Reward-Based Spatial Learning in Teens With Bulimia Nervosa

Marilyn Cyr, PhD, Zhishun Wang, PhD, Gregory Z. Tau, MD, PhD, Guihu Zhao, MA, Eve Friedl, MD, Mihaela Stefan, MA, Kate Terranova, BS, Rachel Marsh, PhD

Objective: To assess the functioning of mesolimbic and fronto-striatal areas involved in reward-based spatial learning in teenaged girls with bulimia nervosa (BN) that might be involved in the development and maintenance of maladaptive behaviors characteristic of the disorder.

Method: We compared functional magnetic resonance imaging blood oxygen level–dependent response in 27 adolescent girls with BN to that of 27 healthy, age-matched control participants during a reward-based learning task that required learning to use extra-maze cues to navigate a virtual 8-arm radial maze to find hidden rewards. We compared groups in their patterns of brain activation associated with reward-based spatial learning versus a control condition in which rewards were unexpected because they were allotted pseudo-randomly to experimentally prevent learning.

Results: Both groups learned to navigate the maze to find hidden rewards, but group differences in brain activity associated with maze navigation and reward processing were detected in the fronto-striatal regions and right anterior hippocampus. Unlike healthy adolescents, those with BN did not engage the right inferior frontal gyrus during maze navigation, activated the right anterior hippocampus during the receipt of unexpected rewards (control condition), and deactivated the left superior frontal gyrus and right anterior hippocampus during expected reward receipt (learning condition). These patterns of hippocampal activation in the control condition were significantly associated with the frequency of binge-eating episodes.

Conclusion: Adolescents with BN displayed abnormal functioning of the anterior hippocampus and fronto-striatal regions during reward-based spatial learning. These findings suggest that an imbalance in control and reward circuits may arise early in the course of BN.

Clinical trial registration information—An fMRI Study of Self-Regulation in Adolescents With Bulimia Nervosa; https://clinicaltrials.gov/; NCT00345943.

Key words: bulimia nervosa, reward, learning, fMRI, virtual reality

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Bulimia nervosa (BN) is characterized by binge-eating episodes that are followed by vomiting or another compensatory means to avoid weight gain. A severe sense of loss of control accompanies the binge-eating episodes.[1] Impulsive behaviors are also common in individuals with BN, suggesting the presence of pervasive difficulties in behavioral self-regulation.[1] Our previous functional magnetic resonance imaging (fMRI) findings demonstrate that self-regulation is impaired in adults[2] and adolescents[3] with BN due to their failure to engage fronto-striatal circuits appropriately, thereby likely contributing to their inability to regulate eating behaviors. Other fMRI data suggest that reward processing is also abnormal in individuals with BN due to functional disturbances in ventral aspects of the fronto-striatal circuits, insular cortex, and mesolimbic areas during the processing of food[4,5] and monetary[6] rewards. These abnormalities implicate the dopaminergic system and likely contribute to the increased drive to eat in binge-eating disorders, thereby contributing in part to the development of BN.[5] Unclear, however, is whether functional deficits in reward circuits are present in adolescents with BN, and how such deficits might alter reward learning processes,[7,8] thereby contributing to the learned associations between food and maladaptive eating behaviors in BN.

In addition to self-regulatory and reward-processing deficits, neuropsychological data suggest some impairment on visuo-spatial tasks in adults with BN.[9,10] Data from adolescents with bulimic behaviors suggest impaired performance on a Rey-Osterrieth Complex Figure Test, deficits that were further accentuated with increased cognitive load.[11] Those findings suggest difficulty with global integration, an element of central coherence that might be related to the disorganized cognitive style as well as the extreme mood states and impulsivity characteristic of adolescents with BN. Thus, adolescents with bulimic behaviors may also have difficulty with spatial learning, a form of learning that relies on episodic memory and requires binding or integrating mental representations of spatial cues into a coherent scene. To date, neither spatial learning nor its neural correlates

This article is discussed in an editorial by Dr. Guido K.W. Frank on page 929.

Supplemental material cited in this article is available online.

have been assessed in adults or adolescents with BN. This type of learning is often assessed in rodents by having them navigate an eight-arm radial maze,[12] a paradigm that we adapted to a virtual reality environment for use with fMRI.[13,14] Both the animal and human tasks require learning to use extra-maze cues to navigate and find hidden rewards. Healthy adults activate temporo-parietal areas when searching the maze, consistent with findings from other studies of healthy individuals performing other spatial navigation tasks.[15,16] Our translational fMRI task also includes a control condition in which the use of spatial cues to find hidden rewards is experimentally disabled, allowing us to assess the neural correlates of reward processing in the absence of spatial learning and thus disentangle the neural correlates of learning and reward. Data from healthy adults show limbic activation (hippocampus and amygdala) when receiving unexpected rewards in the control compared to expected rewards in the learning condition, a finding that may be due to enhanced dopaminergic firing from the ventral tegmental area to the ventral striatum (VS) and these mesolimbic areas in response to unpredicted rewards.[17] Those data were interpreted in terms of learning theory and positive prediction errors (PEs), signals generated when an outcome is better than expected.[18] These signals are typically associated with VS activation in humans,[19] but rodent electrophysiological data suggest that the hippocampus also generates PE signals during learning, signaling a mismatch between expected and experienced contexts.[20] Other fMRI data from healthy adults suggest that the lateral prefrontal regions are also involved in spatial learning, signaling when the outcome of a path choice deviates from the predicted outcome.[21] Thus, learning-related signals in the ventral striatum, limbic, and lateral prefrontal areas can be assessed with spatial learning tasks.

We recently reported that adults with obsessive-compulsive disorder (OCD) do not engage limbic areas (VS, anterior hippocampus, or amygdala) when receiving unpredicted rewards on our reward-based spatial learning task, data that we suggested may be attributed to disturbances in the mesolimbic dopamine pathway.[22] Similarly, adults with BN show reduced VS responses to unexpected gustatory information during reward learning,[23] data suggesting mesolimbic abnormalities akin to those reported in individuals with substance use disorder (SUD).[24] Conversely, adults with severe cocaine use disorder overengage limbic areas (VS and amygdala) when receiving unpredicted monetary rewards on our reward-based spatial learning task.[25] Although these findings from adults with SUD may be confounded by the chronic effects of substance exposure and habitual drug-seeking behaviors,[26] the long-term effects of binge-eating and purging on mesolimbic circuits are less clear.[5] Thus, we sought to explore the functioning of these circuits in adolescents with BN, early in the course of illness and not confounded by significant chronicity.

