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Review

Pathological Overeating: Emerging Evidence for a Compulsivity Construct

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Compulsive eating behavior is a transdiagnostic construct that is characteristic of medical and psychiatric conditions such as forms of obesity and eating disorders. Although feeding research is moving toward a better understanding of the proposed addictive properties of food, the components and the mechanisms contributing to compulsive eating are not yet clearly defined or understood. Current understanding highlights three elements of compulsive behavior as it applies to pathological overeating: (1) habitual overeating; (2) overeating to relieve a negative emotional state; and (3) overeating despite aversive consequences. These elements emerge through mechanisms involving pathological habit formation through an aberrant learning process, the emergence of a negative emotional state, and dysfunctions in behavioral control. Dysfunctions in systems within neurocircuitries that comprise the basal ganglia, the extended amygdala, and the prefrontal cortex result in compulsive eating behaviors. Here, we present evidence to relate compulsive eating behavior and addiction and to characterize their underlying neurobiological mechanisms. A major need to improve understanding of compulsive eating through the integration of complex motivational, emotional, and cognitive constructs is warranted.
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INTRODUCTION

Compulsivity can be defined as repetitive behaviors in the face of adverse consequences, as well as repetitive behaviors that are inappropriate to a particular situation. Individuals suffering from compulsions often recognize that the behaviors are harmful, but they nonetheless feel emotionally compelled to perform them. Compulsivity shares some commonalities with impulsivity in that both constructs involve dysfunction in inhibitory control, likely mediated by frontal cortex projections to subcortical regions, but one defining feature of compulsivity is persistence where compulsivity is clearly repetitive and perseverative (Robbins *et al*, 2012). Compulsivity has historical roots in the symptoms related to obsessive-compulsive disorder, impulse control disorders, and substance use disorders and may involve engagement in compulsive behaviors to prevent or relieve distress, anxiety, or stress (American Psychiatric Association, 2000; Berlin and Hollander, 2014; el-Guebaly *et al*, 2012).

Compulsive behavior is a central feature of the characterization of not only substance use disorders and behavioral addictions, but also of certain eating disorders, namely binge eating disorder (BED), of forms of obesity, as well as of the recently proposed construct of 'food addiction' (American Psychiatric Association, 2013; Davis, 2013; de Zwaan, 2001; Gearhardt *et al*, 2009; Volkow *et al*, 2013). In drug addiction, compulsive behavior manifests as a persistent drive to use drugs and an inability to control use; analogously, food-related pathologies present with an irresistible, uncontrollable urge to overeat despite efforts to control this behavior (Davis and Carter, 2009; Hone-Blanchet and Fecteau, 2014).

Much attention, and some controversy, has been aimed at defining and measuring compulsivity in drug addiction, bringing to light the complexity of the interpretation of compulsivity and its underlying etiology (Belin-Rauscent *et al*, 2015; Everitt, 2014; George *et al*, 2014; Hopf and Lesscher, 2014; Koob, 2013; Piazza and Deroche-Gamonet, 2013; Volkow and Fowler, 2000). However, so far very little work has been done in systematically defining compulsivity in the context of excessive eating behavior, leaving a gap in the current knowledge. The introduction of the Research Domain Criteria (RDoC) framework instituted by the National Institute of Mental Health has encouraged the scientific community to move toward a new way of classifying mental disorders, based on overarching, high-level domains representing validated behavioral functions (The National Institute of Mental Health, 2013). This approach has recently been applied to addiction using a heuristic framework characterizing dynamic domains common to all addictions (Kwako *et al*, 2016); highlighting the

