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Effect of lisdexamfetamine on emotional network brain dysfunction in binge eating disorder

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ABSTRACT

We examined the effects of lisdexamfetamine (LDX) treatment on ventral prefrontal cortex (VPFC) and striatal brain activation in binge eating disorder (BED). We hypothesized that participants with BED have an abnormal brain response to palatable food cues, and that VPFC and striatal regions would respond to such cues after LDX treatment. Twenty women with moderate to severe BED consented to a 12-week, open-label trial of LDX with fMRI before and after treatment. Twenty obese women without BED served as healthy controls and received one fMRI. LDX was started at 30 mg/d with a target of 70 mg/d at week 12. At baseline, women with BED showed greater activation in ventrolateral prefrontal cortex (VLPFC), striatum, and globus pallidus to food pictures and brain activation to food pictures predicted clinical outcome at 12 weeks. After 12 weeks of LDX treatment, BED women showed significant reductions in globus pallidus activation. Reductions in ventromedial prefrontal cortex (VMPFC) and thalamus activation specifically correlated with binge eating and obsessive-compulsive symptom reductions, respectively. Results suggest that BED is characterized by an abnormally large VPFC-subcortical brain response to palatable foods that LDX treatment helps modify. Moreover, VPFC-subcortical activation at baseline is a potential biomarker of LDX response.

1. Introduction

Binge eating disorder (BED) is defined as recurrent and distressing episodes of excessive eating without the inappropriate compensatory weight loss behaviors characteristic of bulimia or anorexia nervosa. An important public health problem, BED is the most common eating disorder, present as a lifetime diagnosis in 2.6% of American adults and 1.9% of adults worldwide (Hudson et al., 2007; Kessler et al., 2013). It is associated with psychiatric and medical morbidity, especially depressive symptoms and obesity, reduced quality of life, role impairment, and increased health care utilization (Hudson et al., 2007; Kessler et al., 2013).

Randomized, double-blind, placebo-controlled trials demonstrate that the stimulant prodrug lisdexamfetamine (LDX) is efficacious in BED (Hudson et al., 2017; McElroy et al., 2014, 2015, 2016). Indeed, LDX has regulatory approval for the treatment of adults with moderate to severe BED. The therapeutic effect of LDX, and stimulants in general, is thought to involve catecholamine neurotransmission within prefrontal cortex (PFC; Berridge et al., 2006) and BED has been associated with PFC dysfunction (Karhunen et al., 2000; Schienle et al., 2009). In one neuroimaging study utilizing single photon emission computed tomography (SPECT), food provocation increased left PFC activation in participants with BED relative to obese controls (Karhunen et al., 2000). In another study, participants with BED showed greater medial-orbital prefrontal cortex PFC activation on functional MRI (fMRI) to food pictures relative to normal-weight, overweight, and bulimia nervosa controls (Schienle et al., 2009). Generally, PFC dysfunction is implicated in appetite dysregulation (Gautier et al., 2001), obesity (Lowe et al., 2009; Ochner et al., 2009), food cravings (Rolls and McCabe, 2007), and impulsivity (Rubia et al., 2001), all of which are closely related to BED (Mussell et al., 1996; de Zwann, 2001; Latner et al., 2009). Based on the integration of PFC-subcortical circuits and the brain dysfunction found in BED, it has been suggested that heightened PFC reactivity to food results in loss of control over eating

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(Schienle et al., 2009).

To date, only two imaging studies have examined whether treatment alters brain function in BED. In one placebo-controlled study of sibutramine, frontal and striatal activity to monetary reward anticipation increased in individuals that stopped binge eating following treatment (Balodis et al., 2014). In another, treatment with the mu-opioid receptor antagonist GSK1521498, compared to placebo, was associated with reduced striatal response to highly palatable food pictures (Cambriadge et al., 2013). Additionally, GSK1521498 has been associated with reductions in pleasurable ratings of sweet foods and calorie intake (Ziauddeen et al., 2013). These findings suggest abnormal PFC and striatal activity in BED, and normalization with treatment, but the exact mechanisms of action remain unclear considering the opposing directions of signal change with treatment (though this may be related to task differences, i.e., use of monetary reward versus food pictures).

