

Altered Temporal Difference Learning in Bulimia Nervosa

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Background: The neurobiology of bulimia nervosa (BN) is poorly understood. Recent animal literature suggests that binge eating is associated with altered brain dopamine (DA) reward function. In this study, we wanted to investigate DA-related brain reward learning in BN.

Methods: Ill BN ($n = 20$, age: mean = 25.2, SD = 5.3 years) and healthy control women (CW) ($n = 23$, age: mean = 27.2, SD = 6.4 years) underwent functional magnetic resonance brain imaging together with application of a DA-related reward learning paradigm, the temporal difference (TD) model. That task involves association learning between conditioned visual and unconditioned taste stimuli, as well as unexpected violation of those learned associations. Study participants also completed the Sensitivity to Reward and Punishment Questionnaire.

Results: Bulimia nervosa individuals showed reduced brain response compared with CW for unexpected receipt and omission of taste stimuli, as well as reduced brain regression response to the TD computer model generated reward values, in insula, ventral putamen, amygdala, and orbitofrontal cortex. Those results were qualitatively similar in BN individuals who were nondepressed and unmedicated. Binge/purge frequency in BN inversely predicted reduced TD model response. Bulimia nervosa individuals showed significantly higher Sensitivity to Reward and Punishment compared with CW.

Conclusions: This is the first study that relates reduced brain DA responses in BN to the altered learning of associations between arbitrary visual stimuli and taste rewards. This attenuated response is related to frequency of binge/purge episodes in BN. The brain DA neurotransmitter system could be an important treatment target for BN.

Key Words: Bulimia nervosa, computational, dopamine, imaging, reward, temporal difference model

Bulimia nervosa (BN) is a severe eating disorder associated with episodic binge eating followed by extreme behaviors to avoid weight gain, such as self-induced vomiting, use of laxatives, or excessive exercise (1). Individuals with BN present with fear of gaining weight, as well as food and body weight-related preoccupations, but are at normal or often high-normal weight. The pathophysiology of BN is largely unknown.

Only a few functional brain imaging studies have investigated the neurobiology of BN. One group (2) found that BN subjects demonstrated increased activity in the anterior cingulate cortex and insula in response to food images, possibly representing the increased emotional salience associated with the images. A second study explored body image perception in a small BN sample ($n = 9$) (3); BN individuals demonstrated a reduced response in the lateral fusiform gyrus when presented with line drawings of body shapes and such reduced responses were thought to reflect an aversion-driven restraint in brain response. A few neurotransmitter-receptor studies have been done in BN. One study reported reduced binding of [123 I]beta-CIT, a radiotracer that binds to brain serotonin (5-HT) and dopamine (DA) transporter receptors (4). Reduced [123 I]beta-CIT binding in BN could be related to altered serotonin (5-HT) (5) or

DA (6,7) brain activity during the ill state. Another study found increased 5-HT type 1A receptor binding in ill BN subjects (8), most prominently in prefrontal, cingulate, and a parietal cortex area. This increased binding could reflect upregulated receptor activity associated with the decrease in central 5-HT function in BN (5).

The compulsive nature of binge episodes and comorbidity with substance use disorders (9) suggested that BN could, at least in part, share vulnerabilities and pathophysiology with substance use disorders. Substance use disorders are largely associated with abnormalities in the neural systems associated with processing salient stimuli and regulating the desire and ingestion of rewarding stimuli such as drugs or food (i.e., the reward system). The neurotransmitter system that has received the most attention in that respect is DA, partially because it is well characterized (10,11). Dopamine regulates the motivational aspects of the reward pathway (12) and seems to adjust to repetitive substance use with gradual desensitization and chronic dysphoria outside of times of acute use (13). Substance use disorders commonly are associated with lower DA D2/3 receptor availability (14), which has implications on reinforcement learning, reward processing, and eventually action selection (15). While DA dysfunction is commonly associated with substance abuse, there are also animal models linking the pathophysiology of binge eating to DA abnormalities. Those studies suggest withdrawal and tolerance development in the context of binge eating (16,17), as well as DA D2 receptor reductions (18). While the animal models suggest a link between DA and BN, DA research in BN has been sparse, but there appear to be reduced DA metabolites in cerebrospinal fluid (6,7) and reduced DA transporter availability in BN (4).

