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Review

The neurobiological basis of binge-eating disorder

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ABSTRACT

Relatively little is known about the neuropathophysiology of binge-eating disorder (BED). Here, the evidence from neuroimaging, neurocognitive, genetics, and animal studies are reviewed to synthesize our current understanding of the pathophysiology of BED. Binge-eating disorder may be conceptualized as an impulsive/compulsive disorder, with altered reward sensitivity and food-related attentional biases. Neuroimaging studies suggest there are corticostriatal circuitry alterations in BED similar to those observed in substance abuse, including altered function of prefrontal, insular, and orbitofrontal cortices and the striatum. Human genetics and animal studies suggest that there are changes in neurotransmitter networks, including dopaminergic and opioidergic systems, associated with binge-eating behaviors. Overall, the current evidence suggests that BED may be related to maladaptation of the corticostriatal circuitry regulating motivation and impulse control similar to that found in other impulsive/compulsive disorders. Further studies are needed to understand the genetics of BED and how neurotransmitter activity and neurocircuitry function are altered in BED and how pharmacotherapies may influence these systems to reduce BED symptoms.

Contents

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1. Introduction

Binge-eating disorder (BED) is the most prevalent eating disorder (Hudson et al., 2007; Kessler et al., 2013) and is now included in the main section of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (American Psychiatric Association, 2013). Despite its high prevalence, the etiology of BED remains understudied, and the underlying neurobiological features of the disorder are poorly understood (Schienle et al., 2009). This article reviews human neuroimaging, neurocognitive and genetic BED data (Table 1) and considers complementary animal data relating to binge eating. Data suggest that compared with individuals without BED (hereafter referred to as non-BED), individuals with BED have greater cognitive attentional biases towards food, decreased reward sensitivities, and altered brain activation in regions associated with impulsivity and compulsivity. It is worth noting at the outset of this review that the concept "food addiction" is an ongoing area of research, with several recent reviews addressing this topic in relation to obesity and eating disorders in great detail (Hebebrand et al., 2014; Meule, 2015; Meule and Gearhardt, 2014; Potenza and Grilo, 2014). Furthermore, available evidence suggests stress and emotional regulation may play a role in BED (Corwin et al., 2011; Gianini et al., 2013; Gluck et al., 2004; Hilbert et al., 2011; Laessle and Schulz, 2009; Larsen et al., 2009; Nicholls et al., 2016; Pendleton et al., 2001; Pinaquy et al., 2003; Rosenberg et al., 2013; Schulz and Laessle, 2012). However, as these models are not the main focus of this review, they are only briefly discussed.

2. Impulsivity-related constructs and other cognitive functions

2.1. Impulsivity and compulsivity

Impulsivity reflects decision-making occurring with limited forethought and represents a multidimensional construct involving tendencies to act rashly, to have increased reward-related drives, and to have disadvantageous decision-making (Dawe and Loxton, 2004). In contrast, compulsivity is characterized by the performance of repetitive and persistent actions that are not related to an overall goal or reward and that can persist despite adverse consequences (Dalley et al., 2011). Increased impulsivity, elevated compulsivity, and altered reward sensitivity/punishment are reported in BED (Carrard et al., 2012; Duchesne et al., 2010; Galanti et al., 2007; Manwaring et al., 2011; Schag et al., 2013; Wu et al., 2014; Wu et al., 2013). Compared with non-BED obese and normal weight individuals, those with BED have increased impulsivity scores on the Barratt (BIS-11) and UPPS impulsiveness scales, decreased self-control, and impaired set-shifting reflective of perseverative/compulsive behaviors (Danner et al., 2012; Duchesne et al., 2010; Fineberg et al., 2014; Galanti et al., 2007; Hege et al., 2015; Manwaring et al., 2011; Schag et al., 2013; Wu et al., 2014; Wu et al., 2013). Impulsivity may underlie the diminished control observed during binge-eating episodes in BED, as higher BIS-11 scores were correlated with larger test meal intake (Galanti et al., 2007). Altered reward sensitivity is observed in overweight/obese BED individuals, as shown by gazing longer at food-related cues during a visual saccade task, with BED individuals having more difficulty inhibiting saccades toward both food- and non-food-related stimuli (Schag et al., 2013). Comorbid depressive symptoms and low self-esteem in individuals with BED are associated with greater impulsivity and sensitivity to punishment (Carrard et al., 2012). Taken together, the behavioral alterations observed in BED individuals indicate that BED may be conceptualized as an impulsive/compulsive disorder.

2.2. Other cognitive functions

Cognitive deficits in executive function, inhibitory control, attention, and mental flexibility are also reported in individuals with BED (Boeka and Lokken, 2011; Duchesne et al., 2010; Mobbs et al., 2011). Obese BED individuals exhibit broad cognitive dysfunction compared with obese non-BED individuals on tasks assessing problem solving, plan formulation and implementation, task scheduling, performance monitoring, cognitive flexibility, and working memory (Duchesne et al., 2010). Obese BED individuals also perform worse than obese non-BED individuals in multiple behavioral-tendency domains (apathy, disinhibition, executive dysfunction) related to prefrontal cortical function (Boeka and Lokken, 2011). While obese BED individuals exhibited impaired inhibitory control, attention, and rates of learning compared with obese non-BED individuals, BED and non-BED obese individuals performed worse than normal-weight individuals, suggesting that obesity alone may be related to impaired functioning (Mobbs et al., 2011).

2.2.1. Food-related attentional and memory biases

Individuals with BED have been shown to exhibit altered attentional and memory biases regarding food-related cues, and to a lesser extent, body-image-related cues (Schmitz et al., 2014; Svaldi et al., 2010a, 2014). Overweight women with BED preferentially attended to food-related stimuli compared with overweight non-BED women, including faster identification of visually obscured food-related words than non-food-related words and a faster fixation on a spatial cue located in the same vicinity as a food-related image (Schmitz et al., 2014). Overweight individuals with BED showed more cognitive interference during performance of a working-memory task than those without BED, regardless of whether the interfering cues were food-related (Svaldi et al., 2014). However, cognitive interference in BED individuals was greater after exposure to food-related stimuli than to neutral stimuli and was substantially greater compared with non-BED individuals when stimuli were presented in a manner representative of everyday situations (Svaldi et al., 2014). These alterations highlight the differential response of BED individuals to environmental cues, particularly to cues related to food.

2.2.2. Decision-making impairment

Decision-making impairments may also be associated with BED. In a probabilistic-reward task, individuals with BED made riskier decisions than non-BED individuals (Svaldi et al., 2010b). Obese individuals with BED also showed reduced preference for delayed rewards and probabilistic rewards compared with obese non-BED individuals and normal-weight individuals, suggesting that impaired decision-making may relate in part to impatience and risk aversion (Manwaring et al., 2011). BED-related decision-making

Table 1
Overview of human studies of the neurobiology of BED.