With these considerations in mind, we examined the effects of LDX treatment on PFC and striatal brain activation in women with BED undergoing a 12-week LDX treatment trial in a pilot neuroimaging study. We chose LDX as the investigational agent in order to explore its mechanism of action in BED as the first drug approved for the illness. We hypothesized that participants with BED would have an abnormal emotional brain network response to highly palatable food cues, and that ventral PFC (VPFC) and striatal brain regions mediating affect and decision-making would respond to such cues after LDX treatment. Specifically, in contrast to prior imaging studies of treatment response, we used a hypothesis-driven, region-of-interest (ROI) approach to test two experimental hypotheses. We predicted that relative to obese but otherwise healthy comparison (HC) women, women with BED would have (1) greater VPFC and striatal activation to highly palatable food cues at baseline and (2) reduced VPFC and striatal activation after 12 weeks of LDX treatment. Relationships between clinical measures of treatment response and regional brain activation were also explored.

2. Methods

2.1. Study design and participants

This study was a 12-week, flexible dose, open-label trial of LDX in 20 women with BED and 20 obese comparison women without BED in which clinical assessments were conducted at the Lindner Center of HOPE and fMRI scans at the Cincinnati Children's Hospital Medical Center.

Fig. 1 depicts the study schematic along with the schedule of primary events. After a 2-week screening period, qualified women with BED entered a 12-week treatment period during which they received open-label LDX. During the treatment period, study visits were conducted weekly for the first 4 weeks and then every 2 weeks for the remaining 8 weeks. After LDX discontinuation at week 12, participants were contacted at week 13 by phone to assess clinical status and adverse events.

Two fMRI scans were performed with the BED participants: one at baseline, before beginning study medication, and another at week 12, within 24 h of taking the last dose of study medication. The HC group had a single study visit at which time an fMRI scan was performed for comparison to the BED baseline scan. The HC group did not receive an endpoint scan for this pilot study. Functional MRI scans were usually conducted in the morning between 8 a.m. and 11 a.m. and following an overnight fast.

The morning after completing the first fMRI scan, LDX was started at 30 mg qAM in women with BED. After 1 week, LDX was increased to 50 mg qAM and after the second week, LDX was increased to 70 mg qAM. A single downward dose titration to 50 mg was allowed during week 3 if 70 mg/d was not tolerated. The LDX dose at week 4 (50 or 70 mg/d) was maintained for the next 8 weeks.

2.2. Participant selection criteria

For the LDX open-label group, participants were recruited from advertisements for a medication trial for women with BED. Eligibility criteria for the study were: (1) met DSM-IV (American Psychiatric Association, 1994) criteria for BED for at least the last six months; (2) reported at least three binge eating days per week for the two weeks prior to LDX initiation prospectively documented in take-home binge diaries; (3) women ages 18–55 years, inclusive. Only women participated in this study for both practical and scientific reasons. Practically, there is 2:1 gender ratio favoring women in 12-month prevalence (American Psychiatric Association, 2013) and scientifically, gender effects on brain activation in response to food cues have been identified (Uher et al., 2006), making gender inclusive enrollment untenable for a small pilot study.

Exclusion criteria were similar to those used in the pivotal trials and included current anorexia or bulimia nervosa; clinically significant depressive symptoms; suicidality; treatment with a psychotropic other than a hypnotic; a suicide attempt within the past year; substance abuse or dependence (except nicotine) within the past six months; lifetime history of mania, hypomania, psychosis, or attention deficit hyperactivity disorder (ADHD); unstable medical illness; clinically significant abnormal laboratory or ECG findings; and pregnancy, lactation, or inadequate contraception. Participants were also ineligible if they began a psychological or weight loss intervention for BED within the past three months, reported misuse of psychostimulants within the past six months, or had a positive drug screen for psychostimulants.

2.3. Participant evaluation

The Institutional Review Board at the University of Cincinnati approved the study protocol. All participants provided written informed consent before administration of any study procedures and were enrolled from September 2015 through March 2017. Women with BED were assessed during the screening phase with the SCID for DSM-IV (to evaluate BED and exclusionary psychiatric diagnoses; First et al., 2002), the Eating Disorder Examination - Questionnaire (EDE-Q) (to confirm the diagnosis of BED; Fairburn and Beglin, 1994), the Montgomery-Asberg Depression Rating Scale (MADRS) (to rule out clinically significant depressive symptoms; Montgomery and Asberg, 1979) and the

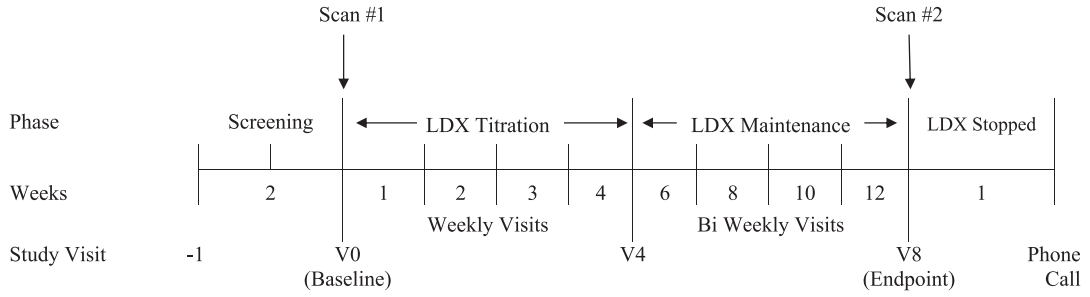

Fig. 1. Clinical schematic of the study and schedule of events.