In this study, we used event-related functional magnetic resonance imaging (fMRI) to investigate DA-related responding in a classical conditioning paradigm (19–21). Before learning, the DA system produces a phasic response to the (unexpected) unconditioned reward stimulus (US). After learning that the US is predictably preceded by a conditioned stimulus (CS), DA response transfers in time, such that it follows the CS but no longer the US. Further,

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after such training, if the CS is followed by an omission of the US, a reduction in DA firing occurs at the time of the expected US. Thus, brain DA response parallels the difference between the amount of reward observed and that predicted, i.e., a reward prediction error. This type of prediction error and learning process can be characterized by a temporal difference (TD) algorithm (11). This algorithm has been explored empirically in both rodent models (21) and event-related human neuroimaging paradigms (20) and is widely thought to be a reasonable description of the learning process. The primary brain areas demonstrating responses that parallel signals produced by a TD model are the ventral striatum and midbrain (21), although the amygdala (22) and insula are also intimately involved in reward processing (23). Our goal was to test whether we would find diminished DA-related taste reward processing across a large brain network that would distinguish BN from control women (CW) individuals.

Methods and Materials

Study Participants

Forty-one female study participants participated in this study (Table 1), 20 individuals with purging type BN and 23 healthy CW, matched for age and level of education. Bulimia nervosa individuals were recruited from the Eating Disorder Center Denver. No BN subject approached for this study declined study participation. Bulimia nervosa individuals showed typical behaviors on mood and personality measures and showed significantly greater sensitivity to punishment and sensitivity to reward (Sensitivity to Punishment and Sensitivity to Reward Questionnaire [SPSRQ]) compared with CW (Table 1). Bulimia nervosa fulfilled all diagnostic criteria for the disorder up to 1 week before the study. Study participants had no electrolyte or other laboratory abnormalities. Among BN individuals, three had a major depressive disorder (MDD) but no other comorbidity, two had MDD and social phobia, one had MDD and social phobia and generalized anxiety disorder, two had MDD and posttraumatic stress disorder, two had MDD and generalized anxiety disorder, and two had social phobia without MDD. No BN subject had a substance use disorder. The study was approved by the

Colorado Multiple Review Board and all subjects signed informed consent.

Assessment Procedures

Psychiatric diagnoses, including BN, or absence of any psychiatric disorders in CW were established by the Structured Clinical Interview for DSM-IV diagnoses (24) applied by a doctoral level interviewer. All participants completed the Eating Disorder Inventory-3 (25,26), Sensitivity to Punishment and Sensitivity to Reward Questionnaire (27), Beck's Depression Inventory (28), and Cloninger's Temperament and Character Inventory (29).

Study subjects met with the principal investigator to ensure diagnosis and underwent a blinded taste test, where subjects were presented with a tray of randomly assorted small cups with six sucrose (Mallinckrodt Chemicals, Phillipsburg, New Jersey) solutions (0%-distilled water, 2%, 4%, 8%, 16%, and 1 mol/L), as well as artificial saliva (25 mmol/L potassium chloride, 2 mmol/L sodium bicarbonate) (20). Study participants rated the solutions blindly for sweetness and pleasantness. This was to test taste sensitivity across groups. Taste test and brain imaging were conducted in all study participants during the first 10 days of the menstrual cycle to keep hormonal variation low (30).

Brain Imaging Procedures

On the study day, participants ate breakfast between 7:00 AM and 8:00 AM, BN individuals according to their meal plan; CW had breakfast matched in quality and calories to the average meal plan breakfast (Table 1.). Bulimia nervosa individuals' meal plan was adjusted so that their morning snack after the study was less study sucrose solution calories, to not add anxiety. Functional magnetic resonance imaging was performed between 8:00 AM and 9:00 AM. Brain images were acquired on a GE Signa 3T scanner (General Electric, Waukesha, Wisconsin). T2* weighted echo planar imaging for blood oxygenation level-dependent (BOLD) functional activity was performed, with $3.4 \times 3.4 \times 2.6$ mm voxel size, 1.4 mm gap, repetition time = 2100 milliseconds, echo time = 30 milliseconds, flip angle 70°, 30 slices. We also acquired structural images (T1 spoiled