Study	Assessment	Study design and participants	Key findings
Neuroimaging studies			
Balodis et al. (2013a)	fMRI	Obese adults with BED ($n = 19$), obese adults without BED ($n = 19$), and normal-weight adults ($n = 19$) performed a monetary incentive delay task	• There were no significant differences on earnings or hit rate for win trials or loss trials between individuals with versus without BED during performance of the task • Individuals with BED had decreased activity across a range of brain regions, including ventromedial prefrontal cortex, inferior frontal cortex, and insular cortex, compared with obese individuals without BED during anticipatory reward/loss processing
Balodis et al. (2013b)	fMRI	Obese adults with BED ($n = 11$), obese adults without BED ($n = 13$), and normal-weight adults ($n = 11$) performed Stroop color-word interference task	• There were no significant group differences in Stroop Effect test performance • Individuals with BED had diminished activity in the right lateral and anterior medial orbital cortex, ventromedial prefrontal cortex, and inferior frontal gyrus (regions associated with inhibitory control) during the Stroop test compared with individuals without BED and normal-weight individuals
Balodis et al. (2014)	fMRI	Obese individuals with BED ($N = 19$) performed a monetary incentive delay task before 4-month treatment with sibutramine and/or CBT	• There were no significant group differences in monetary incentive delay task performance between treatment nonresponders ($n = 10$) and treatment responders ($n = 9$) • Treatment nonresponders showed reduced ventral striatal and inferior frontal gyrus recruitment during the anticipatory phase of reward processing and reduced activity in the medial prefrontal cortex during the outcome phase of reward processing compared with treatment responders
Cambridge et al. (2013)	fMRI	Obese individuals with BED were treated with either placebo ($n = 21$) or a μ-opioid receptor antagonist (GSK1521498; $n = 21$); grip force was measured in response to high- or low-caloric food images and high- or low-reward nonfood images to ascertain the effort participants were willing to expend to view these images	• μ-Opioid receptor antagonism reduced motivation to view the high-caloric food images compared with placebo but increased reported liking of these images • μ-Opioid receptor antagonism reduced right pallidum/putamen activity in response to high-caloric food images compared with placebo
Schienle et al. (2009)	fMRI	Women with BED ($n = 17$) and normal-weight ($n = 19$) and overweight ($n = 17$) women without eating disorders were exposed to high-caloric food pictures, disgust-inducing pictures, and neutral pictures; reward sensitivity ratings were measured with the Behavioral Inhibition/Activation Scales	• Individuals with BED reported greater reward sensitivity than normal-weight individuals and obese women without BED • Individuals with BED showed increased activation in the medial orbitofrontal cortex, anterior cingulate cortex, and insular cortex in response to high-caloric food images compared with normal-weight and obese women without BED; neural responses to disgust-inducing pictures did not differ between groups
Wang et al. (2011)	PET	Dopaminergic activity in response to food or neutral stimuli after treatment with oral MPH or placebo was measured in 16-hour fasted obese individuals with BED ($n = 10$) and obese individuals without BED ($n = 8$)	• Food stimuli significantly increased desire for food only after placebo in individuals with BED and only after MPH in individuals without BED • Baseline D2-like receptor availability, as measured by ^{11}C-raclopride did not differ between obese individuals with BED and obese individuals without BED • MPH produced greater increases in dopamine release in the caudate nucleus of obese individuals with BED in response to food stimuli than in obese individuals without BED • Dopamine release in the caudate was correlated with the severity of binge eating in individuals with and without BED
Weygandt et al. (2012)	fMRI	Women with BED ($n = 17$) and normal-weight ($n = 19$) as well as overweight ($n = 17$) women without eating disorders were exposed to high-caloric food pictures, disgust-inducing pictures, and neutral pictures; reward sensitivity ratings were measured with the Behavioral Inhibition/Activation Scales	• Sensitivity and specificity analyses indicated that activity in the right insular cortex distinguished the BED group from the normal-weight group • Sensitivity and specificity analyses indicated that activity in the right ventral striatum separated the BED group from obese women without BED

Table 1 (*Continued*)

Study	Assessment	Study design and participants	Key findings
Tammela et al. (2003)	SPECT	Radioligand-labeled serotonin transporter binding was recorded in obese women with BED ($n = 7$) and obese women without BED ($n = 6$) before and after successful treatment with combined psychotherapy and fluoxetine	• Serotonin transporter binding in the raphe nucleus increased in symptomatically recovered obese women with BED but was unchanged by treatment in obese women without BED
Karhunen et al. (2000)	SPECT	Obese women with BED ($n = 8$), obese women without BED ($n = 11$), and normal-weight women ($n = 12$) were exposed to a control stimulus (landscape picture) and to a food stimulus (warm freshly cooked lunch)	• Obese women with BED exhibited increases in blood flow in the left frontal and prefrontal cortices in response to the food stimulus; obese individuals without BED and normal-weight individuals showed no change or localized increases in the right hemisphere
Kuikka et al. (2001)	SPECT	Radioligand-labeled serotonin transporter binding was recorded in obese women with BED ($n = 11$) and obese women without BED ($n = 7$)	• Obese women with BED showed decreased midbrain serotonin transporter binding relative to obese women without BED
Hege et al. (2015)	MEG	Overweight/obese women with BED ($n = 17$) and without BED ($n = 17$) were assessed on the Barratt Impulsiveness Scale and in a food-related "go/no-go" task	• Individuals with BED tended to score higher on the Barratt Impulsiveness Scale; "no-go" accuracy tended to worsen more often in individuals with BED in response to food-related stimuli • Individuals with BED did not have a food-specific prefrontal cortical activity increase during the "go/no-go" task
Svaldi et al. (2010c)	ERP	Women with BED ($n = 22$) and overweight women without BED ($n = 22$) were exposed to high- and low-caloric food pictures	• Individuals with BED rated high-caloric food as more forbidden than did individuals without BED • High-caloric food images, but not low-caloric images, elicited larger and longer-lasting late positive potentials, an index of motivated attention, in women with BED compared with women without BED
Tammela et al. (2010)	EEG	EEG was assessed in obese women with BED ($n = 12$) and without BED ($n = 13$) during a resting state (closed eyes) and while attending to a control landscape image or a food stimulus	• Fronto-central beta activity (14–20 Hz) was increased in obese women with BED during all states (resting, control, food stimulus) relative to obese women without BED • Beta activity correlated with the disinhibition factor scores on the Three-Factor Eating Questionnaire and with Binge Eating Scale scores in individuals with BED
Schafer et al. (2010)	Structural MRI	Gray-matter-volume measurements were recorded in women with BED ($n = 17$) and normal-weight women without eating disorders ($n = 19$)	• Individuals with BED had greater gray-matter volume in the anterior cingulate cortex and the medial orbital frontal cortex than normal-weight individuals
Voon et al. (2015a)	Structural MRI	Voxel-based morphometry assessed brain volume, and a 2-step sequential learning task with a probabilistic monetary reward assessed habit formation in obese individuals with BED and without BED	• Obese individuals with BED ($n = 32$) were more likely to use habit-based learning and show perseveration than obese individuals without BED ($n = 31$) • Obese individuals with BED ($n = 20$) had smaller left ventral striatal, lower left lateral orbital frontal cortex, lower bilateral orbital frontal cortex, and lower bilateral caudate volumes than did obese individuals without BED ($n = 20$), with effects in the orbital frontal cortex, caudate, and ventral striatum no longer significant after accounting for habit-based learning
Genetic and heritability studies			
Cellini et al. (2010)	Glucocorticoid receptor gene	Glucocorticoid receptor gene SNPs were examined in individuals with BED ($n = 62$) and in obese ($n = 177$) and normal-weight ($n = 107$) individuals without eating disorders	• The GG genotype of the rs6198 polymorphism occurred more frequently in individuals with BED than in normal-weight controls; the frequency of this genotype in individuals with BED was also elevated in individuals with BED compared with obese individuals without BED, but the difference was not statistically significant

Table 1 (*Continued*)