Using an ecologically valid navigation task adapted from animal research, we assessed the neural correlates of reward-based spatial learning in adolescent females with BN to understand both general reward learning mechanisms and those specific to spatial learning. Given findings of functional deficits in reward circuits in adults with BN,[4,6,23] deficits in visuo-spatial and global integration in adolescents with bulimic behaviors,[11] and our previous report of functional and anatomical abnormalities in the inferior frontal cortices in adolescents with BN,[3,27] we tested two specific hypotheses. First, we hypothesized that whereas both groups of adolescents would engage temporo-parietal areas while navigating the maze, participants with BN would not engage inferior frontal cortices during spatial learning. We also hypothesized that the adolescents with BN would not engage the VS, anterior hippocampus, or amygdala to the same extent as healthy participants when receiving unpredicted rewards in the control condition, or when predicted rewards were not received in the learning condition. In addition, we explored associations of fronto-striatal and temporo-parietal activations with task performance and the severity of BN symptoms.

METHOD

Participants

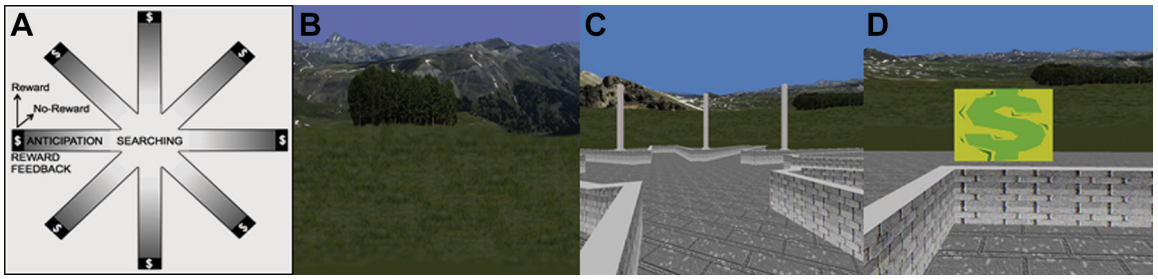
Adolescent females with BN (n = 27) and healthy comparison (HC) females (n=27), group-matched by age, race, and ethnicity, were recruited through flyers, the Internet, and word-of-mouth. Participants with a history of neurological illness, past seizures, head trauma with loss of consciousness, mental retardation, pervasive developmental disorder, or current Axis I disorders (other than depressive or anxiety disorders for the clinical group), as determined by the Kiddie–Schedule for Affective Disorders and Schizophrenia (SADS)–Present and Lifetime Version,[28] were excluded from the study. HC participants had no lifetime Axis I disorders. Bulimic symptom severity and prior diagnoses of anorexia nervosa were assessed using the Eating Disorders Examination.[29] Adolescents in the BN group were included if they had engaged in an average of one binge-eating episode (objective or subjective) and one purging episode per week within the past 3 months, with at least one binge-eating and purging episode occurring in the past month. The Institutional Review Board of the New York State Psychiatric Institute approved this study, including the informed consent and assent procedures for all participants.

Reward-Based Spatial Learning Paradigm

Our reward-based spatial learning paradigm has been described elsewhere.[13,14] Briefly, the paradigm was set within a virtual reality environment consisting of an 8-arm radial maze surrounded by landscape elements (spatial cues) meant to guide navigation (Figure 1). Prior to scanning, participants were administered a practice navigation session at a computer station. During scanning, non-magnetic goggles were used for stimulus presentation, and an MRI-compatible joystick (Current Designs Inc.) was used for navigation. Participants were tasked with navigating the maze environment in search of monetary rewards (denoted with $) that were hidden at the end of the maze arms. They were informed that in each of several task sessions, they could keep any money they found, but that they would lose money if they revisited an arm.

In the learning condition of the paradigm, each of the 8 maze arms was baited with a monetary reward. Participants could make as many arm visits (trials) as needed to collect all 8 rewards and to complete the learning condition (a total of 16 rewards across 2 sessions of the learning condition). To avoid revisiting arms and the associated monetary loss, they had to learn the layout of the spatial

FIGURE 1 The virtual reality (VR) environment. Note: (A) Schematic of the virtual maze depicting the events modeled: searching, reward anticipation, and reward feedback, reward and no-reward; (B) naturalistic spatial cues in the VR maze; (C) participants' view of the maze; and (D) the baited area at the end of an arm, with "$" indicating reward receipt.



cues. To prevent the use of systematic searching strategies in place of spatial learning strategies, each trial began at the center of the maze with the viewing perspective randomly reoriented.

The control condition was designed to provide an experience identical to the learning condition but without any possibility of spatial learning. To accomplish this, the spatial configuration of the same extra-maze cues used in the learning condition was randomized on each trial. The control condition terminated after participants made the same number of arm visits taken to complete the learning condition in the previous session. For example, if a given participant completed the learning condition in 22 trials (i.e., 8 correct and 14 error trials), the control condition for that participant would also consist of 8 rewarded and 14 error trials delivered randomly across the session. By controlling for all salient features of the learning condition (including lower-order stimulus features and higher-order task features), participants were rewarded without regard to their actual performance, and the possibility of spatial learning was therefore experimentally disabled in the control condition. Thus, contrasting neural activity in the learning condition (during spatial learning) and the control conditions (when spatial learning is impossible) reveals the neural correlates of reward-based spatial learning.

The reward-based spatial learning paradigm consisted of 2 sessions of the learning condition each followed by a session of the control condition, for a total of 32 rewarded trials (8 rewards $\times$ 2 conditions $\times$ 2 runs) and a number of unrewarded trials (errors) that varied for each participant. All participants were paid the same amount of money regardless of performance. Behavioral analyses and image acquisition and processing methods are described in Supplement 1, available online.

Image Analysis

As described previously,[22] extraction of subject-level signal differences across the learning and control conditions of the spatial learning task was conducted using general linear models in SPM8. Four regressors corresponded to modeled four events: "searching," the period between the start of a trial until an arm was selected; reward "anticipation," when traversing an arm toward its terminus where the feedback on the trial's outcome is given; "reward," when receiving feedback that the trial was successful and thus resulted in a monetary reward; and "no-reward," at the end of a trial when receiving the feedback that no money was won (Figure 1A). Regressors corresponding to the 4 events were convolved with a canonical hemodynamic response function and for each, a t-contrast vector was applied to the parameters (β_j) estimated for each voxel j producing 4 contrast images for each participant representing each regressor/event (searching, anticipation, reward, no-reward) compared across the 2 conditions (learning, control).

A random-effects "omnibus" analysis (F test in SPM8) was then used to test the significance of interactions between group (BN, HC), condition (learning, control), and event (searching, anticipation, reward, no-reward). To reduce the number of statistical tests, we limited the search space to a mask comprising regions in which we hypothesized, a priori, group differences during spatial learning (inferior frontal cortices) and reward receipt (VS, anterior hippocampus, and amygdala), as defined by the AAL atlas. Monte Carlo simulations (10,000 iterations) were implemented in AFNI (v. 16.0.01, Jan 27, 2016) 3dClustSim using a spatial autocorrelation function with a mean noise smoothness value (full width at half maximum [FWHM]) of 8.64 estimated in AFNI 3dFWHMx, 1-sided thresholding, and a first-nearest neighbor clustering. This approach generated a cluster extent threshold ($\kappa = 16$) that was then applied with an a priori significance threshold of $p < .005$ to correct for multiple comparisons ($p < .05$ familywise error [FWE] corrected). Interactions identified in the omnibus test were further examined in between-group activation maps (also with a voxel threshold of $p < .005$ together with $\kappa = 16$) that defined group differences in activation associated with the learning and control conditions for each event. These maps were generated from the 4 participant-level contrast images that represent each of the 4 events (searching, anticipation, reward, and no-reward) compared across the learning and control conditions. Parameter estimates for individual participants at the cluster maximum peaks of the statistical map for each contrast were derived by extracting subject-level fMRI signal differences across the learning or control conditions and an implicit global baseline that consisted of the unmodeled task components. In exploratory whole-brain analyses, another omnibus analysis followed by additional group comparisons were conducted, with a more lenient voxel threshold of $p < .01$ (uncorrected).