Table 1. Demographic Variables of Study Participants

	CW (n = 23)		BN (n = 20)		U	p
	Mean	SD	Mean	SD		
Age (years)	27.2	6.4	25.2	5.3	190.5	ns
Illness Duration (months)	—	—	74.2	63.7	—	—
Weekly Binge/Purge Episodes	—	—	23.5	16.9	—	—
Body Mass Index (kg/m ²)	21.5	1.2	22.6	5.7	201.0	ns
Novelty Seeking (TCI)	17.9	6.1	22.1	6.7	142.0	.032
Harm Avoidance (TCI)	10.7	6.6	23.0	5.8	50.5	<.001
Depression (BDI)	1.0	1.0	24.5	11.3	.0	<.001
Drive for Thinness (EDI-3)	2.7	3.5	23.1	4.5	1.0	<.001
Bulimia (EDI-3)	.8	1.2	22.7	5.3	.0	<.001
Body Dissatisfaction (EDI-3)	4.4	4.3	30.7	8.0	4.0	<.001
Sensitivity to Reward (SPSRQ)	8.7	3.8	12.3	4.5	122.0	.008
Sensitivity to Punishment (SPSRQ)	7.6	5.0	16.1	4.8	56.0	<.001
Pleasantness 1 mol/L Sucrose	4.8	2.2	5.5	2.9	196.5	ns
Sweetness 1 mol/L Sucrose	8.3	.8	8.7	.6	180.0	ns
Breakfast Calories	511.2	81.3	473.2	95.3	188.5	ns

BDI, Beck's Depression Inventory; BN, bulimia nervosa; CW, control women; EDI-3, Eating Disorder Inventory-3; ns, nonsignificant; SPSRQ, Sensitivity to Punishment and Sensitivity to Reward Questionnaire; SD, standard deviation; TCI, Cloninger's Temperament and Character Inventory; U, Mann-Whitney U test.

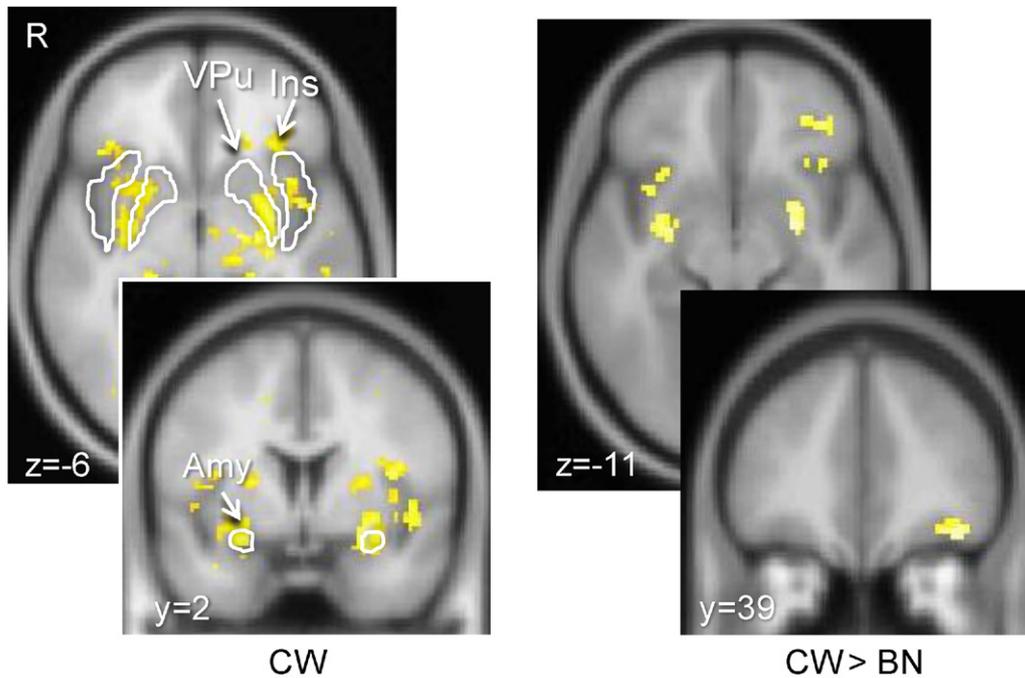


Figure 1. Brain response to unexpected receipt of unconditioned taste stimulus sucrose (US+). Control women (CW) showed typical response in the ventral putamen, as well as insula and bilateral amygdala ($p < .05$, cluster threshold 25 voxels, family-wise error corrected). Bulimia nervosa (BN) women showed significantly reduced brain response compared with CW ($p < .005$ uncorrected, cluster threshold 10 voxels) in bilateral amygdala, insula, and left orbitofrontal cortex. Amy, amygdala; Ins, insula; R, right; VPu, ventral putamen.

gradient recall) for delineation of the brain anatomy and group comparison for anatomical differences.