Study	Assessment	Study design and participants	Key findings
Davis et al. (2007)	*DAT1* dopamine transporter gene	Individuals with BED ($n = 32$) and aged-matched non-obese controls without BED ($n = 46$) were assessed for DAT1 genotypes and for hunger after exposure to a food stimulus after MPH	• Individuals with BED with the 9-repeat DAT1 allele (which is associated with decreased DAT protein and increased synaptic dopamine) showed more appetite suppression following MPH than controls without BED possessing the same allele or any individual possessing the 10-repeat allele (associated with increased DAT protein and decreased synaptic dopamine)
Davis et al. (2008)	*DRD2* dopamine receptor gene	Individuals with BED ($n = 56$), obese individuals without BED ($n = 51$), and normal-weight individuals without BED ($n = 59$) were assessed for reward sensitivity and genotyped for a polymorphism of a DRD2 dopamine receptor-linked gene	• Obese individuals and individuals with BED possessing at least 1 copy of the A1 allele of Taq1A exhibited increased reward sensitivity relative to normal-weight controls
Davis et al. (2009)	*DRD2* dopamine receptor and μ-opioid receptor gene	Obese adults with BED ($n = 66$) and obese adults without BED ($n = 70$) were genotyped for a polymorphism of a DRD2 dopamine receptor-linked gene and a polymorphism of the *OPRM1* μ-opioid receptor gene	• Obese individuals with BED were less likely than obese individuals without BED to have the A1 allele of Taq1A and more likely to have the G allele of *OPRM1*
Davis et al. (2012)	*DRD2* dopamine receptor gene	Obese adults meeting criteria for BED ($n = 79$) and obese individuals not meeting criteria for BED ($n = 152$) were genotyped for a polymorphism of a D2 dopamine receptor-linked gene	• Obese individuals with BED were more likely than obese individuals without BED to be homozygous for the A2 allele of Taq1A, more likely to be homozygous for the T allele of C957T, and less likely to carry the minor T allele of rs2283265
Monteleone et al. (2006a)	5HTT 5HT transporter gene	Women with BED ($n = 77$) and women without eating disorders ($n = 61$) were genotyped for a 5HTT gene polymorphism	• Frequencies of the LL genotype and the L allele for the 5HTTLPR polymorphism were higher in individuals with BED compared with those without BED
Monteleone et al. (2006b)	BDNF gene	Women with BED ($n = 84$) and women without an eating disorder ($n = 121$) were genotyped for allelic variation in the BDNF gene	• There were no differences in the frequency of the 196G/A variants between women with and without BED • Among women with BED, those with the 196A/A variant had higher frequency of binge eating and more severe binge eating ratings than those with the 196G/A variant
Monteleone et al. (2008a)	*CLOCK* gene	Overweight/obese individuals with BED ($n = 107$), overweight/obese individuals without BED ($n = 85$), and normal-weight individuals without BED ($n = 92$) were assessed for a *CLOCK* gene polymorphism (311T/C), which relates to circadian rhythms	• Genotype and allele frequencies did not differ between obese individuals with and without BED
Monteleone et al. (2008b)	FAAH gene	Overweight/obese women with BED ($n = 115$), overweight/obese women without BED ($n = 74$), and normal-weight women without BED ($n = 110$) were assessed for a FAAH gene polymorphism (cDNA 385C to A), which impacts the degradation of endocannabinoids	• Genotype and allele frequencies did not differ between obese individuals with and without BED
Tasca et al. (2013)	IGF-II isoforms	Overweight women with BED ($n = 97$), overweight women without BED ($n = 53$), and normal-weight women without BED ($n = 50$) were assessed for the IGF-II isoforms before and after group psychotherapy	• The mature isoform of IGF-II was significantly higher in obese women with BED compared with normal-weight women without BED, but there were no significant differences between obese women with and without BED • The BIG IGF-II isoform decreased after group psychotherapy, but no difference was reported between obese women with and without BED
Hudson et al. (2006)	Heritability of BED	Blinded family interviews of overweight/obese probands with BED ($n = 150$) and without BED ($n = 150$) and their first-degree relatives ($n = 888$) were conducted to assess the heritability of BED	• BED aggregated in families, independent of obesity status (odds ratio: 2.2)
Javaras et al. (2008)	Heritability of BED	Structural equation modeling assessed the heritability of BED based on family interviews of overweight/obese probands with BED ($n = 150$) and without BED ($n = 150$) and their first-degree relatives ($n = 888$)	• BED aggregated in families, with an estimated heritability of 57%

Table 1 (*Continued*)

Study	Assessment	Study design and participants	Key findings
Mitchell et al. (2010)	Heritability of BED	Structural equation modeling assessed the heritability of BED in female monozygotic twins ($n = 614$) and dizygotic twins ($n = 410$) who self-reported *DSM-IV* BED symptoms; 32 women met full criteria for BED	• BED was moderately heritable, with 45% of heritability accounted for by additive genetics, 13% by common environmental factors, and 42% by unique environmental influences • Among specific BED symptoms, loss of control over eating and distress due to binges were found to have the highest heritability estimates (43%)
Reichborn-Kjennerud et al. (2004)	Heritability of BED	Questionnaire data regarding binge eating behavior from twins ($N = 8045$) from a Norwegian twin registry were used to assess the heritability of BED	• Additive genetic effects accounted for 41% of the heritability of binge eating (with a feeling of loss of control in the absence of compensatory behavior), with individual environmental factors accounting for 59% of the variance
Cognitive studies			
Boeka and Lokken (2011)	Executive function	Obese individuals with BED ($n = 22$), obese individuals with subthreshold BED ($n = 47$), and obese individuals without BED ($n = 82$) were assessed with the Frontal Systems Behavior Scale	• Obese individuals with BED and subthreshold BED exhibited dysfunction on the apathy, disinhibition, and executive function subscales and on total score compared with individuals without BED
Duchesne et al. (2010)	Executive function	Obese women with BED ($n = 38$) and without BED ($n = 38$) were assessed on multiple measures of executive function	• Obese individuals with BED exhibited impaired executive function as assessed on the Digit Span Backward, Zoo Map, Modified Six Elements, Action Program, and Wisconsin Card Sorting tests compared with obese individuals without BED
Galioto et al. (2012)	Executive function, memory, language, attention	Obese individuals with a past or present BED diagnosis ($n = 41$) and obese individuals without BED ($n = 90$) were assessed on multiple cognitive tests	• Obese individuals with a past or present BED diagnosis and without BED exhibited global impairments in cognitive function, but there were no group differences between those with versus without BED
Mobbs et al. (2011)	Attention, inhibitory control	Obese individuals with BED ($n = 16$), obese individuals without BED ($n = 16$), and normal-weight individuals ($n = 16$) were assessed on a food/body-mental flexibility task	• Obese individuals with BED made more errors and omissions than obese individuals without BED and normal-weight controls in the food and body sections of the task, indicating impaired attention and inhibitory control • Obese individuals with BED exhibited less within-session learning than obese individuals without BED, as evidenced by omission rates across sessions
Schag et al. (2013)	Attention, inhibitory control	Overweight/obese individuals with BED ($n = 25$), overweight/obese individuals without BED ($n = 26$), and normal-weight individuals without BED ($n = 25$) were assessed for reward sensitivity and disinhibition in response to food stimuli using visual saccade tracking	• Individuals with BED gazed longer at food stimuli (increased reward sensitivity) and had more difficulty inhibiting saccades toward both food and nonfood stimuli (disinhibition/inhibitory control) than both obese individuals without BED and normal-weight individuals without BED
Schmitz et al. (2014)	Attention, attentional bias	Overweight/obese women with BED ($n = 27$) and overweight/obese women without BED ($n = 33$) were assessed on a test of attentional vigilance in which they identified visually obscured words (food-related and neutral) and a spatial cueing task (food-related and neutral images) to examine attentional bias	• Both obese women with BED and obese women without BED identified obscured food-related words faster than neutral words, with the effect was more pronounced for those with BED • Response times of obese women with BED but not obese women without BED were more rapid in a spatial cueing task in response to food-related cues compared with neutral cues
Svaldi et al. (2014)	Attention, attentional bias	Overweight individuals with BED ($n = 31$) and overweight individuals without BED ($n = 36$) completed an *n*-back working memory tasks in the presence of interfering cues both food-related and neutral. Participants also performed a recent-probe task in which a set of words are presented for a short time each trial and then after a retention an interval, a probe stimulus is presented and the participant is asked to classify it as to whether it was a member of the most recent trial's words; the words used could be food-related or neutral.	• Overweight individuals with BED were more likely than those without BED to show cognitive interference in a working memory task that employed a highly familiar but irrelevant stimulus regardless of whether the interfering cues were food-related or neutral • Cognitive interference in individuals with BED was more pronounced after exposure to food-related stimuli than to neutral stimuli and substantially greater compared with individuals without BED when the working memory task employed more diverse stimuli in a manner that may be more representative of everyday situations

Table 1 (*Continued*)