Columbia Suicide Severity Rating Scale (C-SSRS) (to rule out suicidality; Posner et al., 2007). Women with BED also received a medical history, physical examination, vital signs, laboratory tests, urine pregnancy and toxicology tests, and ECG. At the screening evaluation and each of the following visits, women with BED were given take-home diaries in which they recorded binge-eating episodes (number of episodes per day, types and amounts of food consumed, and duration of the episodes).

Healthy comparison women were evaluated only at baseline with the SCID for DSM-IV (to ensure the absence of BED or another psychiatric disorder), a psychiatric and medical history including urine drug and pregnancy tests, the Binge Eating Scale (BES; Gormally et al., 1982), vital signs, and height and weight (to determine BMI).

2.4. Outcome measures

Cessation from binge eating was defined as no binge-eating days in the last 4 weeks of LDX treatment. Clinical improvement was defined as a Clinical Global Impression Improvement Scale (CGI-I; Guy, 1976) rating of 'Very much improved' or 'Much improved' at study endpoint. Secondary outcomes included scores on the Yale Brown Obsessive-Compulsive Scale modified for binge eating (YBOCS-BE; Deal et al., 2015), BES (Gormally et al., 1982), and body mass index (BMI). Number of binge eating days per week, CGI-I, and safety assessments were conducted at each study visit from baseline (except for CGI-I) and through endpoint (Visit 12); the YBOCS-BE and BES were obtained at baseline and at weeks 4, 8, and 12. Assessed safety measures included adverse events, physical examination findings, clinical laboratory data, and vital signs. Adverse events were obtained through spontaneous patient reporting and by open-ended investigator questioning. A urine toxicology test was performed every 4 weeks. Participant compliance with LDX dosing requirements was monitored using a returned pill count.

2.5. Image acquisition and fMRI

At baseline (week 0) and endpoint (week 12), participants were scanned without sedation on a 3.0 Tesla Philips Achieva Quasar Whole Body MRI/MRS system (Philips, Inc., Cleveland, OH). Participants were asked to perform the Continuous Performance Task with Binge Eating (highly palatable food pictures) and Neutral Distractors (CPT-BEND). During the scan sessions, participants reclined in a supine position on the scanner bed and a radio-frequency (RF) coil was placed over the participant's head. All stimuli were presented using non-ferromagnetic high-resolution video goggles (Resonance Technologies, Inc., Northridge, CA) for viewing input from a personal computer.

2.6. fMRI task

The CPT-BEND paradigm was based on a task originally developed by Yamasaki et al. (2002) and modified by Strakowski et al. (2011). It was written using E-Prime v2.0 (Psychology Software Tools, Inc., University of Pittsburgh, PA, 2002) on a personal computer. The CPT-BEND version is a visual oddball paradigm. Seventy percent of the visual cues are simple colored squares (standards), 10% are simple colored circles (targets), 10% are color pictures of highly palatable foods (food pictures), and 10% are emotionally neutral color pictures (neutral pictures). The food and neutral pictures have been used previously and are available on request from the developers (See Uher et al., 2004). Food picture included savory (e.g., pasta, pizza, bread) or sweet (e.g., cake, pie, chocolate) items presented on plates and emotionally neutral nonfood pictures (e.g., stationery, household objects, flowers) were matched for color and visual complexity (Uher et al., 2004). Each trial required 3.0 s to complete and consisted of a stimulus shown for 2.75 s followed by a fixation cross for 250 ms. Each stimulus required a response (pushing one of two possible buttons) from the participant. The target circles required a unique response (press button 2), whereas the squares and distracter pictures required the same response (press button 1). Responding to the circles has been shown to engage the attentional system (Yamasaki et al., 2002) and viewing the food pictures was expected to generate an emotional response consistent with that seen using emotional distractors in studies of bipolar disorder (Strakowski et al., 2011, 2016). Stimuli of each category (circles, food pictures, and neutral pictures) were presented among a stream of more frequently occurring squares and the stimuli were jittered and not time locked to the TR to avoid slice-timing effects. The task was administered over the course of two fMRI runs of approximately nine minutes each and each incorporating 158 total stimuli. The two runs were concatenated for analysis purposes.

