EMPIRICAL ARTICLE

A Pilot Study Linking Reduced Fronto–Striatal Recruitment during Reward Processing to Persistent Bingeing Following Treatment for Binge-Eating Disorder

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ABSTRACT

Objective: The primary purpose of this study was to examine neurobiological underpinnings of reward processing that may relate to treatment outcome for binge-eating disorder (BED).

Method: Prior to starting treatment, 19 obese persons seeking treatment for BED performed a monetary incentive delay task during functional magnetic resonance imaging (fMRI). Analyses examined how the neural correlates of reward processing related to binge-eating status after 4-months of treatment.

Results: Ten individuals continued to report binge-eating ($BE_{post\text{-}tx}$) following treatment and 9 individuals did not ($NBE_{post\text{-}tx}$). The groups did not differ in body mass index. The $BE_{post\text{-}tx}$ group relative to the $NBE_{post\text{-}tx}$ group showed diminished recruitment of the ventral striatum and the inferior frontal gyrus during the anticipatory phase of reward processing and reduced activity in the medial prefrontal cortex during the outcome phase of reward processing.

Discussion: These results link brain reward circuitry to treatment outcome in BED and suggest that specific brain regions underlying reward processing may represent important therapeutic targets in BED. © 2013 Wiley Periodicals, Inc.

Keywords: binge eating; fMRI; reward; treatment outcome

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Introduction

Binge-eating disorder (BED) is characterized by recurrent binge-eating (eating unusually large quantities of food accompanied by subjective feelings of loss of control) and marked distress in the absence of inappropriate weight compensatory behaviors. BED is a prevalent problem associated strongly with obesity and biospsychosocial impairment[1] and is distinct from obesity and other eating disorders.[2,3] Treatment research has identified some specific effective medication[4] and psychological[5] interventions for BED. Unfortunately, even the best-established treatments do not achieve abstinence from binge-eating in roughly half of patients with BED.[6,7] Identifying potential

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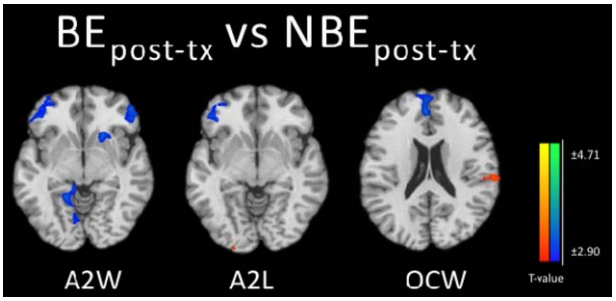
FIGURE 1 Group differences on the Monetary Incentive Delay Task in frontostriatal areas in obese individuals with binge eating disorder (BED) following treatment. Brain activation maps demonstrate differences in the A2 winning phase (A2W, associated with the anticipation of winning money), the A2 losing phase (A2L, associated with the anticipation of losing money), and the outcome (OC) winning phase (OCW, associated with the receipt of a monetary reward). Maps depict differences in BED participants who reported bingeing following treatment (n = 10) contrasted with BED participants who did not report bingeing following treatment (n = 9). All contrast maps are thresholded at an uncorrected level of $p < .05$ two-tailed and family-wise-error-corrected at $p < .05$. Blue color demonstrates areas where bingeing subjects show relatively less activation and red color indicates where bingeing participants show relatively greater activation. The right side of the brain is on the right. BEpost-tx = Binge Eating Post Treatment. NBEpost-tx = No Binge Eating Post Treatment. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]



maintenance factors perpetuating binge-eating behaviors is critical since it could inform both more effective decision-making about treatment prescriptions and development. To date, research has identified relatively few demographic or psychosocial predictors of treatment outcomes for BED,[3,8] and no study has examined neurobiological correlates of treatment response. Neurobiological factors may be particularly well-suited for identifying underlying pathology or maintenance factors that could predict the development of the disorder, the persistence of symptoms, or those factors predicting treatment response. Previous fMRI studies in obese (non-BED) relative to lean individuals show alterations in insular and inferior frontal gyrus regions during food anticipation,[9] as well as altered striatal responding with weight changes.[9–11] To date, very few neuroimaging studies have examined neurobiological factors related to treatment response in BED.