Study	Assessment	Study design and participants	Key findings
Svaldi et al. (2010a)	Memory bias	Overweight individuals with BED ($n = 18$) and overweight individuals without BED ($n = 18$) performed a memory recall test comprised of positive body-related words, positive control words, negative body-related words, and negative control words	• Overweight women with BED recalled fewer positive body-related words and fewer positive control words than did overweight women without BED
Danner et al. (2012)	Decision-making	Women with BED ($n = 19$), obese women without BED ($n = 18$), and normal-weight women without BED ($n = 30$) were assessed on the Iowa Gambling Task	• Obese women with BED and obese women without BED performed worse than normal-weight women, but obese women with BED did not perform worse than obese women without BED; task performance correlated with binge eating severity in the BED group
Davis et al. (2010)	Decision-making	Obese women with BED ($n = 65$), obese women without BED ($n = 73$), and normal-weight women without BED ($n = 71$) were tested on the Iowa Gambling Task and a Delay Discounting measure	• Obese women with BED and obese women without BED performed worse than normal-weight women on both tasks but did not differ from each other
Manwaring et al. (2011)	Decision-making	Obese women meeting *DSM-IV* criteria for BED ($n = 30$), obese women without BED ($n = 30$), and normal-weight women without BED ($n = 30$) were assessed on decision-making using delay and probability discounting tasks	• Across reward types, obese women with BED showed a reduced preference for delayed rewards and probabilistic rewards compared with obese individuals without BED and normal-weight controls
Svaldi et al. (2010b)	Decision-making, cognitive flexibility	Overweight women meeting *DSM-IV* criteria for BED ($n = 17$) and overweight women without BED ($n = 18$) were assessed using the Game of Dice task and the Trail Making Test	• Women with BED were more likely to make risky decisions and show impairments in utilizing feedback processing compared with women without BED on the Game of Dice task • Women with BED exhibited impaired cognitive flexibility on the Trail Making Test compared with women without BED, although both groups fell within the normal performance range
Voon et al. (2015b)	Decision-making	Obese individuals with BED ($n = 30$), obese individuals without BED ($n = 30$) and aged, and gender matched healthy controls completed a probabilistic decision-making task in which on each trial they could choose a risky choice with probabilistic likelihood of winning or losing a monetary reward or a sure choice with a guaranteed outcome (win or lose) of a smaller sum	• Relative to healthy controls, individuals with BED were more likely to make risky choices for moderate probabilities of reward (e.g., 50%) and for low probabilities of loss • Relative to healthy controls, obese individuals without BED were less likely to make risky choices for high probabilities of reward and, like individuals with BED, were more likely to make risky choices for low probabilities of loss • The probability of risky choices did not vary with the size of the reward for individuals with BED but decreased for increasing reward size for healthy controls and for obese individuals without BED
Wu et al. (2013)	Decision-making, inhibitory control	Overweight/obese individuals with BED ($n = 54$) or without BED ($n = 43$) were compared on the Game of Dice task and the Stop Signal task	• Overweight individuals with BED did not differ from overweight individuals without BED on either the Game of Dice decision-making task or on the Stop Signal inhibitory control task

impairments were further delineated in a task in which participants could choose between risky or sure monetary choices (Voon et al., 2015b). Obese individuals with BED were more likely than obese non-BED individuals and age- and gender-matched healthy volunteers to make risky choices in response to moderate probabilities of reward and high probabilities of loss (Voon et al., 2015b), a decision-making pattern similar to that observed in abstinent alcohol-dependent and abstinent stimulant-dependent individuals but not obese individuals (Voon et al., 2015b). Probabilities of making risky choices did not vary with reward magnitude in individuals with BED, whereas they decreased with increasing reward magnitude in age- and gender-matched healthy volunteers and obese non-BED individuals (Voon et al., 2015b). Thus, individuals with BED may exhibit impaired decision-making in situations associated with high risk and ambiguity whereas obese non-BED individuals may be impaired more in ambiguous situations.

However, in studies of BED cognitive and decision-making deficits are not always observed in obese BED versus obese non-BED individuals (Danner et al., 2012; Davis et al., 2010; Duchesne et al., 2010; Galioto et al., 2012; Wu et al., 2013). Despite the fact that the degree of decision-making impairment on the Iowa Gambling Task correlates positively with binge-eating severity among BED individuals (Danner et al., 2012), in one study obese BED and obese non-BED individuals exhibited similar cognitive impairments across multiple domains (memory, attention, executive function, language) (Galioto et al., 2012) and similar impairment on the Iowa Gambling Task (Danner et al., 2012; Davis et al., 2010). These findings suggest that binge eating behaviors in BED individuals are not solely driven by alterations in cognitive function.

In summary, BED can be associated with an array of cognitive alterations related to impulsivity/compulsivity, executive function, attention, and decision making. These alterations suggest that altered function in the cortex and striatum, areas whose function plays a key role in mediating these cognitive functions (Berridge and Kringelbach, 2008; Bromberg-Martin et al., 2010; Everitt and Robbins, 2013; Miller and Cohen, 2001; Naqvi and

Bechara, 2010), is altered in BED individuals. Available evidence regarding altered brain function in BED is summarized in the next section.

3. Brain structure and function

Neurophysiologic and neuroimaging studies have identified changes in individuals with BED that may partially underlie altered impulsivity and reward processing. Obese women with BED compared with non-BED obese women exhibited increased centroparietal cortical long-latency event-related potentials (an index of motivated attention) when viewing high-caloric food pictures but not neutral pictures (Svaldi et al., 2010c). Increased frontal beta-electroencephalographic activity during resting and active states was observed in obese BED women compared with obese non-BED women; increased beta activity correlated with scores on the disinhibition factor of the Three-Factor Eating Questionnaire and Binge-Eating Scale in obese women with BED (Tammela et al., 2010). Obese BED women also demonstrated increased regional cerebral blood flow in left frontal and prefrontal cortices in response to food stimuli, whereas non-BED and normal-weight women showed no change or only localized increases in the right hemisphere (Karhunen et al., 2000). BED individuals compared with obese and normal-weight non-BED individuals exhibited increased reward responsiveness and increased medial orbitofrontal cortical activity in response to high-caloric food images, as assessed by functional magnetic resonance imaging (fMRI) (Schienle et al., 2009). Taken together, these data suggest altered function in cortical and striatal regions is likely to contribute to BED.

3.1. Striatum and insular cortex

Striatal and insular function has been associated with reward sensitivity and impulsivity in BED. During exposure to high-caloric food images, activation in the left ventral striatum separated BED individuals from those with bulimia nervosa (BN), with a sensitivity of 82% and a specificity of 86%. Right ventral-striatal activation during exposure to high-calorie food images differentiated obese BED and non-BED individuals, with a sensitivity of 59% and a specificity of 82%; right-insular activation differentiated BED individuals from obese and normal-weight non-BED individuals, with sensitivities of 77% and 82%, respectively, and specificities of 65% and 90% (Weygandt et al., 2012). Compared with non-BED individuals, obese individuals with BED demonstrated bilateral decreases in ventral-striatal activation during anticipation of monetary reward receipt/loss; upon notification of a monetary reward, obese BED individuals demonstrated diminished insular activity compared with non-BED obese and normal-weight individuals (Balodis et al., 2013a). Obese BED individuals who continued to binge eat following treatment with sibutramine and/or psychotherapy had relatively decreased anticipation-related right ventral-striatal activation, anticipation-related bilateral-inferior-frontal-gyral activation, and outcome-related medial-prefrontal-cortical activation compared with those who did not continue to binge eat (Fig. 1). Given links between anticipation-related ventral-striatal activation and impulsivity (Balodis et al., 2012), these findings suggest possible links between reward-related brain activations, impulsivity, and treatment outcome in BED.