RESULTS

Participants

Functional MRI scans were acquired from 27 adolescents with bulimic behaviors (BN) and 27 age- and body mass index (BMI)–matched healthy comparison (HC) participants (Table 1). The BN group consisted of 9 outpatients and 11 inpatients who were scanned prior to the initiation of treatment, and 7 adolescents who were symptomatic but not seeking treatment. The mean duration of illness was less than 3 years. Of the BN group, 88% met *DSM-5* criteria for BN. The remaining reported subjective bulimic (binge-eating) episodes that were associated with loss of control over eating, which is considered more important than the

TABLE 1 Demographic and Clinical Characteristics of Participants

	Bulimia Nervosa		Healthy Control		Analysis		
Characteristic	**Mean**	**SD**	**Mean**	**SD**	***t***	***df***	***p***
Age, y	16.6	1.5	16.3	2.1	−0.7	52	.46
Height, inches	63.5	2.3	63.8	3.3	0.4	52	.67
Weight, lb	126.2	17.1	126.6	20.4	0.1	52	.94
BMI	22.03	2.0	21.98	1.9	−0.1	52	.95
Duration of Illness, mo	27.5	20.2	–				
WASI IQ Score							
Full-4	105.4	11.6	103.0	16.4	−0.6	50	.56
Verbal	109.2	12.9	105.8	16.0	−0.8	49	.42
Performance	99.8	9.6	97.8	15.0	−0.6	49	.56
EDE Ratings							
OBEs $_{\text{past 28 days}}$	15.3	18.7	–				
SBEs $_{\text{past 28 days}}$	17.0	24.5	–				
LOC eating $_{\text{past 28 days}}$	32.2	29.8	–				
Vomiting episodes $_{\text{past 28 days}}$	15.3	18.7	–				
BDI[a]	23.9	10.6	5.1	7.1	−5.8	31	<.01
CDI	50.6	2.7	52	–	0.5	4	.67
	n	**%**	**n**	**%**			
Race/Ethnicity							
White	16	59.3	9	33.3			
African American	0	0.0	4	14.8			
Hispanic	7	25.9	9	33.3			
Asian	3	11.1	4	14.8			
Other	1	3.7	1	3.7			
Past AN	5	18.5	–				
Medication	9	33	–				

Note: AN = anorexia nervosa; BDI = Beck Depression Inventory; BMI = body mass index; CDI = Children's Depression Inventory; EDE = Eating Disorders Examination; LOC = loss of control (sum of OBEs and SBEs); OBEs = objective bulimic episodes; SBEs = subjective bulimic episodes; WASI = Wechsler Abbreviated Scale of Intelligence.

[a]BDI scores were collected in n = 18 adolescents with bulimia nervosa and n = 15 healthy controls. CDI scores were collected in n = 9 adolescents with bulimia nervosa and n = 12 healthy controls.

amount of food consumed in defining bulimic episodes in adolescents.[30] All participants with BN engaged in vomiting (96%) or another compensatory behavior to avoid weight gain. Five adolescents with BN met *DSM-5* criteria for major depressive disorder (MDD), one for generalized anxiety disorder (GAD), one for social anxiety disorder (SAD), one for specific phobia, one for both MDD and GAD, and one for MDD and multiple anxiety disorders (GAD, SAD, specific phobia, and panic disorder). Nine participants with BN were being treated with selective serotonin reuptake inhibitors at the time of scanning.

Behavioral Performance

Both groups demonstrated learning on the task as evidenced by their significant improvement across runs, taking fewer trials and less time to complete the learning condition in run 2 compared to run 1 (Table S1, Supplement 1, available online). There were no significant group differences in trial duration across runs in the learning condition, or in performance across the learning and control conditions (Tables S1 and S2, Supplement 1, available online).

Analysis of Neural Activity

The omnibus analysis revealed significant 3-way interactions (group-by-condition-by-event) in the right anterior hippocampus and left inferior frontal gyrus (IFG). An exploratory whole-brain analysis revealed additional interactions in bilateral thalamus ($\kappa = 57$) and superior frontal gyrus (SFG; left: $\kappa = 72$, right: $\kappa = 29$), left VS ($\kappa = 27$), and right IFG ($\kappa = 7$). These 3-way interactions are summarized in Figure 2 and Table 2. Examination of group composite maps (group-by-condition interactions) for each event revealed that the interactions in the omnibus analysis derived from group differences in activations associated with spatial navigation and reward processing (the receipt and nonreceipt of rewards) in the learning versus control conditions.

Between-Group Analyses of Neural Activity

Neural Activity During Spatial Navigation. A significant group-by-condition interaction in the right IFG derived from its activation in the HC but not the BN group when navigating the maze and searching for rewards in the learning compared to control conditions ($p < .005$, corrected) (Table 2,

FIGURE 2 Whole-brain analysis indicating three-way interactions (diagnosis-by-condition-by-event). Note: Interactions were detected in right (R) hippocampus (Hi), bilateral thalamus (Thal), and fronto-striatal regions including left (L) ventral striatum (VS), bilateral inferior, and superior frontal gyri ($p < .01$, uncorrected). IFG = inferior frontal gyrus; SFG = superior frontal gyrus.

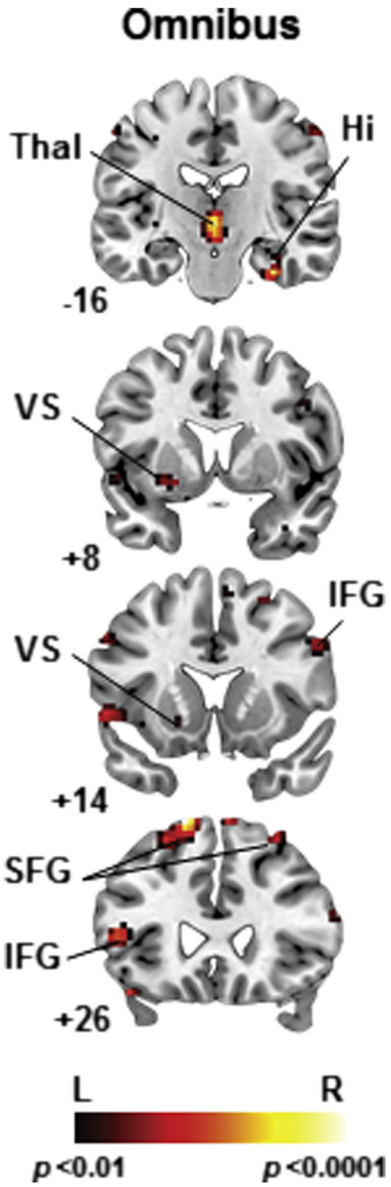


Figure 3). An exploratory whole-brain analysis revealed that both groups activated the temporal and parietal regions during spatial navigation in the learning condition, including the hippocampus, lingual and fusiform gyri, and superior parietal lobule ($p < .01$, uncorrected).