Task Design

We adapted the design used by O'Doherty *et al.* (20). Individuals received three taste stimuli during fMRI imaging: 1 mol/L sucrose solution (100 trials), no solution (100 trials), and artificial saliva (80 trials). Individuals learned to associate each taste stimulus with a paired conditioned visual stimulus (CS) that is probabilistically associated with its US; the CS associated with no-solution (null) appears before 20% of the trials in which sucrose solution is presented as the US (US+) and vice versa (US−). For each subject, the first 10 trials were CS sucrose fractal followed by US sucrose application, but all other trials were fully randomized. The taste stimuli were applied using a customized programmable syringe pump (J-Kem Scientific, St. Louis, Missouri) controlled by E-Prime Software (Psychological Software Tools, Pittsburgh, Pennsylvania). Individual taste application was triggered by magnetic resonance imaging scanner radiofrequency pulse (31). Task duration was 28 minutes.

Brain Imaging Data Analysis

Brain imaging data were preprocessed and analyzed using SPM5 software (Functional Imaging Laboratory, University College London, United Kingdom; <http://www.fil.ion.ucl.ac.uk/spm/software/spm5/>). Data from each subject were realigned to the first volume, normalized to the Montreal Neurological Institute template, and smoothed with a 3-mm full width at half-maximum Gaussian kernel. Each image sequence was inspected and images with artifacts or movement > 1 voxel size were removed. Data were modeled with a hemodynamic response function-convolved boxcar function, using the general linear model, including temporal and dispersion derivatives. A 128-second high-pass filter was applied to remove low-frequency fluctuation in the BOLD signal. As an initial analysis, we developed first-level models in which we predicted the

response in each voxel as a function of each of the five stimulus conditions: expected sucrose, unexpected sucrose, expected null, unexpected null, and expected AS. Two contrasts of interest were computed: unexpected sucrose minus expected null where the visual stimulus is the same and predicts null but there is a positive prediction error signal at the time of the US (US+) and unexpected null minus expected sucrose where the visual stimulus is the same and predicts sucrose but there is a negative prediction error signal at the time of the US (US−). Using a random effects analysis, these contrasts were then compared within and across groups.

Regions of interest for extraction of region-specific brain imaging data were used from the SPM5 Wake Forest University PickAtlas automated anatomical labeling section for the insula, amygdala, lateral orbitofrontal cortex, substantia nigra, and ventral putamen. For the ventral putamen, only the planes below the lateral ventricles were used, as described previously (32,33).

We further modeled each participant's individual trial sequence using the TD algorithm (20,21). On each trial, the predicted value (\hat{V}) at any time (t) within a trial is calculated as a linear product of weights (w_i) and the presence or absence of a CS stimulus 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 (20):

$$\hat{V}(t) = \sum_i w_i x_i(t) \quad (1)$$

Learning occurs by updating the predicted value of each time point t in the trial by comparing the predicted value at time $t + 1$ to that actually observed at time t , leading to a prediction error ($\delta(t)$):

$$\delta(t) = r(t) + \gamma \hat{V}(t + 1) - \hat{V}(t) \quad (2)$$

where $r(t)$ is the reward at time t . The parameter γ is a discount factor, which determines the extent to which rewards arriving earlier are more important than rewards that arrive later during the