2.7. Image reconstruction and pre-processing

All data analyses were performed using Analysis of Functional NeuroImages (AFNI; http://afni.nimh.nih.gov/afni) and SAS, version 9.4 (SAS Institute, Cary, NC). Following acquisition, images were reconstructed using in-house software developed in IDL (Interactive Data Language), which converted raw scanner files into AFNI format. In AFNI, structural and functional images were co-registered using scanner coordinates. Functional images were corrected for motion using a six-parameter rigid body transformation (Cox and Jesmanowicz, 1999). After realignment, all data sets were reviewed and time points were removed from the study that had uncorrected movement artifacts. We used motion correction parameters to calculate the total motion in six directions of rotation and translation from the beginning of each run. The maximum motion of any participant included in the analysis was <4 mm. The average total displacement for all participants was <1 mm. Additionally, each volume was inspected for signal artifact using a semi-automated algorithm in AFNI to identify questionable TRs. These volumes were removed from further analysis if visual inspection indicated uncorrectable head movement, i.e., within-TR head motion, or $>30\%$ of voxels were >2 SDs from the mean signal intensity. On average we removed $<5\%$ of the volumes from each run using these procedures. Finally, motion correction parameters were included as regressors of no interest in the deconvolution step described below. Using tools in AFNI, the structural image set was normalized to Talairach space by warping to a template image (ICBM 452). The functional data were then transformed to Talairach space by adopting the transform applied to the structural image. Binary masking was applied to each image to remove pixels outside the brain. Activation maps were then created for each subject using a deconvolution algorithm that compares the actual hemodynamic response to a canonical hemodynamic response function (e.g., gamma function), creating voxel-wise *t*-maps. An event related design was used to model the experiment, and absolute times for each event (circle target, food distracter and neutral distracter) were used in the deconvolution algorithm. The AFNI software was then used to generate an estimate of the 'fit coefficient' (i.e., beta weight or scaling factor) describing the magnitude of the hemodynamic response relative to the average signal intensity for each event compared to the baseline (the square standards). Additionally, low-frequency components of the signal, including linear and quadratic drift, were removed.

2.8. Conception, creation, and application of the ROI mask

The neurophysiologic networks of emotional modulation as presently conceptualized are based on Strakowski et al. (2016). In these networks, emotional stimuli processed by the amygdala and ventral striatum are modulated by the VPFC with iterative feedback from prefrontal-striatal-pallidal-thalamic feedback loops (Chen et al., 1995; Lane et al., 1998; Phan et al., 2002). An ROI mask was created in AFNI based on these networks. The ROI mask was applied to each individual's fMRI data in order to obtain the average activation within each ROI.

Table 1
Demographics, clinical and cognitive characteristics of the analyzed sample.

	BED BL (n = 18)	HC BL (n = 15)	BED EP (n = 15)
Age, mean yrs. (SD)	37.2 (9.9)	40.0 (8.2)	
Race, black, n (%)	2 (11)	7 (47)[a]	
Onset, mean yrs. (SD)	17.9 (8.6)	–	
BE days/wk, mean (SD)	4.1 (1.1)	–	0.1 (0.4)[c]
BE episodes/wk, mean (SD)	4.4 (1.3)	–	0.1 (0.4)[c]
BES score (SD)	49.7 (5.5)	25.0 (6.4)[b]	22.3 (6.7)[c]
Y-BOCS score (SD)	20.3 (4.2)	–	1.6 (2.8)[c]
MADRS score (SD)	0.5 (1.1)	–	0.0 (0.0)[d]
BMI, kg/m^2 (SD)	40.1 (6.8)	33.6 (6.2)[b]	38.7 (7.8)[c]
Mean RT (SD)	793.5 (179.7)	779.2 (178.0)	658.5 (73.4)[c]
Mean error (SD)	98.0 (7.1)	98.9 (3.0)	99.8 (0.9)

Note: BED = binge eating disorder; HC = healthy comparison; ITT = intent-to-treat; BL = baseline; EP = endpoint; BE = binge eating; BES = Binge Eating Scale; Y-BOCS = Yale-Brown Obsessive Compulsive Scale-Binge Eating; MADRS = Montgomery-Asberg Depression Rating Scale; BMI = body mass index.

[a] BED BL < HC BL, $p \leq 0.05$.
[b] BED BL > HC BL, $p \leq 0.01$.
[c] BED BL > BED EP, $p \leq 0.01$.
[d] Based on n = 6 completed MADRS scores at week 12.