Recently investigators have noted the importance of considering cognitive mechanisms beyond food cue responsivity when investigating the neurobiology of eating disorders like BED.[12] Understanding neural systems underlying eating behaviors in binge-eating disorder (BED) as they relate to treatment response is important for treatment development, as has been proposed for other disorders like drug addictions and pathological gambling.[13,14] While many treatments for BED promote cognitive strategies that may rely upon specific cognitive mechanisms,[5] to date few studies have examined neurobiological underpinnings of these cognitive mechanisms that may bear influence on treatment outcome. Reward processing has been proposed to relate to important aspects of cognitive behavioral therapy in pathological gambling and may also contribute to analogous processes in BED treatment.[14] Neuroimaging studies in BED and non-BED patients have identified functional differences in ventral prefrontal cortex, orbitofrontal cortex (OFC), and ventral striatum.[15,16] However, few studies have examined how activity underlying these cognitive processes may relate to treatment outcome. Anticipatory signaling is an important factor in food intake,[17] and overeating may contribute to reduced responsivity in the striatum.[18] Preclinical studies suggest that high-fat/sugar diets reduce signaling in dopaminergic neurocircuitry, including in the striatum.[18,19] In humans, weight gain is associated with reduced striatal signaling following palatable food consumption.[20]

To date, no study has examined how general reward processing in BED may relate to binge-eating status, independent of weight, following treatment. Previously, our group has employed a widely-used reward processing task (the monetary incentive delay task) and observed reduced striatal activation during an anticipatory phase of monetary reward processing in obese individuals with BED, relative to non-BED obese individuals.[15] Studies examining the neural substrates of reward processing have identified specific phases of reward processing: anticipatory phases tend to recruit striatal activity, whereas outcome phases of reward processing tend to engage more medial areas of the prefrontal cortex.[21,22] Attentional demands appear to show some neuronal network overlap, particularly in anterior-cingulate, OFC, and mesolimbic regions.[23] In this study, we examined the prospective relations of brain activations underlying reward processing to changes in binge-eating status following treatment. We hypothesized that individuals reporting binge-eating following 4 months of treatment would differ from those reporting no bingeing in pre-treatment patterns of brain activations underlying reward processing. Specifically, we hypothesized that individuals showing persistent binge-eating versus those reporting no binge-eating would show at treatment onset relatively diminished fronto–striatal activations during anticipatory and outcome phases of reward processing, including reduced ventral striatal recruitment during reward anticipation. Given the role of the inferior frontal gyrus (IFG) in inhibitory control[24] and altered recruitment of this area in other populations characterized by impaired

impulse control,[25] we hypothesized that anticipatory activity in this region would relate to binge-eating status. Following consumption of a meal, increased recruitment in the medial prefrontal cortex (mPFC), particularly in more dorsal and frontopolar areas, has been linked to dieting success.[26,27] This association may relate to different functions to which mPFC function contributes; e.g., decision-making, emotional processing, intertemporal choice or processing of rewarding outcomes.[22,28–30] Thus, the mPFC may play a central role in self-regulatory control through encoding of value information (e.g. food tastiness), tracking and integrating internal-external signals (e.g. hunger, satiety, diet goal) over time and directing response-set shifts if necessary (e.g. cessation of eating).[31,32]

We therefore hypothesized that BED individuals with persistent binge-eating following treatment would show reduced mPFC recruitment in these areas during processing of reward outcomes.

Method

Participants

Participants included 19 treatment-seeking obese (BMI $>$ 30) adults who met the *DSM-5* criteria for BED (www.dsm5.org) participating in a randomized placebo-controlled trial testing 4-month treatments of sibutramine and cognitive-behavioral-self-help interventions, alone or in combination. These participants are the same group as those described in another study examining the neural correlates of reward processing in BED relative to individuals with normal weight, as well as obese individuals without BED.[15] The 19 participants had a mean age of 43.7 years (SD = 12.7), 14 were female, and 14 identified as white (three were black, two were Native American, and one was Hispanic). Mean BMI was 36.7 kg/m^2 (SD = 4.05). This subset is from a larger clinical research trial, which remains blinded (thus treatment outcomes are reported for the group and not separated by treatment condition). Exclusion criteria included current antidepressant therapy, severe psychiatric problems (psychosis, bipolar disorders, current substance dependence), severe medical problems (cardiac, liver disease), and uncontrolled medical problems such as hypertension, thyroid disease, or diabetes. The study had full Institutional Review Board (IRB) approval and all participants provided written informed consent.