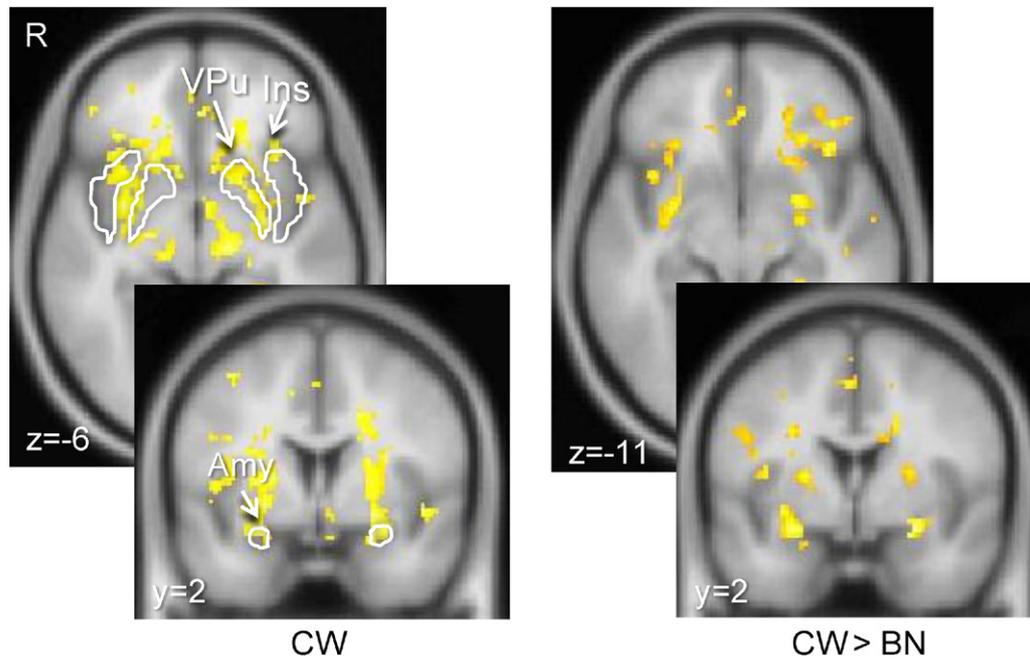


Figure 2. Brain response to unexpected omission of unconditioned taste stimulus sucrose (US⁻). Control women (CW) showed typical response in the ventral putamen, as well as insula and bilateral amygdala ($p < .05$, cluster threshold 25 voxels, family-wise error corrected). Bulimia nervosa (BN) women showed significantly reduced brain response compared with CW ($p < .005$ uncorrected, cluster threshold 10 voxels) in bilateral ventral putamen, amygdala, insula, and left orbitofrontal cortex. Amy, amygdala; Ins, insula; R, right; VPu, ventral putamen.

task. Similar to the O'Doherty *et al.* study (20), we set $\gamma = .99$. The weights w_i are then updated on a trial-by-trial basis according to the correlation between prediction error and the stimulus representation:

$$\Delta w_i = \alpha \sum_t x_i(t) \delta(t) \quad (3)$$

where α is a learning rate. We assigned six time points to each trial and used each subject's individual event history as input. On each trial, the CS (visual fractal) is delivered at time point 1, and the US reward (taste stimulus) is delivered at time point 3. Similar to O'Doherty *et al.* (20), we applied fast ($\alpha = .2$) and slow ($\alpha = .7$) learning rate parameters. The initial reward values were 1 for sucrose and 0 for null.

Statistical Procedures

Whole-brain imaging data were analyzed as above. Behavioral data and brain activation percent signal change were analyzed with SPSS (IBM-SPSS, Chicago, Illinois) software. We initially tested for normality using Kolmogorov-Smirnov tests. When normality was preserved, we used Student *t* test for two independent group comparisons and report adjusted degrees of freedom and *p* values in case of significant variance inequalities across groups. If Kolmogorov-Smirnov tests indicated nonnormal distribution across groups, we used Mann-Whitney tests for independent group comparisons. We assessed percent signal change over time and across groups using repeated measures analyses of variance (ANOVAs). The relationship between predictor and dependent variables was assessed using regression analysis.

Results

Taste Studies

Study groups rated sweetness and pleasantness of study taste solutions similarly. Sweet taste sensitivity across study groups and

the six sucrose concentrations using linear regression analysis showed positive slopes for both groups: BN, $R^2 = .73$, $\beta = .94$, $p < .001$; CW, $R^2 = .71$, $\beta = .85$, $p < .001$; and a condition by group analysis was nonsignificant. For pleasantness, we explored linear, quadratic, and logistic regression, but there was no significant regression result in either group, nor was there a difference in a repeated measures ANOVA analysis with taste condition and group as independent variables.

Brain Imaging Results

There were no significant group differences on the structural (spoiled gradient recall) images.

Control women showed the predicted brain response to the unexpected receipt (US⁺) and omission (US⁻) of sucrose in ventral putamen, insula, and bilateral amygdala (Figures 1 and 2). At lower significance (false discovery rate corrected $q = .00005$), CW also demonstrated responses in midbrain ventral tegmental area (US⁺: 16 voxel cluster size, US⁻: 25 voxel cluster size) and substantia nigra (US⁺: 47 voxel cluster size, US⁻: 45 voxel cluster size). The group comparison indicated that BN individuals had reduced brain response in the ventral putamen, insula, and orbitofrontal cortex compared with CW for both taste conditions (a reduced response means the absolute value of the deviation was smaller: all differences were in the direction of CW having more positive or more negative responses; Figures 1 and 2.). Table 2 shows the individual coordinates for group contrast analysis (US⁺, US⁻). There were no regions that were significantly greater in BN compared with CW. We further extracted time activity curves for amygdala, ventral putamen, and insula for both US⁺ and US⁻ conditions. Both groups showed positive hemodynamic response curves for US⁺ and negative response for US⁻, with CW for all regions more positive for US⁺ and more negative for US⁻. Repeated measures ANOVAs showed the following significant group \times condition interactions: US⁺ insula right, multivariate test Wilk's lambda = .803, $p < .04$;