The 18 ROIs included bilateral ventrolateral PFC (VLPFC; Brodmann's area [BA] 45/47), ventromedial PFC (VMPFC; BA 11/12), subgenual anterior cingulate cortex (ACC; BA 25), rostral ACC (BA 24 and 32), caudate, putamen, globus pallidus, thalamus, and amygdala. We combined the caudate and putamen to create a striatum ROI, bringing the bilateral ROI count to 16. Each of these ROIs, with the possible exception of the amygdala, has been previously implicated in the pathophysiology of BED using fMRI. The amygdala was an ROI of secondary interest due to its role in processing emotionally-valanced stimuli (Strakowski et al., 2011, 2016). The primary variable of interest for analysis of treatment effects was the response to food distracters; specifically, the percent signal change within each ROI was calculated by contrasting responses to food pictures with responses to baseline colored squares from each participant's event-related fMRI results. The contrast between neutral pictures and baseline colored squares was also examined to determine if the brain response was food cue specific.

2.9. Statistical analysis

Demographic and clinical characteristics at baseline were compared between the BED and HC groups using two-sample t-tests for continuous variables and chi-square tests of independence for categorical variables. After generating the ROI data, mixed models, which allowed for the within-subject correlation in the data, were used to test the stated hypotheses. To increase power in the ROI-specific analyses, both right- and left-hemisphere data were included in the models and a laterality interaction effect was included in the models. None of these laterality interaction effects were significant and, thus, the results are presented for the combined right- and left-hemisphere data in eight ROIs. Age, race, and BMI were included as covariates in the data analyses due to a significant difference between groups on these variables and/or a significant correlation with at least one ROI at baseline. Given the very high binge eating cessation and clinical improvement rates, actual changes in binge eating days were used in the analyses instead of these binary outcomes to maximize power. Effect sizes were calculated by transforming the t statistic (t) and degrees of freedom (df) from the models to Cohen's d effect size {$d = 2 * t$/square root (df)}. Correlations were calculated by transforming the F statistic (F) and degrees of freedom from the models to r {r = square root [(F * df_{num})/([F * df_{num}] + df_{den})]}. Finally, exploratory voxel-wise analyses were conducted to visualize whole brain activation to characterize the hypothesis-driven ROI analyses further (See Supplement 1). For the voxel-wise analyses, activation maps were generated to contrast the HC and BED groups at baseline and the BED group at baseline and endpoint. Additional *post-hoc* analyses were conducted as necessary for completeness.

3. Results

3.1. Intent-to-treat sample, neuroimaging data loss, and participant dropout

Twenty women with BED and 20 obese, HC women were enrolled in the study and completed a baseline fMRI scan. Seventeen BED women completed the LDX trial and received an endpoint fMRI scan. Seven baseline scans were removed from the imaging analysis due to uncorrectable motion artifact, two in the BED group and five in the HC group. Additionally, two endpoint scans were removed for motion artifact in the BED group and an additional three women with BED were discontinued from the study before completing the endpoint fMRI scan (15% discontinuation rate) due to either an adverse event [n = 2; a fractured elbow (n = 1) and hypomania (n = 1)] or being lost to follow-up (n = 1). Therefore, the final analyzed sample consisted of 18 BED and 15 HC scans at baseline and 15 BED scans at endpoint.

3.2. Demographic, clinical, and cognitive characteristics

Table 1 presents demographic, clinical and cognitive characteristics for the BED and HC groups. The BED group consisted of significantly fewer African-Americans relative to the HC group. Moreover, the BED group had a significantly higher BMI (participants *were not* required to be obese, i.e., BMI > 30) and, as expected, significantly higher BES ratings as compared with the HC group.

Of the 15 women with BED with scan data at endpoint, 13 (87%) remitted (defined as no binge eating episodes in the previous four weeks) and 15 (100%) responded to treatment with LDX (defined as CGI-$I \leq 2$, much improved). Participants with BED also showed significant reductions in mean binge eating days/wk, episodes/wk, BES scores, YBOCS-BE scores, BMI and CPT-BEND performance speed. Depression ratings on the MADRS remained low and unchanged. Of the 15 participants with second scans, 11 were maintained at LDX 70 mg/d and four were maintained at LDX 50 mg/d. Allowable comorbid conditions included lifetime major depressive disorder with no current symptoms (n = 2; one with current mild trichotillomania) and a current generalized anxiety disorder (n = 1).

3.3. Safety measures

Adverse events occurring in more than 10% of the BED sample were dry mouth (n = 13; 65%), headache (n = 7; 35%), and insomnia (n = 7, 35%). No serious adverse events were reported and there were no clinically significant changes in vital signs or laboratory measures.