Participants underwent fMRI prior to starting treatment, the latter of which was delivered for four months. Following treatment completion, participants were re-assessed (blindly with respect to treatment condition and baseline fMRI findings) on measures of disordered eating.

Assessments and Measures

Monetary Incentive Delay Task (MIDT). The adapted version of the Monetary Incentive Delay Task that we use in the current study has previously been described.[15,25,33] Given that striatal activity is influenced by motor demands during reward processing tasks,[34,35] the modified MIDT used in the current study is designed in such a way so as to control for these. Each trial includes two anticipatory periods as well as an outcome phase. The first anticipatory phase (termed "A1") is not only associated with the prospect of reward but also contains activity related to motor preparation for the button press. The second anticipatory phase ("A2") is associated with the anticipation of reward/loss, and includes the brain activity associated with the button press. This version of the MIDT has been modified from the original[36] in five specific ways. (1) The anticipatory phase is parsed into two periods corresponding with the prospect of reward/loss (A1) and the anticipation of reward/loss (A2). (2) The actual words "Win $1" or "Lose $5" appear in the current version, rather than abstract cues, in an effort to minimize the working memory load. (3) To counterbalance conditions, a neutral stimulus "Win 0" or "Lose 0" was included in this version. (4) Each phase within a trial has been extended by several seconds in order to capture unique contributions of each phase. (5) Motor preparation for the button press is contained within the A1 phase, while A2 includes the motor demands of pressing the button.

All participants completed two runs of the MIDT, with each run consisting of 55 trials that last 12 seconds each. During task performance, participants view a cue for 1000 milliseconds during the A1 phase indicating a potential win or loss of a specific amount of money (either $1 or $5). Participants then fixate on a crosshair for a variable delay of 3–5 seconds. During the A2 phase, a target of variable duration appears on the screen during which participants press a button. Following this, participants fixate on a crosshair again for a variable delay of 4–6 seconds. During the outcome phase, participants receive feedback indicating either a win or a loss of money and view their cumulative earnings on the task for a duration of 1200 milliseconds. The offset of each cue is time-locked with fMRI volume acquisition.

Trial types are pseudorandomly ordered within each session. Task difficulty is based on practice reaction times collected prior to scanning and intentionally set so that participants experience a positive outcome on 66% of trials. To further increase motivation, compensation on the task is performance based, and participants are informed of this aspect prior to task performance.

Eating Disorders Examination Interview (EDE). The EDE assesses the frequency of different forms of disordered eating (including objective bulimic episodes

(OBEs) which correspond to the DSM-5 definition of binge-eating as eating an unusually large quantity of food while experiencing a subjective sense of loss of control), weight-compensatory behaviors, and associated eating-disorder psychopathology. The EDE is a rigorous assessment interview[37] with good inter-rater and test-retest reliability across different weight groups.[38,39] The EDE was administered prior to treatment and re-administered following the 4 months of treatment by doctoral-level research clinicians who were independent of the fMRI protocol and blinded to treatment assignments. The EDE was used determine "remission" (abstinence) from binge eating at post-treatment, which was defined as zero OBEs during the previous 28 days, to serve as the primary outcome in this study.

fMRI Acquisition and Analysis

Image acquisition and analysis followed our previously described procedures.[15,25] Images were obtained with Siemens TIM Trio 3T MRI systems. Localizer images were acquired aligning the eighth slice parallel to the plane transecting the anterior and posterior commissures. Functional images were acquired with a T2*-weighed Blood Oxygen Level Dependent (BOLD) sequence with a TR of 1500 ms, TE of 27, flip angle of 60°, 64 × 64 in-plane matrix, field of view of 220 × 220 and 25 4 mm slices with 1 mm skip. High-resolution 3D MPRAGE structural images were also acquired with a TR of 2530ms, TE of 3.34 ms, flip angle of 7°, 256 × 256 in-plane matrix, and 176 1 mm slices. Each MIDT fMRI run consisted of 486 volumes, including an initial rest period of 9 seconds for signal stability, which was subsequently removed from analyses. Statistical analyses used a Robust General Linear Model approach and each phase of each trial type was separately modeled. Covarying for scanner type in the analyses minimized potential cross-scanner differences. Analyses combined "WIN $1" and "WIN $5" trials, LOSE $1" and "LOSE $5" trials, and "WIN $0 and "LOSE $0" trials in reward, penalty and neutral conditions in order to increase power.

