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 Inc., 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=2800msec, TE=25msec, 90° flip angle, single excitation per image, 24x24cm FOV, a 64x64 matrix, 43 slices 3mm 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 3mm (one 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 x 3 x 3 mm^3 using the functional (EPI) MNI template. The normalized images then underwent spatial smoothing (Gaussian filter of 8mm 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 right anterior hippocampus during reward processing (Figure S1). Both binge-eating and vomiting episodes over the past 28 days correlated positively with activation of right anterior hippocampus (*p's* < .05) during the receipt of rewards in the control condition. Thus, the adolescents with the most severe bulimic symptoms activated 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 depressive disorder (MDD), with 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.

1. Marsh R, Tau GZ, Wang Z, et al. Reward-Based Spatial Learning in Unmedicated Adults with Obsessive-Compulsive Disorder. *Am J Psychiatry.* 2015;172:383-392.

2. Jazzard P, Matthews PM, Smith SM. *Functional MRI—An Introduction to Methods.* New York: Oxford University Press; 2002.

3. Mazaika P, Hoeft F, Glover GH, Reiss AL. Methods and Software for fMRI Analysis for Clinical Subjects. Paper presented at the 15th Annual Meeting of the Organization for Human Brain Mapping, San Francisco, CA; 2009.

4. Friston KJ, Williams S, Howard R, Frackowiak RS, Turner R. Movement-related effects in fMRI time-series. *Magnetic Resonance Medicine.* 1996;35:346-355.

Table S1. Behavioral Performance on the Reward-Based Spatial Learning Task

Comparison		**HC**	**BN**	Main Effect Run F (DF, *p*)
Number of Trials (SD)	Run1	17.6 (9.5)	14.5 (6.0)	**13.46 (1, <0.001)**
	Run2	13.5 (6.3)	10.5 (4.1)	
T Stat Run 1 v 2 (DF, *p*)		**2.08 (21, 0.049)**	**3.20 (24, 0.004)**	
Main Effect Group F (DF, *p*)		2.80 (1, 0.101)		Group x Run 0.17 (1, 0.678)
Performance Speed (SD)	Run1	148.2 (56.6)	149.1 (99.1)	**29.06 (1, <0.001)**
	Run2	94.0 (42.6)	77.0 (28.5)	
T Stat Run 1 v 2 (DF, *p*)		**4.38 (24, <0.001)**	**3.85 (21, <0.001)**	
Main Effect Group F (DF, *p*)		0.01 (1, 0.915)		Group x Run 0.938 (1, 0.34)
Comparison		**HC**	**BN**	Main Effect Run F (*p*)
Trial Duration (SD)	Run1	9.6 (5.2)	9.9 (2.9)	**21.18 (1, <0.001)**
	Run2	7.7 (4.1)	7.6 (2.9)	
T Stat Run 1 v 2 (DF, *p*)		**2.69 (21, 0.014)**	**4.44 (24, <0.001)**	
Main Effect Group F (DF, *p*)		0.10 (1, 0.667)		Group x Run 0.10 (1, 0.753)

Note: Significant findings are denoted in bold. BN = bulimia nervosa; HC = healthy control; Stat = statistic.

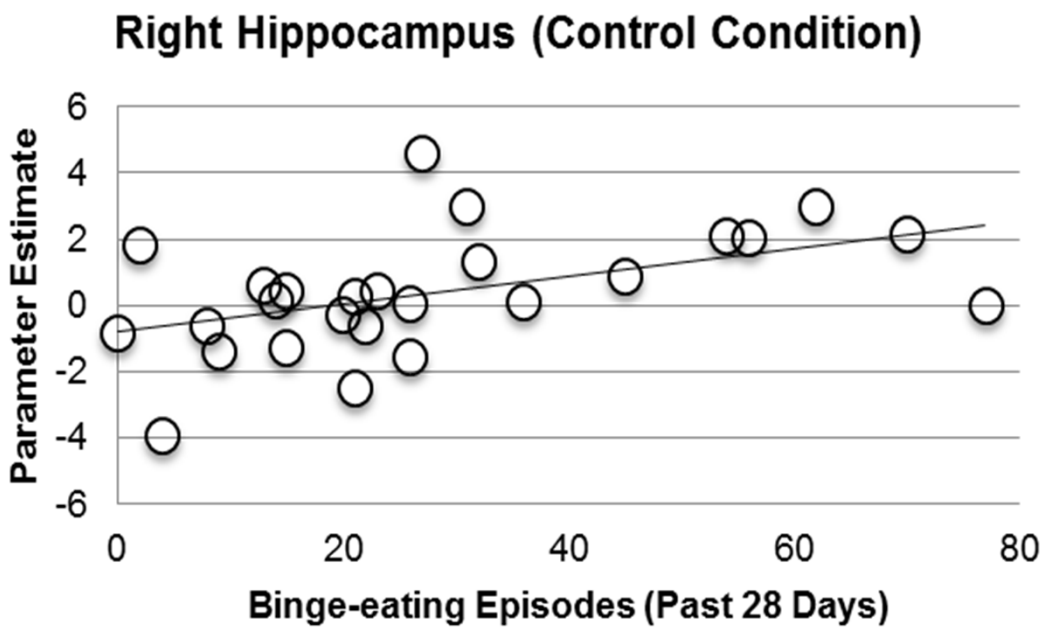
Table S2. Group Comparison of Performance Speed Across the Learning and Control Conditions

