflected in high prediction error response.

The results suggest that a data-driven model of biological and behavioral interactions that promote restrictive or excessive eating behaviors is warranted (Figure 2). Consistent with previous research, trait anxiety correlated positively with the EDI-3 bulimia score, supporting that negative emotions trigger binge eating. Novelty seeking and bulimia are known risk traits for elevated BMI. The negative correlation between BMI and prediction error response supports basic science, indicating a modulatory effect of amount of food intake on dopaminergic circuitry. The positive correlation between prediction error and effective connectivity further implicates dopamine circuitry in modulating brain connectivity and suggests that higher dopaminergic activity strengthens the ventral striatal-hypothalamic food-control circuitry enabling individuals with AN to override normal hunger cues. BN or BED, however, have lower dopaminergic activity than AN, cannot maintain consistent food intake control, which facilitates intermittent binge-eating episodes. The negative correlation between effective connectivity and eating leads to feeling out of control could indicate that stronger food intake control circuitry leads to less of an out-of-control sensation, but this is speculative and requires further study. Behaviorally, higher BMI was associated with higher body dissatisfaction, which correlated positively with intolerance of uncer-
eating disorder behaviors.

... increasing poor self-esteem and further promoting and reinforcing by anxiety, depression, and punishmentsensitivity to punishment, which also correlated positively with Trait Anxiety, consistent with previous research.57-59 Body dissatisfaction triggers drive for thinness, which reinforces and is reinforced by anxiety, depression, and punishment sensitivity, increasing poor self-esteem and further promoting eating disorder behaviors.

Limitations
This study has limitations. The study was well powered for group comparisons, but effect sizes were small to moderate. Correlation analyses in the eating disorder sample showed moderate to large effect sizes, but correlation analyses cannot prove mechanism. The prediction error model is based on dopamine function, but other neurotransmitter systems, such as serotonin, noradrenaline, or adenosine, are likely factors in reward processing and behavior control in eating disorder behaviors.60-62 Furthermore, dopamine neuronal function was not directly measured in this study and functional magnetic resonance imaging prediction error response is only an indirect approximation.63 Whether altered prediction error response affects food intake acutely will require further study, and inverse relationships between this brain response and BMI may also exist in other conditions. The hypothalamus ROI did not separate subnuclei. While HC were studied during the first 10 days of the menstrual cycle to keep hormonal variation low, the eating disorder population was either amenorrheic or had more days from the last menstrual cycle. Not having hormonal measures is a limitation, but days from last menstrual cycle did not correlate with brain response in either group. Because eating disorder results were either higher or lower compared with HC, we do not believe that there was a systemic confound. For the prediction error analysis, we used the unsigned (absolute) prediction error. Pleasantness ratings for the 1 molar sucrose solution varied from very high to very low. Unexpectedly receiving sucrose solution could therefore be associated with positive (better than expected) or negative (worse than expected) prediction error. Studying the absolute prediction error accounts for inter-individual variation and measures degree of deviation from expectation, reducing effects of subjective pleasantness.64,65 Our theoretical framework was primarily based on sensitivity to salient stimuli and adaptation of the related circuitry to food intake. We believe that using the unsigned prediction error yields more reliable results, independent from individual value computation.

Conclusions
Results of this study suggest that behavioral traits are factors in eating disorder initiation and extremes of eating and then alter prediction error-related reward response. This process reinforces in opposite ways the ventral striatal-hypothalamic food control circuitry, which is activated in response to sugar taste as a trait in eating disorders. Clinically it therefore may be important to implement weight gain in eating disorders in people with underweight and weight loss in eating disorders associated with overweight to normalize brain function and behavior. This topic is controversial, though, and the critical question remains what the best BMI for a person is in this context. Furthermore, temperamental traits are biologically oriented behaviors that affect eating disorder behaviors. Treatment modules that specifically target those behaviors may be a key element to promote behavior change and lasting recovery.
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