3.2. Prefrontal cortex and impulse-control networks

Altered cognitive function in BED may relate to reward sensitivity (Balodis et al., 2013b; Schafer et al., 2010; Voon et al., 2015a). During fMRI Stroop performance, obese BED individuals showed

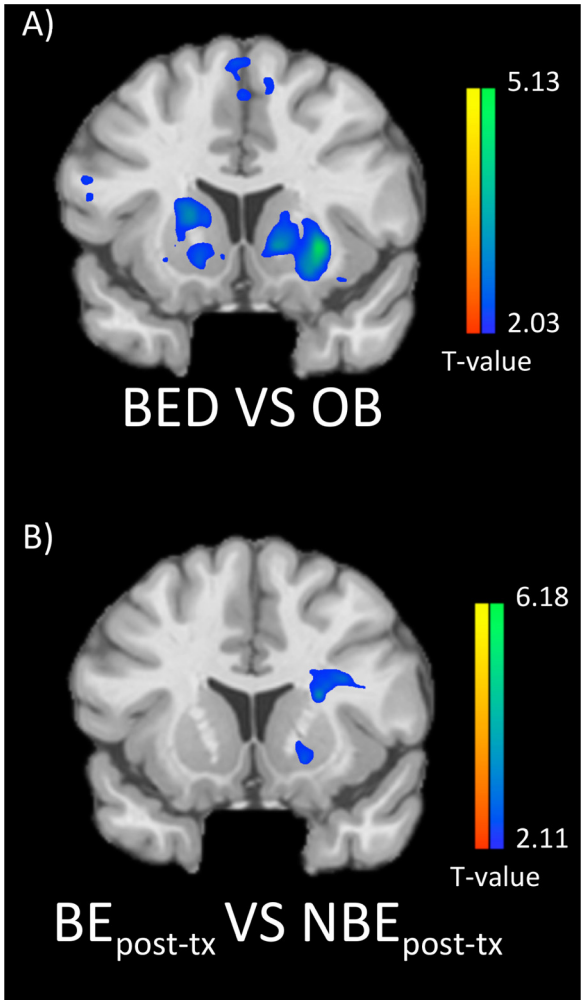

Fig. 1. Functional MRI images of diminished ventral striatal activation in individuals with BED during reward anticipation and its relationship to treatment outcome*. (A) Coronal view ($y = 12$) of ventral striatal regions showing a whole brain contrast between obese individuals with binge eating disorder (BED; $n = 19$) and obese individuals without BED (OB; $n = 19$). (B) Map of differences within the BED group separating those who reported bingeing following treatment (BEpost-tx; $n = 10$) contrasted with BED participants who did not report bingeing following treatment (NBEpost-tx; $n = 9$). Brain activation maps demonstrate differences in the A2 winning phase (A2W; associated with the anticipation of potentially winning money). All contrast maps are thresholded at an uncorrected level of $p < 0.05$ two-tailed and family-wise-error corrected at $p < 0.05$. Blue color demonstrates areas where participants show relatively less activation. The right side of the brain is on the right. *Unpublished data obtained from Iris Balodis and Marc Potenza; see Balodis et al. (2014) for study description.

diminished activity in impulse control-related cortical areas (i.e., ventromedial-prefrontal, inferior-frontal, and insular) compared with non-BED individuals in the absence of differences in task performance (Balodis et al., 2013b). During a habitual learning test, BED individuals were more likely than non-BED individuals to use habitual learning strategies and to show perseveration, with obese BED versus non-BED individuals demonstrating smaller left-ventral-striatal, bilateral-caudate, and orbital-frontal-cortical volumes (Voon et al., 2015a). However, when behavior was covaried, group differences in the medial orbitofrontal cortex, caudate, and ventral striatum were no longer significant, suggesting that individual differences in learning bias may be related to these findings (Voon et al., 2015a). Increased attentional impulsiveness measured on the BIS-11 was related to decreased response inhibition in a visual go-nogo task and to hypoactivity in prefrontal networks in obese BED and non-BED individuals, with BED indi-

viduals exhibiting higher attentional impulsiveness scores and a trend towards worse performance in response to food-specific stimuli than non-BED individuals (Hege et al., 2015). Results from a pilot study suggest that the level of hypoactivity in frontal cortical reward circuitry in BED relates to treatment response, with those with greater hypoactivity exhibiting persistent bingeing following treatment (Balodis et al., 2014). Structural MRI has revealed differences in gray-matter volumes in the anterior-cingulate and medial-orbitofrontal cortices in BED individuals (Schafer et al., 2010) and selective atrophy in the right striatum, right ventral-insular cortex, and right orbitofrontal cortex (Woolley et al., 2007) in individuals with frontotemporal dementia who develop binge-eating behaviors. The precise clinical relevance of these findings remains to be determined. However, given the preponderance of evidence, it seems reasonable to hypothesize that altered cortical function contributes significantly to the altered reward sensitivity and impulsivity observed in BED individuals.

4. Genetics

BED aggregates in families (Hudson et al., 2006); heritability estimates for BED range from 41% to 57% (Javaras et al., 2008; Mitchell et al., 2010; Reichborn-Kjennerud et al., 2004). As with most psychiatric disorders, the genetics of BED are likely to be complex and involve interactions with environmental factors (see Table 1 for descriptions of genetics studies). Therefore, multiple genetic studies have assessed potential substrates that might contribute to the neurobiologic alterations in BED.

4.1. Dopaminergic- and opioidergic-associated genetic polymorphisms

Compared with normal-weight non-BED individuals, obese BED and non-BED individuals have displayed elevated reward sensitivity if they carry ≥1 copy of the A1 allele of the Taq1A polymorphism (Davis et al., 2008). This polymorphism is downstream of the *DRD2* gene and is located within the *ANKK1* gene (Neville et al., 2004); it is associated with reduced D2-like receptor density in healthy volunteers (Jonsson et al., 1999; Pohjalainen et al., 1998) and in alcohol-dependent individuals (Yang et al., 2007). The allelic frequency of A1 is lower among obese BED individuals compared with obese non-BED individuals (Davis et al., 2009, 2012). The A2 allele of the Taq1A polymorphism (known as rs1800497), which is associated with increased dopamine signaling (Noble et al., 1991), and the rs6277 polymorphism of the *DRD2* gene (known as C957T), which is associated with increased D2-like receptor binding in [^{11}C]raclopride studies (Hirvonen et al., 2004), are more common in obese BED individuals than in obese non-BED individuals (Davis et al., 2009; Davis et al., 2012). BED individuals with a copy of the 9-repeat allele of the dopamine transporter gene *(DAT1)*, which is associated with decreased dopamine levels of transporter protein and increased levels of synaptic dopamine, exhibited more methylphenidate-induced appetite suppression than BED individuals who were homozygous for the 10-repeat allele and non-BED individuals regardless of genotype (Davis et al., 2007).

The "gain of function" G allele (known as G^+) of the A118G polymorphism of the μ-opioid-receptor-encoding gene appears more common in obese individuals with BED than in obese non-BED individuals (Davis et al., 2009). The higher frequency of Taq1A A2/A118G G^+ genotypes observed in BED individuals suggests that these individuals may be prone to elevated food-related hedonic responses through dopaminergic and opioidergic influences on reward-related processes (Davis et al., 2009).

All of these studies are interesting, but they involved relatively small samples (Table 1). While replication studies are required to substantiate these findings, the evidence to date supports the concept that BED has genetic underpinnings that include altered dopaminergic systems that may contribute to impulsivity, compulsivity, and reward/reinforcement (Avena and Bocarsly, 2012; Buckholtz et al., 2010; Kenny et al., 2013; Nakanishi et al., 2014).

4.2. Other polymorphisms

In addition to dopaminergic and opioidergic genes, serotonergic, glucocorticoid, brain-derived-neurotrophic-factor, *CLOCK*, endocannabinoid, and insulin-like-growth-factor-2 genes have been investigated (Cellini et al., 2010; Kuikka et al., 2001; Monteleone et al., 2006a, 2008a,b, 2006b; Tammela et al., 2003; Tasca et al., 2013); however, results have either been equivocal or suggested no association with BED. Although there are no published genome-wide association studies in BED, a study comparing individuals with bipolar disorder who either exhibited or did not exhibit binge-eating behaviors reported multiple single-nucleotide polymorphisms in association with binge-eating behaviors (Winham et al., 2014). As with all genetic association studies, it remains possible that the implicated genes are more related to specific disorder-associated domains (e.g., impulsivity, compulsivity, or reward sensitivity) rather than the disorder as a whole.