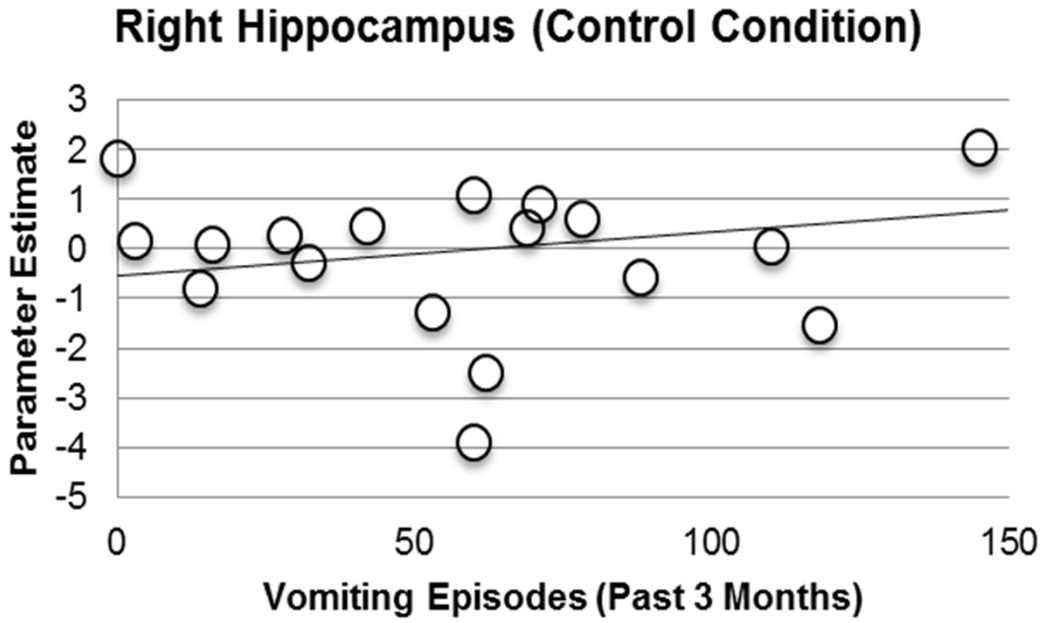
Comparison		**HC**	**BN**	Main Effect Condition F (DF, *p)*
Run 1 Performance Speed (SD)	Learning	148.2 (56.6)	149.1 (99.1)	0.49 (1, 0.487)
	Control	149.7 (62.2)	138.2 (81.5)	
T stat Learning v Control (DF, *p*)		-0.23 (24, 0.819)	0.93 (25, 0.362)	
Main Effect Group F (DF, *p)*		0.07 (1, 0.797)		Group x Condition 0.84 (1, 0.364)
Run 2 Performance Speed (SD)	Learning	94.0 (42.6)	77.0 (28.5)	0.06 (1, 0.812)
	Control	96.9 (43.5)	77.0 (29.5)	
T stat Learning v Control (DF, *p*)		-0.68 (23, 0.502)	0.34 (25, 0.736)	
Main Effect[b] Group F (DF, *p)*		2.96 (1, 0.092)		Group x Condition 0.52 (1, 0.474)
Total Time (SD)	Learning	233.6 (77.3)	230.4 (120.4)	0.28 (1, 0.597)
	Control	237.9 (84.4)	217.0 (99.6)	
T stat Learning v Control (DF, *p*)		-0.61 (21, 0.551)	0.91 (24, 0.371)	
Main Effect[b] Group F (DF, *p)*		0.19 (1, 0.661)		Group x Condition 1.08 (1, 0.304)