3.4. ROI based brain activation: baseline and treatment effects

The mixed model comparing brain activation in all ROIs in the HC and BED groups at baseline did not show a significant group effect [$F(1, 28) = 1.50$, $p = 0.23$]. As seen in Table 2, in separate mixed models for each ROI, the BED group showed significantly greater independent brain activation to high-palatability food pictures relative to the HC group in VLPFC [$t(28) = 2.01$, $p = 0.05$], striatum [$t(28) = 2.19$, $p = 0.04$], and globus pallidus [$t(28) = 2.44$, $p = 0.02$]. In four of the five remaining ROIs, the BED group also had numerically greater brain activation levels relative to the HC group. Effect sizes ranged from 0.20 to 0.92. In the neutral cue comparison condition only subgenual ACC had significantly lower activation ($p < 0.05$) in the BED group, indicating that the baseline effects in VLPFC, striatum and globus pallidus were specific to food cues.

The mixed model comparing baseline and endpoint brain activation

Table 2
Effect size (Cohen's *d*) and statistical significance levels for brain activation in response to highly palatable food pictures in each of eight *a priori* defined regions-of-interest (ROI) comparing binge eating disorder (BED) and healthy comparison (HC) groups at baseline.

Baseline ROI	Effect size *d*	*p* =
VMPFC	0.44	0.26
VLPFC	0.76	0.05
Subgenual ACC	−0.20	0.59
Rostral ACC	0.51	0.18
Striatum	0.83	0.04
Globus pallidus	0.92	0.02
Amygdala	0.39	0.32
Thalamus	0.51	0.19

Note: Positive effect size corresponds to higher activation in the BED group. VMPFC = ventromedial prefrontal cortex; VLPFC = ventrolateral prefrontal cortex, ACC = anterior cingulate cortex.

Table 3
Effect size (Cohen's *d*) and statistical significance levels for brain activation in response to highly palatable food pictures in each of eight *a priori* defined regions-of-interest (ROI) comparing the binge eating disorder (BED) group at baseline and endpoint.

ROI	Effect size *d*	*p* =
VMPFC	0.83	0.14
VLPFC	0.77	0.17
Subgenual ACC	0.14	0.79
Rostral ACC	0.11	0.84
Striatum	0.38	0.49
Globus pallidus	1.15	0.05
Amygdala	0.08	0.88
Thalamus	0.71	0.21

Note: Positive effect size corresponds to lower activation after 12 weeks of LDX treatment as compared to baseline. VMPFC = ventromedial prefrontal cortex; VLPFC = ventrolateral prefrontal cortex, ACC = anterior cingulate cortex.

in all ROIs in the BED group revealed a significant overall effect for time [$F(1, 14) = 54.4$, $p < 0.01$]. As seen in Table 3, in separate mixed models for each ROI, after 12 weeks of LDX treatment, the BED group had significantly reduced activation in a single independent region, the globus pallidus [$t(14) = 2.16$, $p = 0.05$]. Although changes in the other ROIs did not reach statistical significance, all showed a numerical decrease in activation, and VMPFC and VLPFC had large effect sizes ($d = 0.83$ and 0.77, respectively). Effect sizes ranged from 0.08 to 1.15. In the neutral cue comparison condition no group differences were observed in any individual ROIs, indicating that the treatment effect in globus pallidus was specific to food cues.

3.5. Baseline and change relationships between ROI activation and symptom severity

As an exploratory correlational analysis within the BED group, we examined relationships between baseline ROI activation levels and baseline Y-BOCS-BE and BES scores. At baseline, Y-BOCS-BE scores were significantly positively correlated with activation in the VMPFC, subgenual ACC and thalamus ROIs ($r = 0.61$, $p = 0.02$; $r = 0.53$, $p = 0.04$; $r = 0.57$, $p < 0.03$, respectively). There were no statistically significant relationships between ROI activations and BES scores ($p > 0.05$).

We also examined relationships between baseline ROI activation levels and *change* in number of binge eating days/week and Y-BOCS-BE scores within the BED group. Higher brain activation in the VMPFC and subgenual ACC ROIs at baseline was associated with greater reductions in binge eating days/week ($r = -0.55$, $p = 0.03$ and $r = -0.69$, $p < 0.01$, respectively). There were no statistically significant relationships between ROIs and Y-BOCS-BE ($p > 0.05$).