5. Translational considerations: animal and human data

BED is characterized by impulsive and compulsive consumption of highly palatable foods, which is regulated by brain reward systems (Avena and Bocarsly, 2012; Avena et al., 2008; Mathes et al., 2009). Although multiple neurotransmitter systems (including dopaminergic, cholinergic, noradrenergic, opioidergic, GABAergic, and glutamatergic systems) may contribute to binge-eating behaviors, dopaminergic and opioidergic neurotransmission appear critical to reward, including reward-related food consumption (Avena and Bocarsly, 2012; Avena et al., 2008; Bello et al., 2014; DiFeliceantonio et al., 2012; Mathes et al., 2009). Dopaminergic neurotransmission in the nucleus accumbens/ventral striatum (NAc) is linked to motivational and energy-dependent aspects of food seeking and opioidergic neurotransmission is involved in hedonic aspects of reward (Castro and Berridge, 2014; Salamone et al., 2003; Wise, 2008). Although the reduction in food consumption in animal models (Nathan and Bullmore, 2009) and the reduction in the motivation to view high-caloric food images in BED individuals (Cambridge et al., 2013) that occurs following the blockade of μ-opioid receptors suggest that opioid systems contribute to BED, treatment with μ-opioid receptor antagonists does not reduce binge eating in BED individuals (McElroy et al., 2013; Ziauddeen et al., 2013). While food is a natural reward, data suggest that similar changes in dopaminergic neurotransmission in brain reward circuitry may underlie binge-eating behaviors (Furlong et al., 2014) and drug abuse (Everitt and Robbins, 2013). These changes in dopaminergic neurotransmission may contribute to increased impulsivity, compulsive behaviors, and altered reward sensitivity seen in these disorders (Blum et al., 2014; Everitt and Robbins, 2013; Fineberg et al., 2014; Richard et al., 2013; Stice et al., 2013).

5.1. Ventral midbrain-nucleus accumbens (NAc) dopaminergic pathways

Increased impulsivity has been associated with altered dopaminergic neurotransmission in the ventral midbrain and NAc. Studies in animals and healthy humans have reported that increased impulsivity is correlated with decreased ventral-striatal and ventral-midbrain dopamine D2-like receptor levels and with increased dopamine release in the anterior caudate and NAc

(Belin et al., 2008; Buckholtz et al., 2010). Pathway analysis suggests increased dopamine release in the NAc and anterior caudate observed with increased impulsivity is mediated by decreased ventral-midbrain dopamine D2-like receptor levels, with these receptors being autoreceptors on dopamine neurons regulating dopaminergic neuronal firing (Buckholtz et al., 2010). In primates, initial rates of cocaine self-administration and acquisition of cocaine self-administration have been correlated with decreased NAc/striatal dopamine D2-like receptor levels (Nader et al., 2008). Therefore, impulsivity may represent a critical risk factor for substance abuse, and this may be linked to altered dopamine D2-autoreceptor regulation of ventral-midbrain dopamine neurons, leading to increased dopamine neurotransmission in the NAc.

Studies in rodents indicate that the development of compulsive drug abuse and binge-eating reflect progressive changes in the locus of dopaminergic control of drug and food consumption from a reward/ventral-striatal mode of consumption to a goal-directed/posterior dorsomedial striatal mode to a chronic habitual/compulsive mode involving anterior dorsolateral striatal dopaminergic neurotransmission (Everitt and Robbins, 2013; Furlong et al., 2014; Murray et al., 2012). In primates, there is a similar evolution of cocaine-induced decrements in both striatal function and dopaminergic neurotransmission, particularly decrements in dopamine D2-like receptor levels (Nader et al., 2008; Porrino et al., 2004). In humans with substance addiction, as well as in animal models of compulsive drug and food intake/binge-eating, there are decreased striatal dopamine D2-like receptor levels, decreased striatal dopaminergic release, and increased reward thresholds (Avena, 2010; Johnson and Kenny, 2010; Lee et al., 2009; Martinez et al., 2012; Volkow et al., 1993; Volkow et al., 1996). Decreased striatal dopamine D2-like receptor levels have been inversely correlated with impulsivity in human methamphetamine abusers (Lee et al., 2009). In contrast, PET studies with the dopamine D3 preferring radioligand, [^{11}C]PHNO, which selectively labels dopamine D3 receptors in the substantia nigra, report increased nigral dopamine D3 receptor levels in cocaine and methamphetamine abuse that was positively correlated with impulsiveness and risky decision making (Boileau et al., 2012; Payer et al., 2014); similarly nigral dopamine D3 receptor levels were positively correlated with impulsiveness in pathological gamblers although mean nigral dopamine D3 receptor levels did not differ from those in healthy individuals (Boileau et al., 2013).

Rodents fed a high-sugar/high-fat "cafeteria-style" diet become obese and demonstrate elevated reward thresholds and decreased NAc dopamine release (Geiger et al., 2009; Johnson and Kenny, 2010). In human cocaine-dependent individuals, decreased dopamine release in the anterior caudate and NAc correlated with abnormal reward behavior, particularly preference of cocaine versus monetary reward (Martinez et al., 2007). The development of compulsive food intake/binge-eating was accelerated in obese rats fed a cafeteria-style diet when dorsolateral striatal dopamine D2 receptor levels were decreased using a lentivirus-induced knockdown approach (Johnson and Kenny, 2010). Similarly, rodents intermittently exposed to a sugar solution develop sugar-bingeing/addiction but do not become obese (Avena, 2010); these sugar-bingeing rodents have decreased dorsal striatal dopamine D2-like receptor levels and increased μ-opioid and dopamine D1-like receptor levels in the NAc (Avena, 2010; Colantuoni et al., 2001). In contrast, genetic upregulation of striatal D2-like receptor levels in rats trained to self-administer cocaine significantly decreases cocaine self-administration (Thanos et al., 2008). While a cafeteria-style diet may produce obesity, elevated reward thresholds, and decreased dopamine release, it is the development of decreased dopamine D2-like receptor levels, particularly in the dorsolateral striatum, which appears to lead to compulsive food and drug use. In animal models, obesity and binge-eating can be produced separately and are associated with dissociable changes in dopaminergic neurotransmission. The function of GABAergic systems within the NAc has also been demonstrated to play an important role in the regulation of impulsivity in rats selected for high or low impulsivity (Caprioli et al., 2014), so it is conceivable that changes in NAc inhibitory GABA function may be of importance in the increased impulsivity in BED by virtue of its role in integrating dopaminergic neurotransmission.

5.2. Direct and indirect striatonigral pathways

The onset of compulsive behaviors appears to relate to an altered balance of signaling between the direct and indirect striatonigral pathways. Dopamine D1 receptors, which are linked to reward, are largely located in the direct striatonigral pathway; dopamine D2 receptors, which are linked to behavioral flexibility, are largely confined to the indirect pathway (Kenny et al., 2013; Nakanishi et al., 2014). Hypofunction of the indirect pathway is linked to perseverative and compulsive behaviors. In animal models of compulsive food and drug abuse, as well as in human studies of dopamine D1-like and D2-like receptors in cocaine-use disorders, both decreased striatal dopamine D2-like and increased or unchanged levels of dopamine D1-like receptors are observed, consistent with relatively increased signaling in the direct versus indirect pathways (Colantuoni et al., 2001; Furlong et al., 2014; Kenny et al., 2013; Martinez et al., 2004, 2009; Nader et al., 2002; Park et al., 2013). This imbalance in signaling through the direct and indirect striatonigral pathways associated with decreased dorsolateral striatal dopamine D2-like receptor levels, in combination with relatively higher dopamine D1-like receptor signaling, may mediate the development of compulsive drug and food intake.

While multiple studies in animals demonstrate a role for dopaminergic neurotransmission in binge-eating behaviors, there is only a single study of dopaminergic neurotransmission in BED individuals (Wang et al., 2011). While this study concluded that obese BED individuals had increased dopamine release in the caudate, the study was limited by the small number of participants (10 obese BED and 8 obese non-BED individuals) and questions regarding the confounding effects of methylphenidate, which the authors reported using to amplify the effects of visual food stimuli (Wang et al., 2011). [^{11}C]Raclopride positron emission tomographic (PET) studies were performed in a baseline state, following visual food stimuli, and following methylphenidate administration with and without visual food stimuli (Wang et al., 2011). The difference between dopamine D2-like receptor levels after methylphenidate administration with food stimuli compared with baseline levels (without methylphenidate) was used to estimate food-stimuli—induced dopamine release (Wang et al., 2011). However, this comparison confounds the effects of methylphenidate with food stimuli. This study also reported no difference in baseline dopamine D2-like receptor levels in striatal subregions between obese BED and obese non-BED individuals (Wang et al., 2011). This lack of a significant difference in striatal dopamine D2-like receptor levels, which has been reported in animal models, may reflect a lack of power due to the small cohort size and/or species differences. In regard to other neurotransmitters which are of interest in BED, there has been a single [^{123}I]nor-β-CIT study of midbrain serotonin transporters in binge-eating individuals that reported reduced levels (Kuikka et al., 2001). Although [^{123}I]nor-β-CIT has been used as a tracer for measurement of serotonin transporters, it has high affinity for the dopamine transporter and midbrain uptake may reflect levels of both serotonin and dopamine transporters (Bergstrom et al., 1997; Oya et al., 1999).