Neural Activity During Reward Processing. A significant group-by-condition interaction in the right anterior hippocampus ($p < .005$, corrected) and an additional interaction in left SFG (k=25; $p < .01$, uncorrected) derived from group differences across the learning and control conditions during the receipt of rewards (Table 2, Figure 4). In HC adolescents, activation of these regions was greater in response to receiving rewards in the learning compared to control conditions. Conversely, in adolescents with BN, deactivation of the right anterior hippocampus (along with the left SFG) was detected in the learning condition (when receiving expected rewards) and accompanied by activation of the right anterior hippocampus in the control condition (when receiving unexpected rewards).

Our exploratory whole-brain analysis also revealed group-by-condition interactions in bilateral thalamus ($\kappa = 23$), left SFG ($\kappa = 20$), and IFG ($\kappa = 55$) that were produced by group differences across the learning and control conditions when rewards were not received ($p < .01$, uncorrected) (Table 2, Figure 5). Specifically, these interactions derived from greater activation of these regions

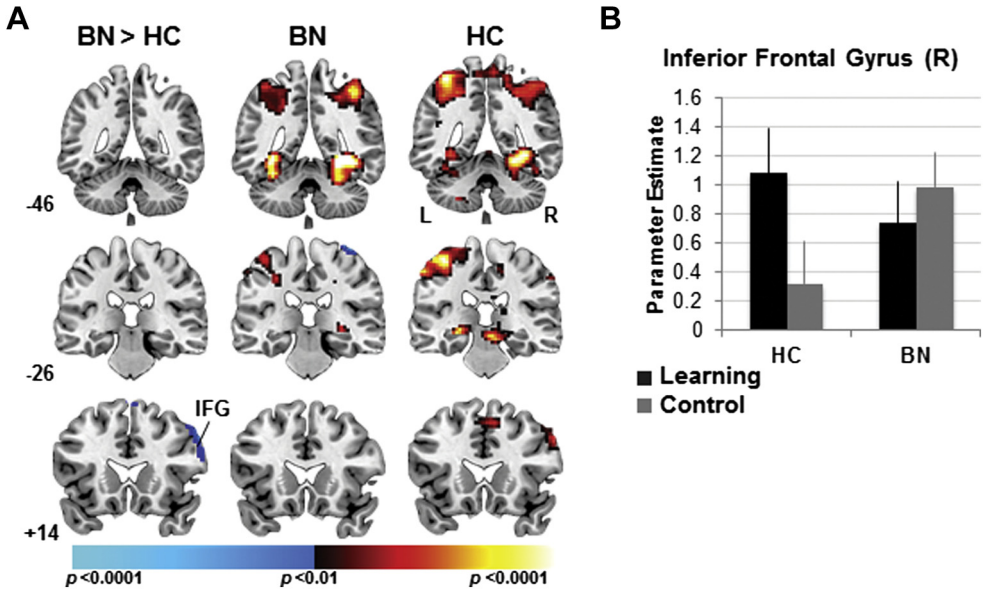
TABLE 2 Group Differences in Neural Activity Associated With Spatial Navigation and Reward Processing Across the Learning and Control Conditions

Region	Size	No. of Voxels	MNI Coordinates x	y	z	Statistic
Omnibus Test						
Hippocampus (anterior)[a]	R	36	33	−16	−29	5.63
Thalamus	L, R	57	0	−16	−2	5.81
Striatum (ventral)	L	27	−30	−1	−8	3.94
Superior frontal gyrus	L	72	−15	26	64	6.36
	R	29	30	32	55	4.65
Inferior frontal gyrus[a]	L	66	−48	26	10	4.55
	R	7	51	14	34	3.85
Spatial Navigation (Searching)						
Inferior frontal gyrus[a]	R	50	57	20	37	−3.13
Reward Receipt						
Hippocampus (anterior)	R	73	36	−19	−20	−3.40
Striatum (ventral)	L	3	−27	8	−8	−2.48
Superior frontal gyrus	L	25	−15	26	64	−3.50
No Reward						
Thalamus	L, R	23	0	−13	1	−3.15
Superior frontal gyrus	L	20	−21	32	55	−2.89
Inferior frontal gyrus	L	55	−54	17	−2	−2.89

Note: F statistics are reported for the omnibus analysis, and T statistics are reported for group differences in activations associated with the learning and control conditions for each event (p < .01, uncorrected). Montreal Neurological Institute (MNI) coordinates are provided for the peak (maxima) voxel within each cluster.

[a]Clusters significant at p < .005 after correction for multiple comparisons (p < .05 familywise error corrected).

FIGURE 3 Neural activity during spatial navigation. Note: (A) Group differences (left column) in activations associated with searching the maze in the learning versus the control condition detected in right inferior frontal gyrus. Group average activations for the adolescents with bulimia nervosa (BN; center) and healthy control adolescents (HC; right), with increases in signal during searching in the learning vs. control condition are shown in hot colors, and increases during searching in the control vs. learning condition in cool colors. These maps are thresholded at a two-sided significance threshold ($p < .01$, uncorrected). (B) Parameter estimates at the peak voxel of labeled right inferior frontal gyrus (IFG; 57 20 37) cluster in both conditions and for both groups. Error bars represent ±1 standard error of the mean.



in the learning relative to the control condition in HC adolescents, and from greater activation in the control relative to the learning condition in participants with BN.

Clinical Correlates. The frequency of bulimic behaviors was significantly associated with activation of the right anterior hippocampus during reward processing (Figure S1, Supplement 1, available online). Both binge-eating and vomiting episodes over the past 28 days correlated positively with activation of the right anterior hippocampus ($p < .05$) during the receipt of rewards in the control condition. Thus, the adolescents with the most severe bulimic symptoms activated the left anterior hippocampus in response to receiving unexpected rewards (control condition).

Potential Confounding Effects. A comparison of the map generated from our a priori omnibus analysis with maps generated in omnibus analyses excluding adolescents with BN taking medications, with concurrent MDD, with concurrent anxiety, or with lifetime AN suggests that these potential confounds did not contribute to the group differences in brain activations associated with reward-based spatial learning (Figure S2, Supplement 1, available online). Likewise, excluding the adolescents with BN who did not meet *DSM-5* criteria for BN or were not seeking treatment in our clinic did not alter these findings.