Functional images were preprocessed using SPM5 (Welcome Functional Imaging Laboratory, London UK), normalized to the Montreal-Neurological-Institute template and smoothed with a 6 mm kernel FWHM (full-width half-maximum). First-level modeling was conducted using robust regression to reduce influence of outliers. Motion and high-pass filter parameters were included as additional regressors of no interest. The Neuroelf analysis package (www.neuroelf.net) was used for second-level random effects analysis. Correction for multiple comparisons was conducted using Monte-Carlo simulation (e.g. AlphaSim), using combined voxel-wise and cluster thresholds of 91 to result in a $p < .05$ family-wise-error (FWE) correction. In order to control for treatment condition and potential influences of scanner type, both variables were controlled for within our analyses. Specifically, the percent signal BOLD change was extracted from the significant cluster from each participant into a multivariate ANOVA with post-treatment binge eating and treatment condition entered as factors and the scanner type entered as a covariate. Adding these controls did not affect the reported results, with the exception of two clusters. These clusters are marked with an asterisk in Table 1 and clarified at the bottom: "when controlling for treatment group and scanner, this cluster no longer reaches statistical significance."

Task-related brain activations have been described elsewhere.[15] To examine between-group differences, we compared activity in the ten individuals who continued to report binge-eating ($BE_{post\text{-}tx}$) following treatment and the nine individuals who did not ($NBE_{post\text{-}tx}$). We examined between-group differences during the A1Win, A2Win, OCWin, A1Loss, A2Loss, and OCLoss phases in pair-wise *t*-tests.

Results

Based on independently administered EDE interview findings, 10 (53%) of the 19 BED participants were categorized as still binge-eating at post-treatment ($BE_{post\text{-}tx}$) and 9 (47%) were categorized as not binge-eating ($NBE_{post\text{-}tx}$; i.e., having achieved "remission" defined as zero OBEs during previous 28 days) at post-treatment. The two groups did not differ in BMI at baseline [$F(1,17) = 0.75$, $p > .05$], post-treatment BMI [$F(1,17) = 1.05$, $p > .05$], nor did they differ on binge eating episodes at baseline [$F(1,17) = 0.001$, $p > .05$]. These two groups also did not differ in age [$F(1,17) = 0.21$, $p > .05$], gender [X^2 (2, $N = 19$) = 0.51, $p > .05$], race [X^2 (2, $N = 19$) = 0.38, $p > .05$] or ethnicity [X^2 (2, $N = 19$) = 0.28, $p > .05$].

Affective Responses

A group-by-trial-type repeated-measures ANOVA examining affective responses to the incentive value of different trial types (winning, neutral, losing) showed a main effect of trial type [$F(2,34) = 64.19$, $p < .001$]. Pairwise comparisons revealed that, in a stepwise fashion, participants reported significantly greater cue-elicited "happiness" when winning, relative to neutral or losing trials ($p < .01$). There was no significant difference in affective ratings between those individuals who reported binge eating post-treatment, and those who did not [$F(1,17) = 1.65$, $p > .05$] and no group-by-trial-type interaction [$F(2,34) = 0.53$, $p > .05$].