Table 2. Coordinates of Brain Response Across Groups and Conditions

MNI Coordinates				<i>p</i> (SVC FWE)	Cluster		Anatomical Region
x	y	z	Z		Size	<i>p</i> Corrected	
US+ Receiving Sucrose Unexpectedly, CW > BN							
–40	40	14	3.38	.261	50	.008	Lateral orbitofrontal cortex, left
–40	4	16	3.28	.333	30	.044	Insula, left
–28	–4	–12	3.49	.034	15	.031	Amygdala, left
28	–6	–12	3.26	.050	8	.054	Amygdala, right
US– Omission of Sucrose Unexpectedly, CW > BN							
32	2	–6	3.42	.023	11	.028	Ventral putamen, right
–30	24	–20	3.47	.208	35	.014	Insula, left
30	28	4	3.57	.166	108	<.001	Insula, right
–26	–2	–14	3.88	.009	14	.029	Amygdala, left
30	–4	–14	3.55	.023	38	.003	Amygdala, right
Temporal Difference Model Regression, All Expected and Unexpected Sucrose and No-Solution Trials, CW > BN							
–40	14	–14	4.37	.005	249	<.001	Lateral orbitofrontal cortex, left
36	22	–20	3.33	.132	180	.001	Lateral orbitofrontal cortex, left
–40	4	14	3.69	.051	69	.032	Insula, left
28	22	–12	3.39	.128	74	.027	Insula, right
–24	2	–12	3.41	.019	13	.051	Amygdala, left
28	–6	–12	2.98	.054	12	.050	Amygdala, right
32	2	–8	3.10	.030	25	.019	Ventral putamen, right

Montreal Neurological Institute (MNI) coordinates are based on whole brain analysis ($p < .005$ uncorrected, 10 voxel contiguity); the small volume FWE correction is based on the MNI automated anatomical labeling atlas derived anatomical regions. There were no regions that were significantly greater in bulimia nervosa compared with control women.

BN, bulimia nervosa; CW, control women; FWE, family-wise error; SVC, small volume correction; US, unconditioned stimulus.

US– amygdala right, multivariate test Wilk's lambda = .80, $p < .04$; amygdala left, multivariate test Wilk's lambda = .790, $p < .03$.

Comorbid Conditions. Major depressive disorder could be affecting brain response in reward conditioning (34) and could have affected our results. Ten of the BN individuals did not have an MDD episode and were not on psychoactive medication. Group comparisons, between unmedicated BN without comorbid depression and CW, for the US+ and US– conditions revealed similar, that is ventral putamen, insula, orbitofrontal, and amygdala, differences between groups (CW > BN) but at a lower significance level for the whole brain comparison ($p < .05$, 100 voxel cluster threshold).

For the TD model regression analysis, we assessed the relationship between BOLD signal and prediction errors generated by models with either a slow ($\alpha = .2$) or a fast ($\alpha = .7$) learning rate. For both groups, the fast learning rate provided the better fit. In the CW group, the regression analysis using the prediction error values from the model to predict brain response showed activation in the ventral putamen, insula, and amygdala (Figure 3). With lower significance threshold (false discovery rate corrected $p < .0005$), ventral tegmental area and substantia nigra were also significant. Relative to CW, BN individuals showed reduced regression weights in the bilateral putamen, amygdala, insula, and orbitofrontal cortex (Figure 3). Table 2 shows individual coordinates for group contrast analysis (TD model regression). There were no regions significantly greater in BN compared with CW. Also here, comparing the 10 unmedicated, nondepressed BN individuals with an age-matched CW subset showed regional very similar brain response patterns but at lower significance ($p < .05$, 100 voxel cluster threshold).

Correlations with Behavioral Variables

Age, body mass index, duration of illness, or sensitivity to reward or punishment did not correlate significantly with region of interest derived strength of activation (parameter estimates) within groups

for any of the conditions. However, logarithmic regression analysis revealed that binge/purge frequency significantly predicted TD model regression response in the BN group for the left insula and substantia nigra (Figure 4), as well as left amygdala (adjusted $R^2 = .357$, standardized beta = $-.625$, $p < .003$), right amygdala (adjusted $R^2 = .298$, standardized beta = $-.579$, $p < .007$), right insula (adjusted $R^2 = .205$, standardized beta = $-.497$, $p < .026$), left ventral putamen (adjusted $R^2 = .250$, standardized beta = $-.538$, $p < .014$), and right ventral putamen (adjusted $R^2 = .257$, standardized beta = $-.545$, $p < .013$).