DISCUSSION

We investigated the neural correlates of reward-based spatial learning in adolescents with BN using a translational fMRI paradigm. In the learning condition, participants had to learn to use cues in the virtual environment to navigate the maze and to find hidden rewards. In the control condition, randomization of the scene experimentally disabled learning by making it impossible to use the cues for navigation. Both the healthy and BN groups exhibited spatial learning, similarly taking less time and fewer trials to find all rewards across task runs. However, we detected group differences in the activation of the cortical, limbic, and subcortical regions associated with spatial navigation and reward processing. Our a priori analyses revealed that only healthy adolescents engaged the right IFG when searching the maze and the right anterior hippocampus when receiving (expected) rewards in the learning condition. In contrast, adolescents with BN engaged the right anterior hippocampus when receiving (unexpected) rewards in the control condition—especially those with the most severe BN symptoms—and deactivated this region upon receipt of (expected) rewards in the learning condition. Our exploratory whole-brain analyses revealed that both groups of adolescents activated temporo-parietal areas typically engaged during maze navigation.[16] Unlike their healthy counterparts, adolescents with BN did not engage the left SFG and VS when receiving (expected) rewards or the bilateral thalamus and left IFG when such rewards were not received in the learning condition. Only adolescents with BN engaged the bilateral thalamus, left SFG, and IFG when not receiving (or expecting) rewards in the control condition. Together, these findings describe abnormal functioning of anterior hippocampus and fronto-striatal circuits during reward-based spatial learning in adolescents with BN.

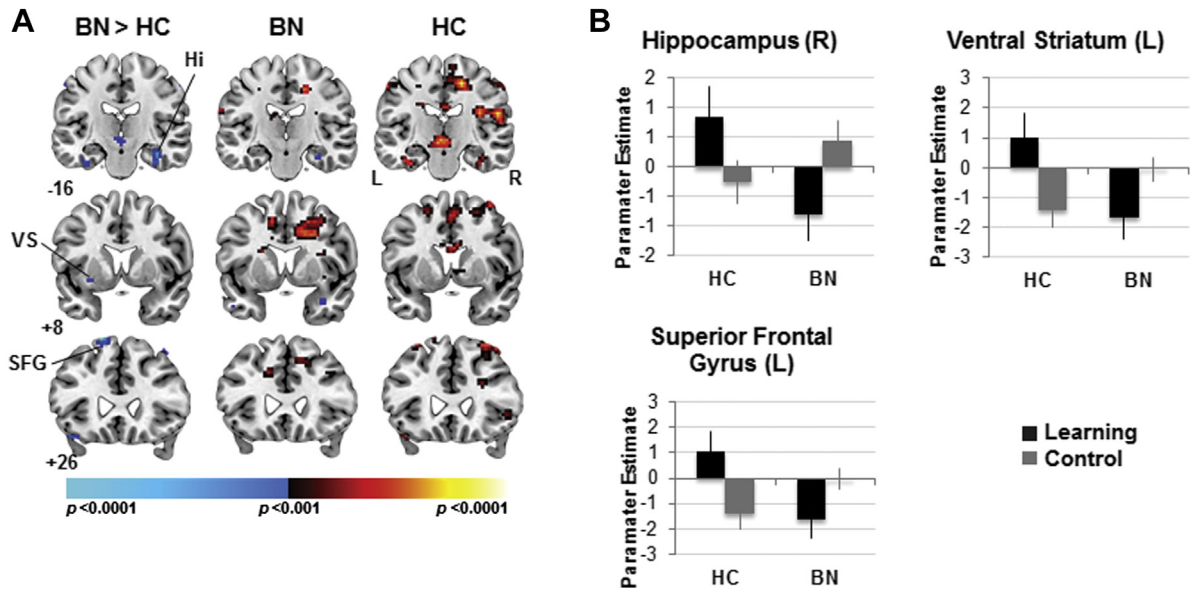
Unlike healthy adolescents, those with BN did not engage the right IFG when navigating the maze and searching for rewards in the learning condition, a finding consistent with the failure of adolescents[3] and adults[2] with BN to engage the inferior frontal cortices during self-regulation, and with findings of smaller local volumes within these cortices in BN compared to those in healthy individuals.[31] Right IFG supports self-regulatory capacities, as evidenced by its activation during successful response inhibition in healthy individuals.[32,33] Although we did not formally measure self-regulation here, maze navigation indeed requires the mobilization of attentional resources within the frontal cortices in healthy individuals.[34] Activation of the right IFG was detected during navigation in the learning versus control conditions and correlated with performance speed in healthy adolescents. Thus, deficient IFG activation during navigation in adolescents with BN further suggests that deficits in this inferior frontal attentional[35] and regulatory system are likely involved in the pathogenesis of BN.

Adolescents with BN engaged the anterior hippocampus when receiving unexpected rewards in the control condition and deactivated the anterior hippocampus and VS when receiving expected rewards in the learning condition. The anterior hippocampus is intrinsically connected to the VS,[36] and healthy adults activate these regions in response to unexpected reward receipt on this task,[13,22] data interpreted in light of positive PEs (i.e., signals generated when an outcome is better than expected) typically associated with VS activation in healthy individuals.[19] In contrast, expected value signals are generated when actual and expected outcomes match.[37] Both PE and expected value signals within the lateral prefrontal cortex, striatum, hippocampus, and midbrain have been detected in healthy individuals.[38,39] Thus, increased activation of the anterior hippocampus, VS, and SFG upon receipt of unexpected rewards may suggest increased sensitivity to positive PEs in adolescents with BN, whereas their deactivation of the anterior hippocampus and VS during the receipt of expected rewards may suggest insensitivity to EVs.

In contrast to previous findings from adults, healthy adolescents activated neither VS nor anterior hippocampus in the control condition, and instead engaged these regions when receiving rewards in the learning condition, perhaps suggesting that healthy adolescents are insensitive to positive PEs, consistent with data suggesting their increased sensitivity to negative PEs[40] (i.e., when expected rewards are omitted). Whereas healthy adolescents are sensitive to negative PEs, adolescents with BN may be more sensitive to positive PEs (i.e., receiving unexpected rewards). Moreover, activation of anterior hippocampus during unexpected reward receipt in the control condition was greatest in the adolescents who engaged in the most frequent binge-eating behaviors, suggesting that these adolescents may be most sensitive to positive PEs.

Data suggest that adults with BN are less sensitive than their healthy counterparts in their reward circuit responses to both positive and negative PEs when learning associations between conditioned visual and unconditioned taste

FIGURE 4 Neural activity during reward receipt. Note: (A) Group differences (left column) in activations associated with reward receipt in the learning versus control conditions detected in right hippocampus (Hi), left ventral striatum (VS), and bilateral superior frontal gyrus (SFG). Group average brain activations for the adolescents with bulimia nervosa (BN; center) and healthy control adolescents (HC; right), with increases in signal associated with reward receipt in the learning vs. control condition are shown in hot colors, and increases in the control vs. learning condition in cool colors. These maps are thresholded at a two-sided significance threshold ($p < .01$, uncorrected). (B) Parameter estimates at the peak voxel of labeled, hippocampal (36 −19 −20), VS (−27 8 −8), and superior frontal clusters (L: −15 26 64) in both conditions for both groups. Error bars represent ±1 standard error of the mean. L = left; R = right.