TABLE 1. Post-treatment BED Group differences during MIDT Trials

$BE_{post\text{-}tx}$ vs. $NBE_{post\text{-}tx}$								
				MNI Coordinates				
MIDT Phase	Structure	BA	Left/Right	*x*	*y*	*z*	*k*	*T*-value
A1Win	Inferior parietal lobule/precentral gyrus/middle frontal gyrus	40	R	39	–27	42	111	3.73
	Middle frontal gyrus/postcentral gyrus/middle frontal gyrus	6	L	–27	–3	45	139	3.71
	Inferior frontal gyrus	47	L	–42	30	–12	104	–5.13
	Superior frontal gyrus/anterior cingulate gyrus/ medial frontal gyrus	10	L	–9	66	27	357	–4.97
A1Loss	Inferior temporal gyrus/middle temporal gyrus/superior temporal gyrus	37	L	–57	–72	–6	155	5.43
	Precentral gyrus/middle frontal gyrus/superior frontal gyrus/cingulate gyrus	6	R	24	–15	60	275	3.89
	Cuneus/superior temporal gyrus/insula	18	R	30	–63	21	315	3.61
	Superior parietal lobule/precuneus/inferior parietal lobule	7	L	–24	–51	42	127	3.40
	Precuneus/superior parietal lobule	19	R	24	–78	48	250	3.35[a]
	Superior frontal gyrus/medial frontal gyrus	10	L	–9	66	27	207	–5.45
A2Win	Superior frontal gyrus/medial frontal gyrus	10	L	–9	66	27	125	–4.77
	Inferior frontal gyrus	47	R	45	42	–12	163	–4.21
	Inferior frontal gyrus/middle frontal gyrus	46	L	–39	42	0	133	–3.88
	Ventral striatum/lentiform nucleus/caudate/putamen/insula	–	R	21	18	–6	161	–3.83
	Cerebellum	–	L	–21	–51	–33	195	–3.82
	Parahippocampal gyrus/declive	19	L	–18	–48	–6	136	–3.48[a]
A2Loss	Precuneus	19	R	30	–63	45	91	4.71
	Inferior parietal lobule/supramarginal gyrus	40	L	–36	–45	48	123	4.41
	Middle occipital gyrus/lingual gyrus	18	L	–27	–99	3	147	4.19
	Angular gyrus	39	L	–27	–60	39	113	3.90
	Thalamus/caudate	–	R	9	–33	6	179	3.80
	Inferior frontal gyrus	46	L	–42	42	0	104	–4.04
	Medial frontal gyrus/superior frontal gyrus	9	L	6	42	15	104	–3.38
OCWin	Superior temporal gyrus/middle temporal gyrus	22	L	–63	–9	0	162	5.59
	Inferior parietal lobule/postcentral gyrus/precuneus/superior parietal lobule	40	L	–48	–48	57	468	4.71
	Precentral gyrus/superior frontal gyrus	6	L	–33	–12	69	113	4.02
	Superior temporal gyrus	22	R	63	–39	9	114	3.91
	Cingulate gyrus/middle frontal gyrus/	24	R	9	–6	39	341	3.87
	Medial frontal gyrus	9	L	–3	45	24	130	–3.91
OCLoss	Postcentral gyrus	40	R	51	–27	60	112	4.54
	Superior temporal gyrus	22	L	–54	3	–9	140	4.44
	Postcentral gyrus/precentral gyrus	2	L	–51	–21	42	180	3.83
	Middle frontal gyrus	6	R	24	–3	39	95	–4.91
	Precentral gyrus/caudate			–24	–3	33	124	–4.35

$BE_{post\text{-}tx}$, reported binge eating post-treatment; $NBE_{post\text{-}tx}$, no reported binge eating post-treatment;
BA, Brodman's area; k, voxel cluster size (each voxel = $3mm^3$).
[a]When controlling for treatment group and scanner, this cluster no longer meets statistical significance.

In-Scanner Behavior

Multiple one-way ANOVAs examining behavioral responses in-scanner showed no significant group differences between groups on earnings [$F(1,17) = 1.18$, $p > .05$], mean reaction time [$F(1, 17) = 4.21$, $p > .05$] or mean hit rate for win/loss trials [$F(1, 17) = 2.92$, $p > .05$].

Table 1 summarizes between-group differences during the prospect, anticipation and outcome phases of reward and loss processing. Since our focus was on the A2 and OC phases given their particular relevance, we do not elaborate on the A1 phase here. Below, results highlight and describe between-group differences related to our hypotheses (i.e., fronto–striatal areas).