Finally, we examined relationships between *change* in brain activation for each of the eight ROIs and *change* in number of binge eating days/week, Y-BOCS-BE and BES scores. Changes in VMPFC activation were positively correlated with changes in BES scores ($r = 0.72$, $p = 0.01$) and changes in thalamus activation were positively correlated with changes in Y-BOCS-BE scores ($r = 0.73$, $p = 0.01$).

3.6. Exploratory voxel-wise analysis

An exploratory whole brain analysis showed that while the BED group activated amygdala and VLPFC at both baseline and endpoint, the HC group failed to activate these brain regions. Conversely, while the HC group under-activated VMPFC at baseline, the BED group failed to activate VMPFC at either baseline or endpoint. In general, activation appeared lowest in the HC group at baseline, highest in the BED group at baseline, and intermediate in the BED group at endpoint. However, whole brain voxel-wise contrasts failed to substantiate these differences and instead revealed that none of these, or other, qualitative differences met threshold activation levels comparing either the HC vs. BED groups at baseline or the BED group at baseline vs. endpoint on high-palatability food stimuli. Composite functional brain maps, *post-hoc* contrasts, and further discussion of the exploratory voxel-wise analysis are provided as supplemental material.

4. Discussion

For this pilot study, we examined the effects of LDX treatment on VPFC-subcortical brain network activation during an emotional eating task in women with BED undergoing a 12-week treatment trial of LDX. The primary ROI analyses partially confirmed our predictions of significantly greater VPFC and striatal activation in women with BED relative to healthy women at baseline, and significantly reduced activation in these same regions after 12 weeks of LDX treatment.

In the primary ROI analysis, as predicted, women with BED over-activated VLPFC and striatum relative to overweight comparison women at baseline. They also over-activated the globus pallidus. Overall, there appeared to be a tendency toward generalized over-activation in the brains of BED women in response to food pictures as reflected by moderate to large effect sizes on seven of eight fronto-subcortical ROIs sampled (with the exception of subgenual ACC).

At endpoint, only the globus pallidus demonstrated a statistically significant activation reduction after 12 weeks of LDX treatment, but *not* the predicted VPFC or striatum regions. As this represents a pilot study, it should be noted, however, the VMPFC and VLPFC average effect size was 0.80, suggesting that VPFC activation might be a candidate biomarker for treatment related activation reductions in a larger trial. That the globus pallidus was the only structure that was both significantly over-activated at baseline relative to controls and then significantly reduced with treatment suggests that this subcortical structure may be pivotal in the functional neuropathogenesis of BED. Overall, however, there was a tendency for each of the eight ROIs sampled to demonstrate activation reductions with treatment.

The exploratory correlational analyses helped to qualify the ROI findings. They suggest that cortico-thalamic aspects of the Ventromedial Circuit have primary responsibility for symptom/activation relationships in BED. Specifically, at baseline, only Y-BOCS-BE scores were significantly correlated with activation in the VMPFC, subgenual ACC and thalamus. These results may suggest that increased baseline brain activation in BED is primarily related to elevated obsessive/compulsive symptomatology rather than binge eating symptoms *per se*. They also indicate that despite a lack of mean activation differences, relationships between VMPFC, subgenual ACC and thalamus activation and obsessive/compulsive symptoms may help to moderate the brain response of women with BED pre-treatment.

Certain of these same structures, namely VMPFC and subgenual ACC, showed greater brain activation at baseline associated with

greater reductions in binge eating behavior. These results suggest that over-and-above the relationship between increased VMPFC and subgenual ACC activation and increased obsessive/compulsive symptoms at baseline, increases in these cortical areas also predicted the greatest post-treatment binge eating reductions.

Looking specifically at *change* scores, changes in VMPFC activation were positively correlated with changes in BES scores and changes in thalamus activation were positively correlated with changes in Y-BOCS-BE scores. These results suggest that only when change was accounted for in both brain activation and clinical outcome scores did brain/behavior relationships occur on a formal BED severity measure (i.e., the BES), indicating mutual reductions with LDX treatment. Taken together, the above correlational results further indicate that the Ventromedial Circuit including VMPFC, subgenual ACC and thalamus are of primary importance in brain-behavior relationships at both pre- and post-treatment time points in BED.