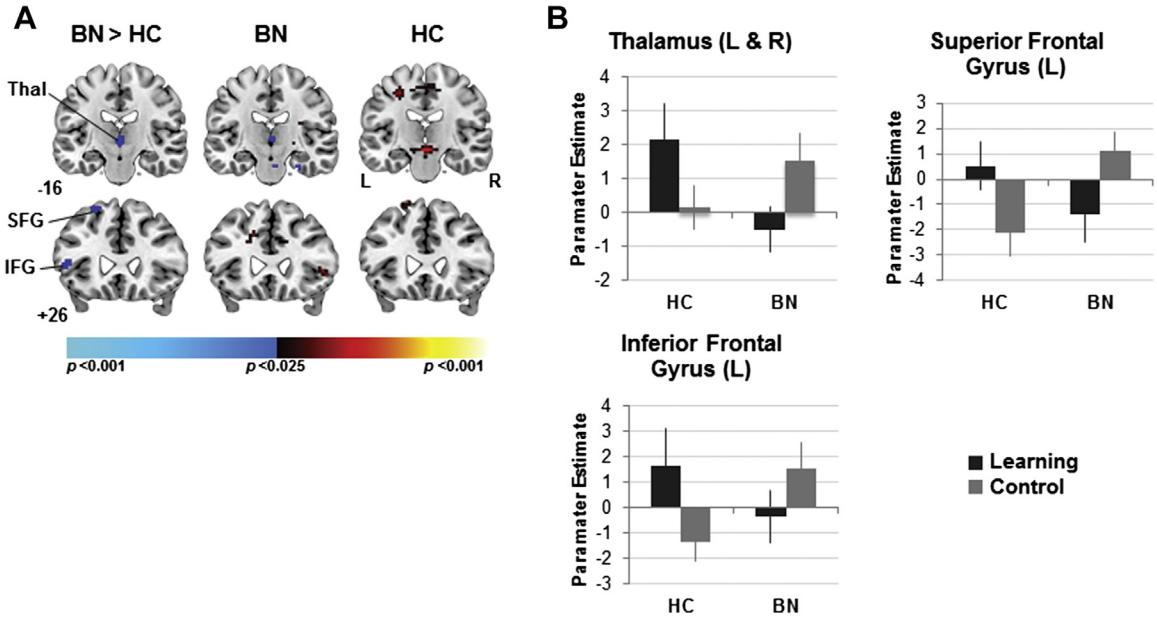
stimuli.[23] Women with BN showed reduced activation of the bilateral amygdala, left insula, and OFC in response to the unexpected receipt of unconditioned taste stimuli, and reduced activation of the bilateral amygdala, insula, and right VS in response to the unexpected omission of those stimuli. Although these findings cannot be compared directly with ours, given the differences across tasks and ages of our study samples, they converge in suggesting abnormal functioning of reward circuitry during learning in BN. We can also speculate that such functional abnormalities may be greater in adults with persistent BN, especially in the context of food-related stimuli.

BN is conceptualized as a "food addiction" based on behavioral and neurobiological features common across BN and substance use disorders (SUDs).[41] Dopaminergic dysfunction in reward circuits is documented in adults with both SUDs[24] and BN.[42] Cocaine-dependent men also show altered functioning of reward circuitry on our spatial task,[25] further pointing to dopaminergic, reward-circuit dysfunction in both disorders. Such functional abnormalities may influence the initial learning of binge–purge behaviors, consistent with the role of VS in the early stages of reinforcement-based learning[8] (in drug addiction[7]). Thus, dysfunction in the VS target of the midbrain dopaminergic system may contribute to neural changes that lead to BN. Given the differences between study samples (i.e., age, sex, illness chronicity, cocaine exposure), future studies should assess the functioning of the dopaminergic reward system trans-diagnostically and developmentally, over the course of these illnesses.

Together with the documented functional/anatomical abnormalities in lateral PFC in BN, our findings may reflect an imbalance in the circuits that support top-down (attentional and regulatory) and more bottom-up (reward) processes that characterizes eating disorders.[43] Longitudinal studies are required to determine whether this imbalance is associated with the developmental trajectory of BN or may be a target for the development of novel treatments (or additions to evidence-based treatments) aimed, for example, at enhancing control over disordered eating behaviors or diminishing the salience of food rewards. Brain stimulation techniques, such as repetitive transcranial magnetic stimulation, targeting reward circuits via the striatal, hippocampal, or prefrontal regions, might achieve this goal. In addition, a better understanding of reward learning in BN could inform future research aimed at assessing how reward circuit function might change following treatments based on the principles of conditioning and learning (i.e, cue exposure with response prevention of binge-eating or vomiting).[44]

This study is limited by the modest sample size and the inclusion of adolescents with BN and comorbid depression and anxiety disorders. However, the presence of these comorbidities did not contribute significantly to our findings, and inclusion of these cases is consistent with the true presentation of BN in adolescents in the population.[45] Although inclusion of adolescents who did not meet

FIGURE 5 Neural activity during no-reward receipt. Note: (A) Group differences (left column) in activations associated with no reward receipt in the learning versus control conditions detected in bilateral thalamus (Thal), left inferior and superior gyri. Group average activations for the adolescents with bulimia nervosa (BN; center) and healthy (HC; right) participants with increases in signal associated with no reward receipt in the learning vs. control condition are shown in hot colors, and increases in the control vs. learning condition in cool colors. These maps are thresholded at a two-sided significance threshold ($p < .01$, uncorrected). (B) Parameter estimates at the peak voxel of labeled thalamic (left [L] and right [R]: 0 −13 1), inferior (L: −54 17 −2) and superior (L: −21 32 55) frontal clusters. IFG = inferior frontal gyrus; SFG = superior frontal gyrus; VS = ventral striatum. Error bars represent ±1 standard error of the mean.



DSM-5 criteria for BN may have decreased our ability to detect group differences in brain activations, our inclusion criteria were consistent with those used in other studies of adolescents[11,46] and consistent with data suggesting that the loss of control during eating is more definitive of binge episodes for adolescents than the amount of food consumed.[30] Moreover, our detection of significant group differences in activations with this sample suggests that the functional abnormalities reported herein are likely robust and relevant to adolescents with subclinical BN. We did not control for hunger/satiety or menstrual status. Hunger might affect attentional and executive processes[47] that are required for maze navigation but unlikely involved in reward processing. Although menstrual status may affect reward-related neural functioning,[48] we have no reason to believe that menstrual status differed across the BN and healthy adolescents in this study. Finally, findings from our exploratory analyses must be interpreted with caution, as they were not corrected for multiple comparisons.