During reward anticipation (A2Win), $BE_{post\text{-}tx}$ relative to $NBE_{post\text{-}tx}$ individuals demonstrated relatively diminished activity in left superior frontal gyrus extending to medial frontal gyrus; right IFG extending to superior frontal gyrus; left IFG extending to middle frontal gyrus; and right ventral striatum extending to claustrum (**Figure 1**), caudate and putamen. During loss anticipation (A2Loss), $BE_{post\text{-}tx}$ relative to $NBE_{post\text{-}tx}$ participants showed increased activity in the right thalamus extending to caudate and diminished activity in left IFG

(**Figure 1**); and bilateral medial frontal gyrus extending to the superior frontal gyrus. During winning outcomes (OCWin), $BE_{post\text{-}tx}$ relative to $NBE_{post\text{-}tx}$ participants showed increased activity in right postcentral gyrus; right superior frontal gyrus; right cingulate gyrus extending bilaterally to middle and medial frontal gyri; and left medial frontal gyrus extending bilaterally (**Figure 1**). During losing outcomes (OCLoss), $BE_{post\text{-}tx}$ relative to $NBE_{post\text{-}tx}$ participants showed increased activity in right postcentral gyrus; left superior temporal gyrus; and left postcentral gyrus extending to precentral gyrus. Diminished activity during OCLoss in $BE_{post\text{-}tx}$ relative to $NBE_{post\text{-}tx}$ participants was observed in right middle frontal gyrus extending to caudate; and left precentral gyrus extending to caudate.

Discussion

Previously we observed relatively diminished fronto–striatal activity during reward and loss processing in obese individuals with BED as compared with non-BED obese individuals with similar BMIs.[15] The current study extends these finding by showing that among the BED group, there is additional variation in the recruitment of fronto–striatal circuitry during reward/loss processing; individuals who continue to binge following treatment (compared to those refraining from bingeing) show at treatment onset relatively less activation of specific fronto–striatal brain regions during specific phases of reward/loss processing. Notably, the two groups did not differ in binge-eating frequency at baseline. The observation of relatively reduced ventral striatal activity during reward anticipation in the group continuing to binge resonates with findings of reduced striatal activity to food exposure or behavioral control linked to weight gain.[11,20,26] Obese patients who report continued binge-eating following treatment were characterized prior to treatment by diminished anticipatory activity in right ventral striatum and bilateral IFG during the A2Win/A2Loss phases, and diminished mPFC activity in the OCWin phase, relative to obese BED participants who ceased binge eating. Together with our prior report,[15] these findings not only indicate that BED patients as a group show relatively diminished activation of reward circuitry, but also suggest that within this group, individuals with less recruitment of reward circuitry show persistent bingeing compared to those with relatively greater recruitment.

These pilot results suggest a link between cortico–striatal hypofunctioning during reward/loss processing and bingeing treatment outcome in BED. Relatively diminished reward-anticipation-related activation of the ventral striatum has been observed in disorders characterized by impaired impulse control (e.g., pathological gambling, alcohol dependence, tobacco smoking), and within these groups the degree of activation relates inversely clinically relevant measures like impulsivity[15,40] and disorder severity.[41,42] Thus, the extent to which impulsivity and other measures of illness severity may relate to reward/loss-related neural activity, and the extent to which impulsivity may relate to bingeing and treatment outcome in BED more generally, warrants additional investigation. The IFG is implicated in inhibitory control,[24] and greater IFG recruitment during food-cue exposure has been associated with sustained weight loss.[27] The mPFC, recruited during rewarding outcomes, has been linked to emotional arousal and a central regulator of eating behavior through top–down control promoting the inhibition of food reward.[22,26,27,43–45] In the current study, successful cessation of binge eating was associated with greater recruitment of mPFC activity in dorsomedial parts extending to the frontal pole. Successful dieters have demonstrated increased activity in these areas in response to food cues or following meal consumption.[26,27] Importantly, these dorsal areas of the mPFC are part of a medial network with visceromotor output to the OFC, as well as the ventral striatum and hypothalamus.[46] While this network is ascribed an important role in eating behavior, it is also implicated in the regulation of mood and behavior.[46] For example, relatively diminished mPFC activation has been observed in populations characterized by impaired impulse control (e.g., in pathological gambling during simulated gambling or cognitive control[42,47]). Therefore, mPFC activity may represent an important neurofunctional marker related to reward processing and behavioral control more generally and weight control more specifically.