This study represents an initial neuroimaging investigation of treatment-related brain biomarkers in BED. Although there are no extant neuroimaging data to compare with the current LDX findings, much of the neuropsychological and brain imaging research to date confirm abnormal VPFC and striatal brain function in decision making and reward monitoring in BED (Fellows and Farah, 2007; Bechara et al., 1999). In a recent longitudinal study of monetary reward processing involving nonfood stimuli and BE behavior in adolescent girls, greater VMPFC and caudate activation to winning money were related to a greater severity of concurrent BE behavior, suggesting that enhanced subjective reward sensitivity is a state marker of BE (Bodell et al., 2017). In another study, participants with BED demonstrated greater activation in ventral striatum relative to a HC group in response to food stimuli, and aberrant ventral frontostriatal activation was associated with increased reward sensitivity and BE behavior (Lee et al., 2017). Additionally, increased VPFC activation to food stimuli in BED has been demonstrated relative to healthy individuals (and bulimia nervosa; Schienle et al., 2009). The present study extends this finding by showing large effect size reductions in VPFC activation, in addition to significant striatal activation reduction, after 12 weeks of LDX treatment for BED.

In contrast to reports of increased frontostriatal activity, decreased ventral striatum activity during reward anticipation and decreased PFC activity during outcome processing in BED relative to healthy obese participants has been reported as well (Balodis et al., 2013). The present results suggest common neurophysiological pathways for processing decisions related to reward and food stimuli. Although food pictures appear to have a higher intrinsic degree of reward for individuals with BED, further research will be needed to confirm this possibility.

Regardless of the direction of initial brain activation in BED, recent reviews clearly implicate frontostriatal circuits in processing of food stimuli (Donnelly et al., 2018; Garcia-Gargia et al., 2013). The VPFC forms an iterative neural circuit with striatum and thalamus (Alexander et al., 1986) that is thought to modulate emotional tone set by the amygdala, which in turn feeds back to the ventral striatal reward system. Based on the integration of these circuits and the PFC dysfunction found in BED, it has been hypothesized that heightened PFC reactivity to food cues might translate reward sensitivity into loss of control over eating (Schienle et al., 2009). Indeed, a neurophysiological model recently proposed by Chen et al. (2016) demonstrates that most decision making and reward processing studies of persons with eating disorders are consistent with ventral reward network dysfunction in the cognitive processing of food cues. Michaelides et al. (2012) contend, based on a review of neuroimaging studies in adolescents and adults with BED and obesity, that brain abnormalities in frontostriatal circuits are likely related to developmental psychopathology. Wang et al. (2011) concluded, using positron emission tomography (PET) and [^{11}C] raclopride, that increased dopamine release in the striatum of binge eaters may be responsible for decreased self-regulatory processes in BED, although this effect was only achieved using oral methylphenidate to strengthen dopamine detection.

As with any clinical study, this study was limited by a number of factors including a relatively small sample size, especially after neuroimaging data loss, lack of endpoint scans for the HC participants, and lack of a placebo-control group. Without placebo control, it is impossible to determine whether the decreases in brain activation were due to LDX, as opposed to simply being in a treatment program, reporting on binge eating behaviors, or to decreases in binge eating behaviors alone. It is also unknown if the results would generalize to individuals with BED of lesser severity. Additionally, we did not collect data on the time from last dose, so we cannot determine whether the second scan was mainly influenced by the acute effect of the last dose or the effect of long-term treatment. Finally, given the pilot nature of this study and to mitigate Type II error, no corrections were made for multiple statistical comparisons. All of these factors would be expected to limit interpretability and should be considered. However, the CPT-END (Continuous Performance Task with Emotional and Neutral Distractors) from which the CPT-BEND was derived has shown good test-retest stability over eight weeks in healthy subjects (Strakowski et al., 2016); mitigating concerns that activation reductions with BED treatment are the result of practice effects. Despite these limitations, both BED and HC participants were well characterized and this pilot study demonstrates a neurophysiological change in the direction of healthy brain activation after short-term treatment for BED. It should prove useful in informing larger, longer-term neuroimaging studies of LDX and other treatments in individuals with BED, which are greatly needed.

Disclosures

Dr. McElroy has been a consultant to or member of the scientific advisory boards of Alkermes, Avanir, Bracket, F. Hoffmann-La Roche Ltd., Mitsubishi Tanabe Pharma America, Myriad, Naurex, Novo Nordisk, Opiant, Shire and Sunovion. She has been a principal or co-investigator on studies sponsored by the Alkermes, Allergan, Avanir, Azevan, Brainsway, Marriott Foundation, Medibio, Myriad, National Institute of Mental Health, Neurocrine, Novo Nordisk, Shire and Sunovion. She is also an inventor on United States Patent No. 6,323,236 B2, Use of Sulfamate Derivatives for Treating Impulse Control Disorders, and along with the patent's assignee, University of Cincinnati, Cincinnati, Ohio, has received payments from Johnson and Johnson, which has exclusive rights under the patent.

Dr. Guerdjikova and Ms. Mori have been consultants to Bracket.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2019.03.003.

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