In summary, we assessed the neural correlates of spatial learning and reward processing in adolescents with BN using a translational fMRI paradigm that we previously used in studies of adults with OCD[22] and with SUDs.[25] These findings from adolescents with BN point to functional abnormalities within the anterior hippocampus and fronto-striatal regions associated with reward-based learning, and suggest that an increased sensitivity to positive PEs, together with deficient engagement of the inferior frontal cortices, may contribute to the purported imbalance between top-down control and more bottom-up reward circuits that characterizes eating disorders.[43] Indeed, abnormal activation of anterior hippocampus and VS during the receipt of unexpected rewards (and increased sensitivity to positive PEs) in adolescents with BN suggests altered bottom-up representations of action–outcome associations that may contribute to the learned associations between food cues and maladaptive binge-eating behaviors. These functional abnormalities also suggest deficits in the integration of contextual information during spatial learning and reward processing that are likely related to the cognitive disorganization, extreme mood states, and impulsivity characteristic of adolescents with BN. &

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Drs. Cyr, Tau, Friedl, and Marsh and Mr. Zhao, and Mss. Stefan and Terranova are with the Division of Child and Adolescent Psychiatry, the New York State Psychiatric Institute and the College of Physicians and Surgeons, Columbia University, New York. Mr. Zhao is also with School of Information Science and Engineering, Central South University, Changsha, China. Dr. Wang is with the Division of Translational Imaging, the New York State Psychiatric Institute and College of Physicians and Surgeons, Columbia University.

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Correspondence to Rachel Marsh, PhD, Columbia University and the New York State Psychiatric Institute, 1051 Riverside Drive, Unit 74, New York, NY 10032; e-mail: MarshR@nyspi.columbia.edu

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SUPPLEMENT 1

METHOD

Behavioral Analyses

Participants who demonstrate learning on the task should require fewer trials and be faster at obtaining all 8 rewards during the second compared with the first learning condition (e.g., run 2 versus run 1). To test for group differences in learning, linear mixed models with repeated measures over scan runs were implemented in SAS version 8.0 (SAS Institute, Cary, NC). Separate models were conducted for trials (number of navigation attempts taken to obtain the 8 possible rewards in the learning condition), performance speed (time taken to collect the 8 rewards), and trial duration (mean time taken to complete each trial = performance speed / trials) entered as dependent variables with run (run 1, run 2) entered as the within-subjects factor, and group as the between-subjects factor. Statistical significance of group-by-run interactions in the models for trials, performance speed, and trial duration denoted group differences in learning.

An additional analysis was conducted to assess differences across the bulimia nervosa (BN) and healthy control (HC) groups in performance across the learning and control conditions. Performance speed (time taken to obtain the 8 possible rewards in both runs across conditions) was entered as a dependent variable in a linear mixed model with condition (learning, control) entered as a within-subjects factor, and group entered as a between-subjects factor. This analysis yielded statistics for group-by-condition interactions and main effects of group and condition for performance speed across conditions. Because the total number of trials required in the learning condition determined those values for the control condition for each participant, this variable was not compared statistically across the learning and control conditions.

Image Acquisition and Processing

Images were acquired with a GE Signa 3 Tesla LX scanner (Milwaukee, WI) and a standard quadrature GE head coil using previously described procedures.[1] In brief, T1-weighted sagittal localizer guided positioning of functional axial echoplanar images (EPI) parallel to the anterior commissure–posterior commissure line. Parameters for EPI acquisition with T2*-sensitive gradient-recall, single-shot, echo-planar pulse sequence were TR = 2,800 milliseconds, TE = 25 milliseconds, 90° flip angle, single excitation per image, 24 × 24-cm field of view, a 64 × 64 matrix, 43 slices 3 mm thick, no gap, and covering the entire brain. The performance of each participant in the learning condition determined the number of EPI volumes collected (maximum 322 volumes/run).

Our SPM8 (Wellcome Department of Imaging Neuroscience, London, UK; http://www.fil.ion.ucl.ac.uk/spm) and FSL (FMRIB Software Library; www.fmrib.ox.ac.u) image preprocessing procedures were batched in MATLAB 7.9 (Mathworks, Natick, MA) and have been previously described.[1] In brief, these procedures included slice-time correction with windowed Fourier interpolation, motion correction, and realignment.[2] ArtRepair was used to correct images with estimates for peak motion exceeding 3 mm (1 voxel) translation,[3] and runs with more than 15% of repaired images were discarded.[4] The images were then normalized to Montreal Neurological Institute (MNI) space of $3 \times 3 \times 3$ mm^3 using the functional (EPI) MNI template. The normalized

TABLE S1 Behavioral Performance on the Reward-Based Spatial Learning Task

Comparison	HC	BN	Main Effect Run *F* (*df*, *p*)
Number of Trials (SD)			13.46 (1, <.001)
Run1	17.6 (9.5)	14.5 (6.0)	
Run2	13.5 (6.3)	10.5 (4.1)	
T Stat Run 1 vs. 2 (*df*, *p*)	2.08 (21, .049)	3.20 (24, .004)	
Main Effect Group *F* (*df*, *p*)	2.80 (1, .101)		Group × Run 0.17 (1, .678)
Performance Speed (SD)			29.06 (1, <.001)
Run1	148.2 (56.6)	149.1 (99.1)	
Run2	94.0 (42.6)	77.0 (28.5)	
T Stat Run 1 vs. 2 (*df*, *p*)	4.38 (24, <.001)	3.85 (21, <.001)	
Main Effect Group *F* (*df*, *p*)	0.01 (1, .915)		Group × Run 0.938 (1, .34)
Trial Duration (SD)			21.18 (1, <.001)
Run1	9.6 (5.2)	9.9 (2.9)	
Run2	7.7 (4.1)	7.6 (2.9)	
T Stat Run 1 vs. 2 (*df*, *p*)	2.69 (21, .014)	4.44 (24, <.001)	
Main Effect Group *F* (*df*, *p*)	0.10 (1, .667)		Group × Run 0.10 (1, .753)

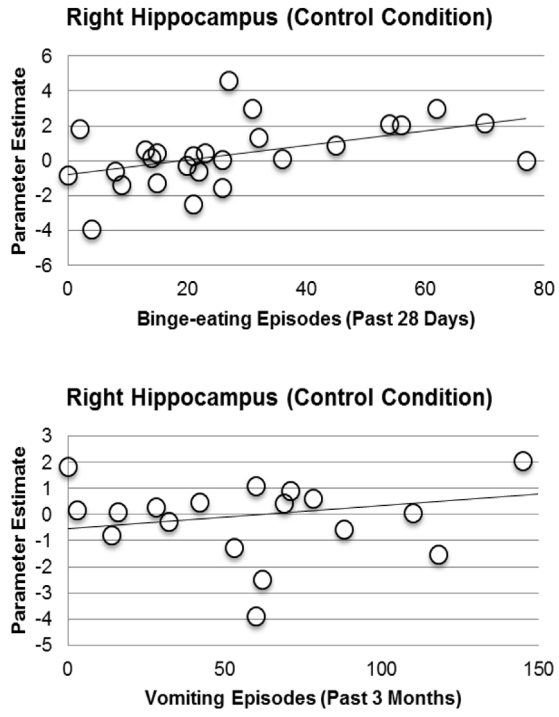
Note: BN = bulimia nervosa; HC = healthy control; Stat = statistic.