Although to date there has been little evidence for a role of dopaminergic systems in binge-eating in BED individuals, a role for dopamine systems in the impulsivity and addictive behavior

is better defined. Impulsivity was correlated with ventral striatal dopamine D2-like receptor levels in rodents (Belin et al., 2008), but with ventral midbrain dopamine D2-like receptor levels in humans (Buckholtz et al., 2010). Further studies of dopamine neurotransmission in BED are needed, and aspects of dopamine function that have been linked to impulsivity warrant consideration in this regard (Boileau et al., 2013; Payer et al., 2014; Potenza and Brody, 2013). Although an in-depth discussion of the role of dopaminergic transmission in obesity is beyond the scope of this review, it is worth noting that alterations in dopaminergic tone and phasic dopaminergic signaling have been implicated in mediating the behavioral characteristics of obesity (Horstmann et al., 2015; Kessler et al., 2014).

Alterations in hedonic and reward-related responses and observed brain activity patterns in reward-related areas in individuals with BED share similarities with those in substance-use disorders and addictions. Additionally, diminished control over eating and self-sustaining aspects of binge-eating are reminiscent of the behavioral features of addiction (Bello and Hajnal, 2010; Gearhardt et al., 2011; Mathes et al., 2009). The concept, neurobiology, and clinical utility of "food addiction" represents an ongoing area of research (Hebebrand et al., 2014; Meule, 2015; Meule and Gearhardt, 2014; Potenza and Grilo, 2014) that has been investigated in regard to BED based on the observation that there are common neurobiological substrates for BED and addiction (Brownell and Gold, 2012; Gearhardt et al., 2011). Although the topic remains controversial (Avena et al., 2012; Ziauddeen et al., 2012a,b), it is worth noting that BED individuals who score high on the Yale Food Addiction Scale (YFAS), which was developed to assess the concept of food addiction (Gearhardt et al., 2009), report more severe binge-eating pathology than those with lower YFAS scores, and food addiction as indexed by the YFAS is prominent among BED individuals (Gearhardt et al., 2012). Further research is needed to clarify more definitively the relationship between food addiction and binge eating in BED.

6. Summary

The neurobiological basis of BED is slowly being elucidated. Specifically, BED individuals exhibit increased impulsivity, compulsivity, and altered reward sensitivity (Galanti et al., 2007; Manwaring et al., 2011; Schag et al., 2013; Wu et al., 2013), along with enhanced attentional biases directed toward food and impaired cognitive function (Boeka and Lokken, 2011; Duchesne et al., 2010; Mobbs et al., 2011; Schmitz et al., 2014; Svaldi et al., 2014). As schematically outlined in Fig. 2, the neurobehavioral profile observed in BED appears to be subserved by brain regions, including the ventral striatum, which underlies goal-seeking behaviors, motivation, and reward sensitivity; the dorsal striatum, which underlies habitual and compulsive behaviors; the prefrontal cortex, which underlies executive function (Berridge and Kringelbach, 2008; Bromberg-Martin et al., 2010; Everitt and Robbins, 2013; Miller and Cohen, 2001); and the insula, which underlies interoception, decision-making, taste perception, and feeding regulation (Naqvi and Bechara, 2010; Small, 2010). These regions may relate to BED in a similar manner as they do to addictions and impulse-control disorders (Arnsten, 2011; Greenberg et al., 2010; Hyman et al., 2006; Li and Sinha, 2008; Morein-Zamir and Robbins, 2014).

Although multiple neurotransmitter systems (dopaminergic, serotonergic, cholinergic, noradrenergic, GABAergic, opioidergic, and glutamatergic systems) are likely involved in the neuropathophysiology of BED, human neuroimaging (Balodis et al., 2015) and animal (Kenny et al., 2013) studies suggest that altered dopamine function is an important contributor to BED and binge-eating behaviors. We hypothesize that binge-eating reflects an imbalance between the direct striatonigral output pathway (and its associated D1-like receptors that underlie reward) and the indirect striatopallidal pathway (and its associated D2-like receptors that underlie behavioral flexibility) (Kenny et al., 2013; Nakanishi et al., 2014). The putative hypofunction of the indirect pathway, as reflected by the reduced D2-like receptor levels reported in animal models of binge-eating (Kenny et al., 2013), relative to the direct pathway may in part mediate the compulsive eating behaviors seen in BED (Fig. 3). In animals models of drug abuse, the development of this imbalance may result from chronically increased dopamine release (Nakanishi et al., 2014); in animal models of binge-eating behaviors, restricted access to highly palatable foods produces similar patterns of altered dopaminergic neurotransmission (Avena, 2010) and may lead to the development of binge-eating behaviors.

There is a currently a paucity of neuroimaging studies of cerebral neurotransmission in humans with BED and of studies describing the effects of therapeutic agents on corticostriatal activity in BED individuals (Balodis et al., 2015). As such, potential future research directions in this area are summarized in Table 2. In this regard, it is worth noting that while evidence indicates that stress and emotional regulation may play a role in BED (Corwin et al., 2011; Gianini et al., 2013; Gluck et al., 2004; Hilbert et al., 2011; Laessle and Schulz, 2009; Larsen et al., 2009; Nicholls et al., 2016; Pendleton

Table 2
Future areas of research.

- Clinical neuroimaging assessment of the neurochemical basis of BED
- Utilize PET to examine endogenous DA, NE, 5-HT, opiate and other systems (e.g., gluamatergic) in the striatum and cortex of obese individuals with versus without BED and to assess changes in these neurotransmitter systems after pharmacological pertubations (e.g., following amphetamine challenge) or behavioral and/or pharmacological interventions (i.e., during specific therapies) for BED

- Clinical neuroimaging assessment of cognitive functioning in BED
- Utilize FMRI to examine functional activity in and connectivity patterns in regions of the striatum (dorsal versus ventral) and cortex of obese individuals with versus without BED at baseline and following pharmacological pertubations or behavioral and/or pharmacological interventions for BED during the performance of specific cognitive tasks or at rest
- Utilize structural measures (e.g., volumetric and diffusion-weighted MRI) to examine differences in obese individuals with versus without BED at baseline and following behavioral and/or pharmacological interventions for BED

- Clinical neuroimaging assessment of the role of stress and emotional regulation in BED
- Utilize FMRI to examine functional activity in regions of the striatum (dorsal versus ventral) and cortex of obese individuals with versus without BED at baseline and following pharmacological pertubations or behavioral and/or pharmacological interventions in response to stress
- Utilize FMRI to examine functional activity in regions of the striatum (dorsal versus ventral) and cortex as it relates to stress and emotional regulation in obese individuals with versus without BED

- Investigate individual differences as they relate to neurobiological and clinically relevant measures in BED
- Assess relationships between individual differences (relating to genetics [including genome-wide association studies], environmental exposures [including food availability, poverty, trauma, and other factors], neurocognition [see above], and other factors [for example, transdiagnostic measures not listed above that are linked to the RDoC and PhenX initiatives]) and the development, progression and remission of BED, both with respect to natural history of BED and interventions targeting BED

5-HT—serotonin; BED—binge-eating disorder; DA—dopamine; FMRI—functional magnetic resonance imaging; MRI—magnetic resonance imaging; NE—norepinephrine; PET—positron emission tomography; RDoC—Research Domain Criteria; PhenX: https://www.phenx.org.