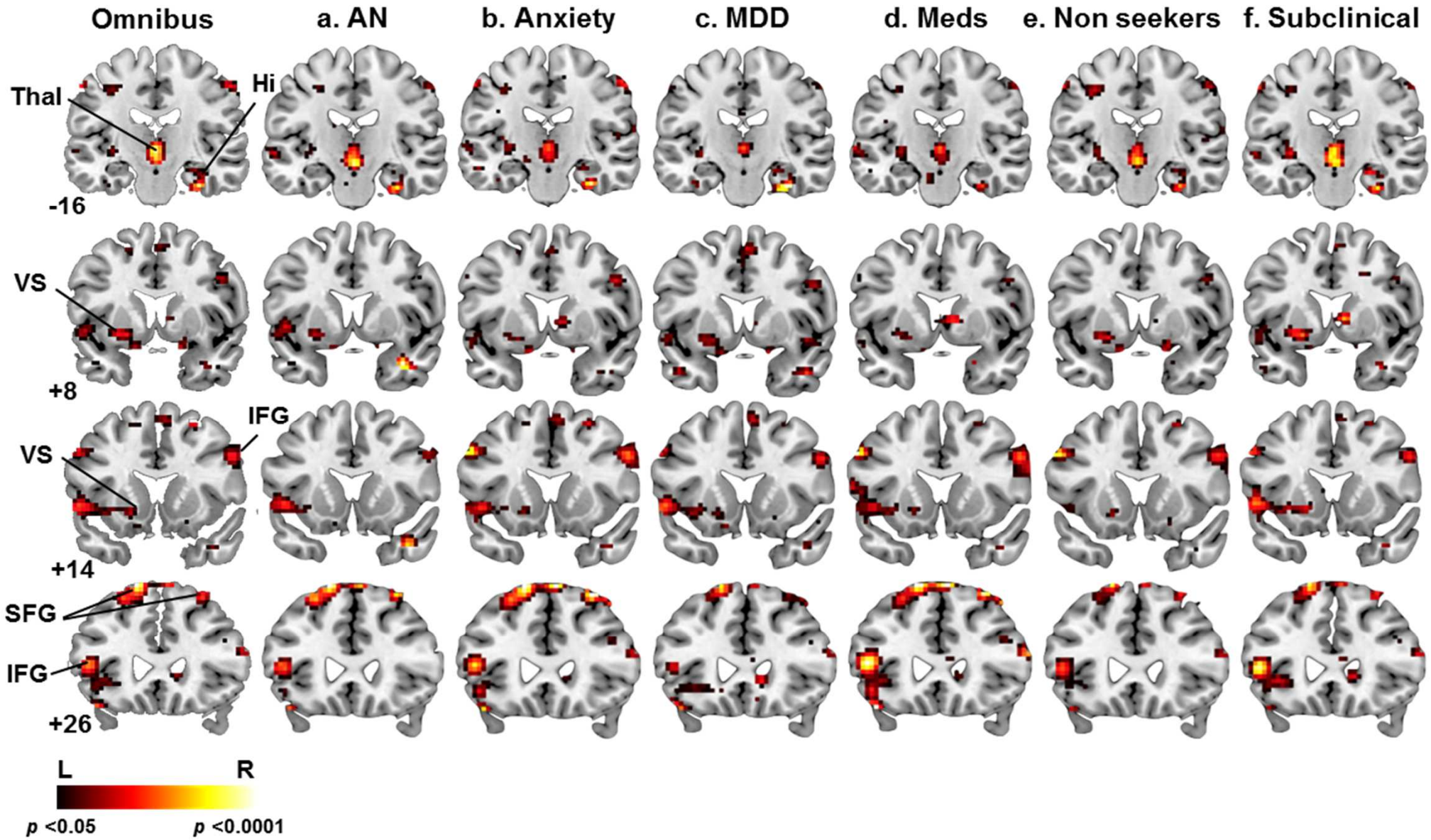
Note: BN = bulimia nervosa; HC = healthy control.

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

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 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, and (d) those who were taking medications, (e) those who were not seeking treatment, and (f) those who were subclinical bulimia nervosa (BN) according to *DSM-5* criteria. Note: IFG = inferior frontal gyrus; MDD = major depressive disorder; Meds = medications; SFG = superior frontal gyrus.


Right Hippocampus (Control Condition)
Parameter Estimate
6
4
2
0
-2
-4
-6
0
20
40
60
80
Binge-eating Episodes (Past 28 Days)


Right Hippocampus (Control Condition)
Parameter Estimate
3
2
1
0
-1
-2
-3
-4
-5
0
50
100
150
Vomiting Episodes (Past 3 Months)


Omnibus
a. AN
b. Anxiety
c. MDD
d. Meds
e. Non seekers
f. Subclinical
Thal
Hi
-16
VS
+8
IFG
VS
+14
SFG
IFG
+26
L
R
p <0.05
p <0.0001