TABLE S2 Group Comparison of Performance Speed Across the Learning and Control Conditions

Comparison	HC	BN	Main Effect Condition F (*df, p*)
Run 1 Performance Speed (SD)			0.49 (1, .487)
Learning	148.2 (56.6)	149.1 (99.1)	
Control	149.7 (62.2)	138.2 (81.5)	
T stat Learning vs. Control (*df, p*)	−0.23 (24, .819)	0.93 (25, .362)	
Main Effect Group *F* (*df, p*)	0.07 (1, 0.797)		Group × Condition
			0.84 (1, .364)
Run 2 Performance Speed (SD)			0.06 (1, .812)
Learning	94.0 (42.6)	77.0 (28.5)	
Control	96.9 (43.5)	77.0 (29.5)	
T stat Learning vs. Control (*df, p*)	−0.68 (23, .502)	0.34 (25, .736)	
Main Effect Group *F* (*df, p*)	2.96 (1, .092)		Group × Condition
			0.52 (1, .474)
Total Time (SD)			0.28 (1, .597)
Learning	233.6 (77.3)	230.4 (120.4)	
Control	237.9 (84.4)	217.0 (99.6)	
T stat Learning vs. Control (*df, p*)	−0.61 (21, .551)	0.91 (24, .371)	
Main Effect Group *F* (*df, p*)	0.19 (1, .661)		Group × Condition
			1.08 (1, .304)

Note: BN = bulimia nervosa; HC = healthy control.

FIGURE S1 Clinical correlates: scatterplots showing the positive correlations of binge-eating (top) and vomiting (bottom) episodes with activation of the right hippocampus during reward receipt in the control condition. Note: One outlier (with 3.6 standard deviations from the mean binge-eating episodes in the sample) was removed from these analyses and plots.



images then underwent spatial smoothing (Gaussian filter of 8 mm full width at half maximum) and high-pass temporal filtering with a discrete cosine transform (cutoff at 1/128 Hz).

RESULTS

Behavioral Performance

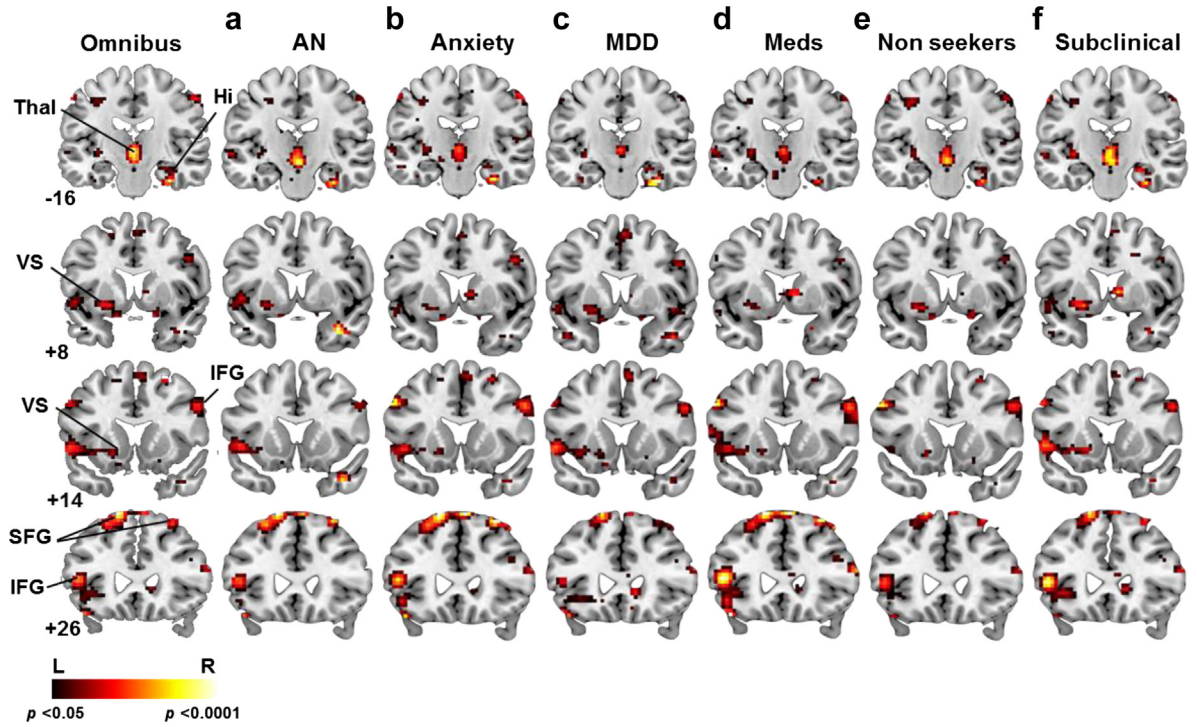
Both groups demonstrated learning on the task, as evidenced by their significant improvement across runs, taking fewer trials and less time to complete the learning condition in run 2 compared to run 1 (Table S1). There were no significant group differences in trial duration across runs in the learning condition (Table S1) or in performance across the learning and control conditions (Table S2).

Exploratory Imaging Analyses

Clinical Correlates. The frequency of bulimic behaviors was significantly associated with activation of the right anterior hippocampus during reward processing (Figure S1). Both binge-eating and vomiting episodes over the past 28 days correlated positively with activation of the right anterior hippocampus ($p < .05$) during the receipt of rewards in the control condition. Thus, the adolescents with the most severe bulimic symptoms activated the left anterior hippocampus in response to receiving unexpected rewards (control condition). Finally, no significant relationship was found between brain activation and illness duration.

Potential Confounding Effects. A comparison of the map generated from our a priori omnibus analysis with maps generated in omnibus analyses excluding adolescents with BN taking medications, with concurrent major

FIGURE S2 Medication and comorbidity effects: diagnosis-by-condition-by-event interactions were still detected in right hippocampus (Hi), bilateral thalamus (Thal), and fronto-striatal regions, including the left ventral striatum (VS), bilateral inferior, and superior frontal gyri (red), when we excluded (a) the bulimic adolescents with a history of anorexia nervosa (AN), (b) those with comorbid anxiety, (c) those with comorbid depression, (d) those who were taking medications, (e) those who were not seeking treatment, and (f) those with subclinical bulimia nervosa (BN) according to *DSM-5* criteria. Note: IFG = inferior frontal gyrus; MDD = major depressive disorder; Meds = medications; SFG = superior frontal gyrus.



depressive disorder (MDD), concurrent anxiety, or lifetime anorexia nervosa (AN) suggests that these potential confounds did not contribute to the group differences in brain activations associated with reward-based spatial learning (Figure S2). Likewise, excluding the adolescents with BN who did not meet *DSM-5* criteria for BN or were not seeking treatment in our clinic did not alter these findings.

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