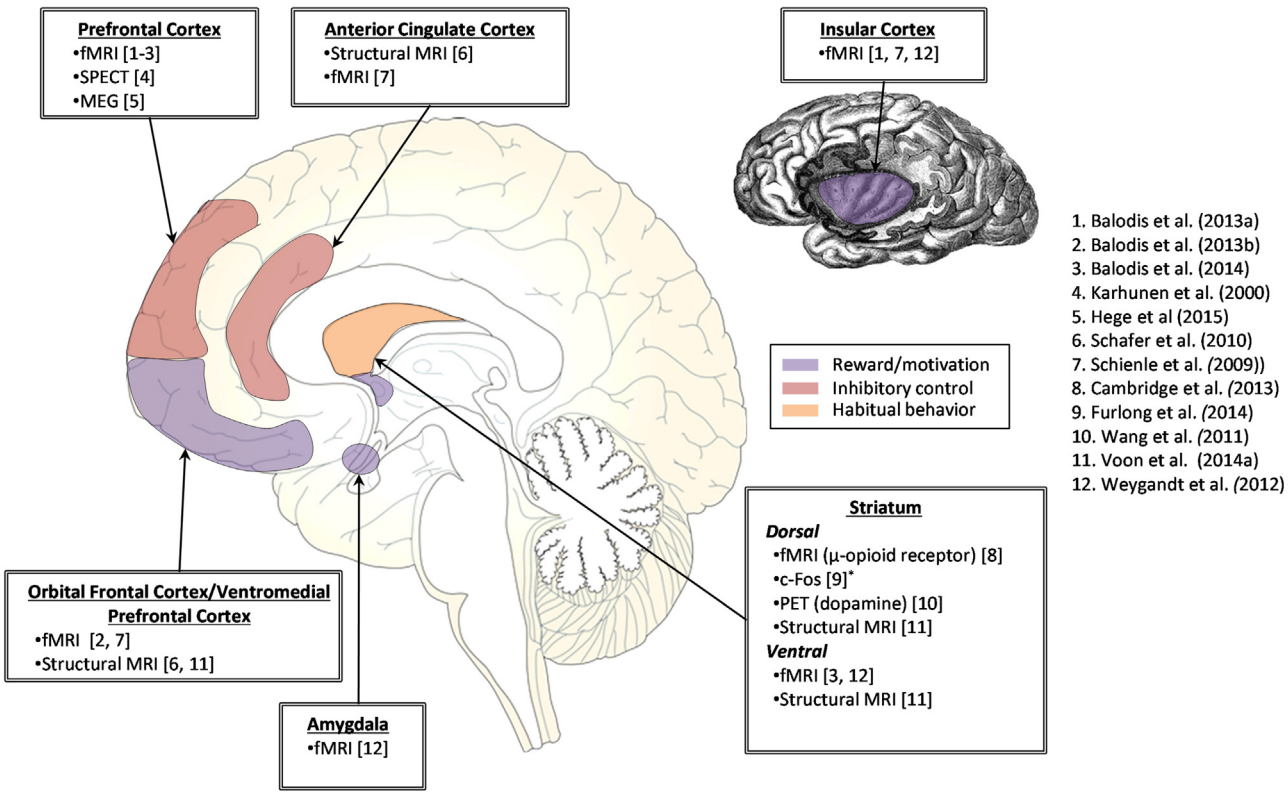

Fig. 2. Schematic representations of brain circuitry implicated in BED and a proposed neurobiological model with respect to reward/motivation, inhibitory control, and habitual behavior.
*Denotes data based on animal studies.

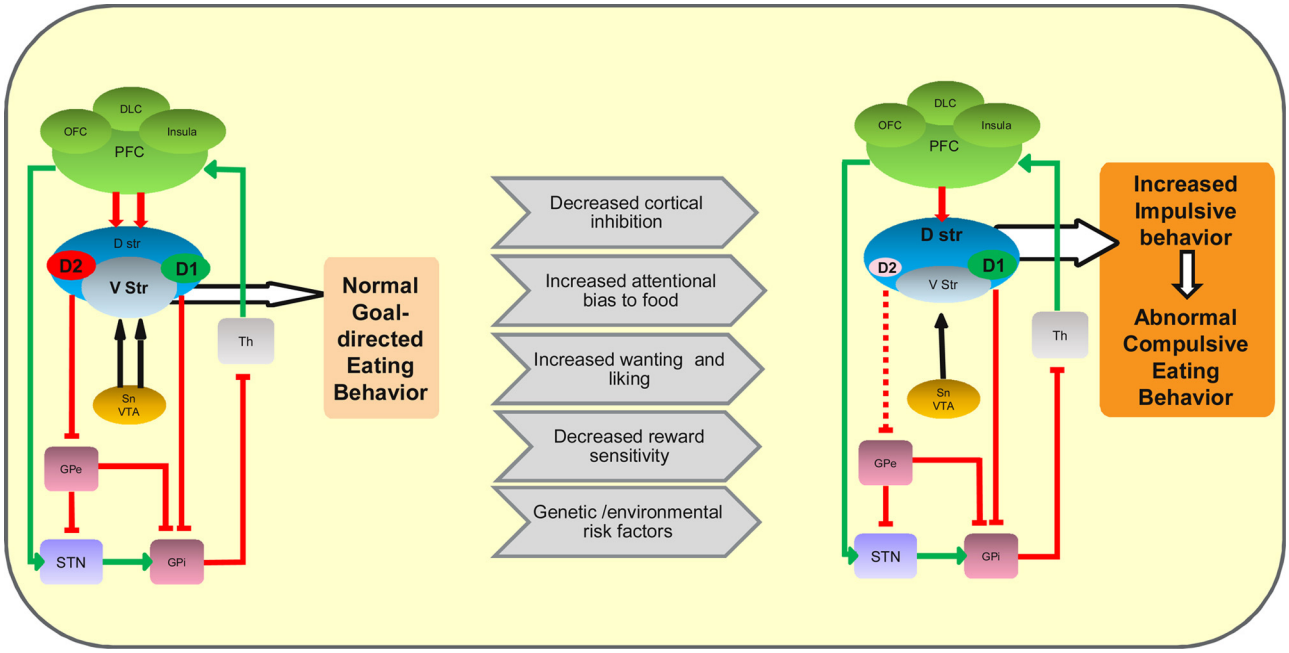

Fig. 3. Cortical/basal-ganglionic/thalamic pathways involved in reward-related feeding behaviors. "Normal" reward-related feeding behavior is shown on the left side of figure. The transition to binge-eating behaviors involves a transition from a ventral-striatal reward-based mode of reward-related food consumption to a dorsal-striatal impulsive/compulsive mode of reward-related food consumption. This adaptive change is proposed to involve decreased cortical inhibition of reward-related food consumption, decreased reward sensitivity related to decreased striatal dopamine release, and an imbalance in the function of the indirect versus direct striatonigral pathways, which is hypothesized to underlie compulsive food intake. The development of decreased striatal dopamine D2-like receptor expression has been associated with hypofunction of the indirect pathway, with relative preservation of the direct pathway function associated with dopamine D1-like receptor signaling leading to binge-type eating behaviors. Red and green lines indicate inhibitory and excitatory pathways, respectively. The red dotted line indicates reduced activity. Black arrows indicate dopamine-containing neurons from the substantia nigra/ventral tegmental midbrain nuclei.
PFC—prefrontal cortex; OFC—orbitofrontal cortex; DLC—dorsolateral cortex; insula—insular cortex; D str—dorsal striatum; V str—ventral striatum; D1—dopamine D1-like receptor; D2—dopamine D2-like receptor; Th—thalamus; Sn VTA—substantia nigra, ventral tegmental area nuclei; GPe—globus pallidus external segment; GPi—globus pallidus internal segment; STN—subthalamic nucleus.

et al., 2001; Pinaquy et al., 2003; Rosenberg et al., 2013; Schulz and Laessle, 2012), neuroimaging studies in individuals with BED have not been conducted that would link altered stress and emotional regulation in individuals with BED to altered brain function. In conclusion, PET studies of cerebral neurotransmission in BED individuals are needed to more clearly delineate the neurochemistry of BED and how pharmacotherapies may interact with these neurobiological systems to reduce the symptoms of BED. Concurrent fMRI may provide insight into how neurochemical function relates to the cognitive processes underlying BED, and the integration of these approaches into clinical trials will help elucidate the mechanisms of action of specific interventions for BED.

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Competing interests

Dr. Kessler holds stock in PharmRx Therapeutics, Inc. and has consulted for Shire and Covectra, Inc. He has received funding from the National Institute of Drug Abuse, and has consulted for the Federal Public Defenders Office in Nashville, Tennessee.

Dr. Hutson is an employee of Shire and holds stock and/or stock options in Shire.

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