Discussion

This is, to our knowledge, the first study that investigated reward learning in BN. The results indicate that BN is associated with reduced responsiveness to unexpected receipt or omission of taste reward stimuli, and this was further supported by the relationship between brain responses and model-based predictors that are associated with the actual degree of reward associated with each trial. Further, the response associated with the model-based regressor was predicted by binge/purge frequency. These results strongly suggest reduced DA reactivity in BN that is related to illness severity. Additionally, SPSRQ sensitivity to reward and punishment were elevated in the BN group.

Food consumption is intimately connected to the brain reward system. This system has been hypothesized to be an important factor in the pathophysiology of excessive eating and resulting obesity (35,36) and is highly related to the taste of foods (37). Gustatory inputs from the tongue, immediately after food contact and before gut involvement, project via brainstem and thalamus to the primary taste cortex comprised by insula and frontal operculum, from there project to the ventral striatum and amygdala, and subsequently project to the hypothalamus, midbrain, and frontal cortex (38). Hence, a highly complex network is involved in taste

Figure 3. Temporal difference model derived trial by trial reward regression with brain response. Control women (CW) showed ventral putamen, small midbrain, and amygdala response ($p < .05$, cluster threshold 25 voxels, family-wise error corrected). Bulimia nervosa (BN) women showed significantly weaker regression compared with CW in bilateral ventral putamen, amygdala, insula, and lateral orbitofrontal cortex ($p < .005$ uncorrected, cluster threshold 10 voxels). Amy, amygdala; Ins, insula; R, right; VPu, ventral putamen.

processing. In addition to the transmission of taste quality, there are learned associations between food and pleasurable experience that create an internal representation of food stimuli that becomes activated when we see, smell, or think of food (37). Thus, there is a cognitive or cephalic phase that involves desire or craving, as well as a consummatory phase in the food reward processing cycle. Bulimia nervosa has commonly been associated with addiction disorders (9) because of the episodic and often compulsive nature of bingeing on highly palatable foods. The motivation to approach food and other rewards, called “wanting,” has been associated with the neurotransmitter DA (35). The same neural pathways that reinforce those natural appetitive behaviors are also activated in response to addictive drugs (39). This has led to the hypothesis that prone individuals could become addicted to food, including increased preference and tolerance as well as reduction of dysphoria, behaviors that are common in substance-using individuals (13,40). Animal models support the notion that episodic excessive food intake could have similar brain correlates as found in individuals with substance use. That is, rodents trained to engage in binge eating showed tolerance and withdrawal symptoms, and obese rats developed a level of DA release to food as seen with typical addictive substances (16,41). Additionally, rodents showed addiction-like DA D2 receptor downregulation to overconsumption of food in brain reward circuits (18). Our results of reduced brain response to both unexpected receipt and omission of sweet taste stimuli in BN in this DA-anchored task suggest that BN is, in fact, associated with altered functional brain DA response. We propose that this may be due to the episodic excessive food stimulation resulting in desensitization of DA circuits. Little is known whether abstinence from BN type behaviors would help recover abnormal brain function in the disorder. Recent research in animals suggests that overconsumption of food manipulates DA receptor function (18). This could imply that the reverse is also possible: neurotransmitter function could recover with normalization of eating behav-

ior. However, this is unknown and it is possible that such alterations might be long lasting, as indicated by animal studies showing that brain reward response did not immediately recover with weight restoration (42) and that drugs of abuse can cause persistent DA abnormalities after recovery (43).

The originally reported DA brain regions responsive to the TD model involved the ventral putamen and midbrain (44). Our group results indicate group differences for the ventral putamen, amygdala, insula, and orbitofrontal cortex. Newer models of reinforcement learning and conditioning integrate more brain regions that respond to the US or CS (10) and include the amygdala as excitatory and driving DA activation. The primary gustatory cortex part of the insula is not considered in the current version of that model. However, the insular cortex provides neuronal inputs to the ventral striatum (38,45,46), moderates substance use and novelty-seeking behaviors via its DA D1 (47) and D2 (48) receptors, and is an important part of taste and reward circuits (23). The orbitofrontal cortex is also closely connected to ventral striatum and amygdala and is important for reward learning (49). In aggregate, the above studies suggest that in the BN group, the US activates insula and amygdala to a lesser degree than in the CW. This may lead to reduced activation in the ventral putamen (thought to reflect DA) and less involvement of the orbitofrontal cortex. This mechanism could be due to excessive episodic DA release and potential subsequent downregulation of DA D2 receptors (18). Such a downregulated DA taste reward system could then be part of an addiction-like pattern of need for episodic excessive food stimulation, while fears of gaining weight could then drive the purging behavior to compensate.