Relative to the $NBE_{post\text{-}tx}$ group, the $BE_{post\text{-}tx}$ group demonstrated diminished activation in the left IFG as well as the mPFC extending to frontopolar areas, across both the A2Win and A2Loss anticipatory phases. Although our hypotheses centered on fronto–striatal regions, group differences were also observed in other areas; increased activity during A2Loss was observed in the $BE_{post\text{-}tx}$ group in occipital, thalamic and precuneus areas, suggesting greater recruitment of attentional networks during the anticipation of loss in this group; this may represent an imbalance in neural systems implicated in impulse control and those involved in attention, as reduction in craving in some populations is linked to a disengagement

of attentional systems.[48] During outcome phases there was also some overlap of group differences in win and loss conditions; the $BE_{post\text{-}tx}$ group demonstrated significantly increased activity in the left superior temporal gyrus as well as the left inferior parietal lobe and postcentral gyrus across both the winning and losing outcome phases. While these brain regions have been associated with aspects of reward processing in obesity and impulse control[49,50] in general, further research is necessary to clarify the roles that these areas might have with respect to binge eating and treatment response.

The current findings are limited by a small sample size and multiple treatment conditions. Therefore, future research should examine larger samples and specific treatments. Reward circuitry may additionally be affected by menstrual phase. Unfortunately, information on menstrual phase was not collected in all female participants. Therefore, we were not able to control for this possible influence. Additionally, studies involving multiple fMRI assessments are warranted. Specifically, longitudinal studies, as well as those involving pre- and post-treatment scanning across treatment modalities, will be important in clarifying changes occurring with treatment and relating these to changes in weight and eating pathology. For example, it has not been established whether binge-eating or general overeating may accelerate a decrement in striatal signaling. Nonetheless, the current and extant findings[20,51] suggest a feed-forward process in which blunted striatal responses contribute to future weight gain and/or persistent binge-eating by altering basic reward processing signaling related to self-regulation. Anticipatory signaling occurs at a time point prior to choice, thereby positioned to influence decision-making and behavior, such as the choice to consume food. Indeed, energy intake appears influenced by anticipatory signaling, rather than the actual reward experienced during food consumption.[17] These findings suggest the intriguing possibility that effective psychotherapeutic or pharmacological interventions for BED may relate to increasing activity in fronto–striatal circuits. The findings also identify neural substrates that may be useful in guiding anatomically specific therapies. Our results of significant differences in dorsal mPFC and ventral striatal areas are consistent with emerging neurostimulation studies in other populations with eating pathologies. For example, repetitive transcranial magnetic stimulation (rTMS) targeting the dorsolateral prefrontal cortex has demonstrated effectiveness in reducing cue-induced food craving in bulimic disorders.[52] In preclinical models, deep brain stimulation of the ventral, but not the dorsal, striatum reduces binge eating,[53] demonstrating anatomical specificity for modulation of particular eating behaviors. Additionally, fMRI does not directly interrogate neurochemical function. As such, alternate and complementary ligand-based methodologies are important and may be used to investigate the specific neurochemicals, receptors, transporters, and/or other molecular entities involved in BED and its treatment. For example, D2-like dopamine receptors in the striatum have been linked to obesity, and direct assessment of dopamine systems in conjunction with fMRI measures of reward processing and treatment outcome in BED would provide a more robust understanding of the neurobiological factors underlying the clinical phenomena. The investigation of responses to and anticipation of receipt of palatable foods is important to obesity and BED. A next step in understanding reward processing may involve the conjoint consideration of food and non-food reward processing in BED and obesity. Such studies may more precisely define how reward processes may go awry in BED and obesity and point toward mechanisms that might be modified in the treatment of these conditions. Recently, the National Institute on Mental Health (NIMH) has cited the importance of considering intermediary phenotypes that may link more closely to biological processes than diagnostic conditions per se.[54] Reward processing represents an important intermediary phenotype that appears to have important links to disorders characterized by impaired impulse control such as BED, pathological gambling, and alcoholism.[25,40,55] While the current study represents an important advance toward understanding brain mechanisms related to treatment outcome in BED, future studies directly examining the possibilities that these findings raise are needed.

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