The reduced response in BN was greater for the unexpected omission of the sweet taste than for the unexpected receipt. Reinforcement learning involves both the DA D1 and D2 receptors, but there are brain region specific actions, such as both receptors acting comparably in the nucleus accumbens (50). However, stimulation

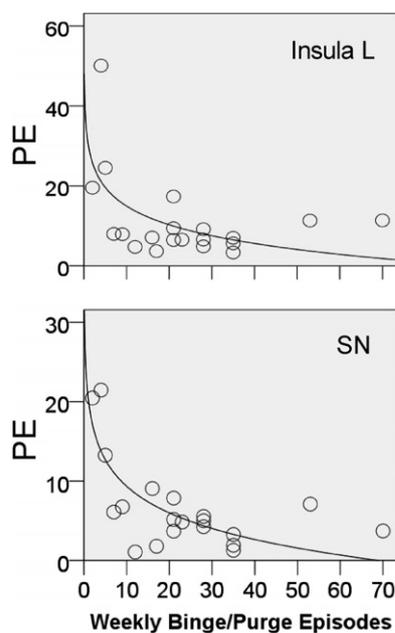


Figure 4. Logarithmic regression. Temporal difference model response (parameter estimates) was inversely predicted by number of weekly binge/purge episodes in the bulimia nervosa individuals for the left insula (adjusted $R^2 = .285$, standardized beta = $-.568$, $p < .009$) and substantia nigra (adjusted $R^2 = .562$, standardized beta = $-.765$, $p < .001$). L, left; PE, parameter estimates; SN, substantia nigra.

of D2 receptors in the amygdala reduced seeking of drug rewards, while D1 stimulation did not (51). The DA D1 receptor is excitatory and probably stimulated by phasic DA stimulation like in the US+ condition, while the DA D2 receptor is inhibitory and stimulated by tonic (baseline) DA (15). Thus, with the notion that excessive food intake is specifically associated with DA D2 receptor abnormalities (18,52), this could then be reflected by the stronger response in the US– condition, which is dependent on changes in tonic DA release.

The concept that excessive eating behavior is associated with altered brain DA changes is further supported by the fact that the number of binge/purge episodes directly predicted TD model brain activation. Others studying cerebrospinal fluid monoamines found that binge/purge frequency predicted lower DA metabolites (6,7), and our study now suggests that this behavior is directly associated with functional DA brain reward pathways.

This is the first study that reports increased sensitivity to punishment as well as sensitivity to reward from the SPSRQ in BN individuals. Previously, we found similar increases in anorexia nervosa (53), and our findings indicate that both eating disorders are characterized by generally heightened sensitivity to salient stimuli. This is important because this instability in relation to environmental stimuli could drive high harm avoidance in eating disorders.

Limitations

The sample size was not large, but 20 participants per cell are usually regarded as providing high reliability (54). Brain imaging results in psychiatry can be confounded by comorbid conditions. We addressed this by comparing unmedicated BN without comorbid diagnosis with matched CW, and those analyses also showed lower activation in the BN group. This indicates that our results are not likely to be an effect of comorbidity or medication. The use of fMRI can only be a proxy for DA function, and although there is reasonable evidence that fMRI BOLD response reflects DA activity well (19), there is potential for error and these studies will need to be

combined with neurotransmitter receptor studies. Furthermore, while we found correlations of brain biology with BN-specific behavior, those self-report measures could be inflated. In our sample, for both groups the fast learning rate was the better fit with similar differences across groups between slow and fast learning rate parameter estimates in the target brain regions. In our studies, the artificial saliva was rated as rather aversive and therefore introduced an additional taste. While removing artificial saliva from the model simplifies learning, this could be related to the better fit of the fast learning rate across both groups.

Conclusion

In summary, our results indicate that DA-related reward function is reduced in BN; these results are in line with food addiction studies in animals and could indicate a downregulation of DA function in response to episodic, excessive food intake and DA overstimulation. Dopamine-specific drugs that target to correct this reduced sensitivity may hold promise as treatment agents in the future.

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