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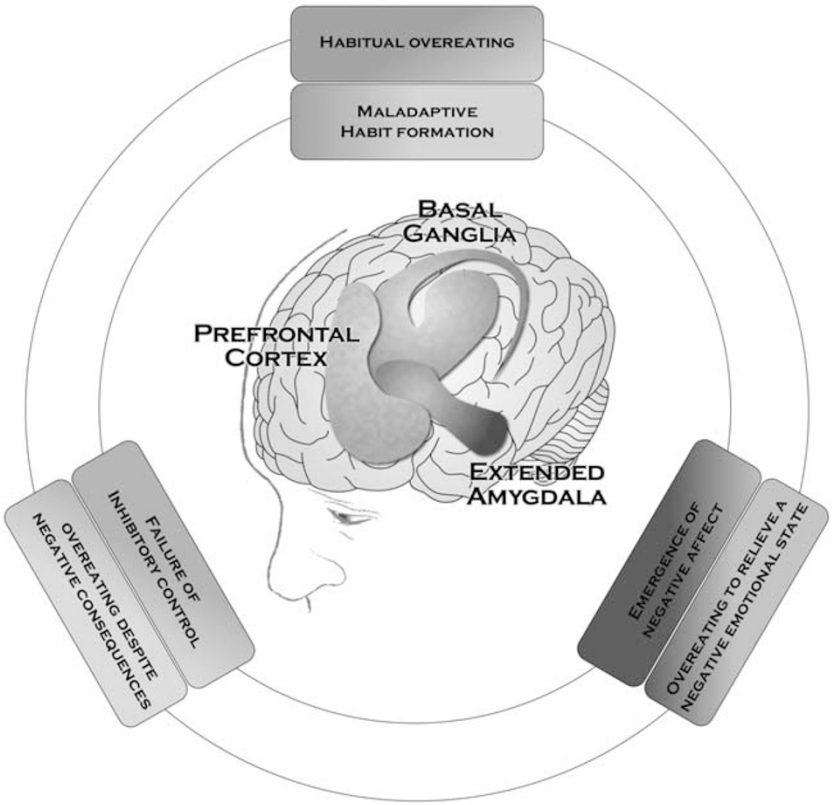

Figure 1 Neurobiology of the elements of compulsive overeating. The key systems that underlie the elements of compulsive eating are: (1) the basal ganglia, (2) the extended amygdala, and (3) the prefrontal cortex. The basal ganglia (shown in blue) consist of multiple subcortical nuclei, such as the nucleus accumbens (NAc), which is involved in the rewarding and reinforcing effects of food, and the dorsal striatum, which is involved in instrumental learning and habitual behavior. The basal ganglia contribute to habitual overeating that can arise from maladaptive habit formation processes. The extended amygdala (shown in red) is a basal forebrain composite structure encompassing the central nucleus of the amygdala (CeA), the bed nucleus of the stria terminalis (BNST), and a transition area in the medial and caudal portions of the NAc. The brain stress systems in the extended amygdala mediate overeating to relieve a negative emotional state that emerges from withdrawal processes. Prefronto-cortical regions (shown in green) include the medial prefrontal (mPFC, comprised of dorsolateral (dlPFC) and ventromedial (vmPFC) regions), anterior cingulate (ACC), and orbitofrontal (OFC) cortices; these areas control cognitive functions such as decision-making and response inhibition through interactions with subcortical structures such as the basal ganglia and the extended amygdala. Dysfunctions in the PFC are hypothesized to underlie overeating despite aversive consequences, reflecting failures in inhibitory control over behavior. Figure modified from Koob GF, Arends MA, Le Moal M. Drugs, Addiction, and the Brain. Academic Press, San Diego, 2014. A full color version of this figure is available at the *Neuropsychopharmacology* journal online.

need for an evaluation of compulsive eating as a potential transdiagnostic construct across feeding-related disorders, as well as its underlying neural circuits.

This review aims to describe the compulsive eating behavior, which appertains to disorders of eating, such as BED, some forms of obesity, and food addiction. In addition, it intends to clarify the most commonly accepted definitions of compulsivity postulated in the context of drug addiction as they apply to compulsive eating behavior. Drug addiction has been characterized as being composed of three stages: binge/intoxication, withdrawal/negative effect, and preoccupation-anticipation; these three stages, which provide a powerful impetus for the compulsive drug-seeking behavior, reflect incentive salience/pathological habits, reward deficits/stress surfeit, and executive function deficits, respectively (Koob and Volkow, 2016). We here claim that these same processes are responsible for the development of compulsive eating behavior of highly palatable food (ie, preferred foods rich in fat and/or sugars). Therefore, by analogy, three elements of compulsive eating behavior can be derived: (1) habitual overeating (Smith and Robbins, 2013; Tomasi and Volkow, 2013); (2) overeating to relieve a negative emotional state (Cottone *et al*, 2009a; Parylak *et al*, 2011); (3) overeating despite aversive consequences (Cottone *et al*, 2012; Johnson and Kenny, 2010; Figure 1). Similarly to what is observed in drug addiction, these elements of compulsive eating behavior are not always differentiable through observation, but can be attributed to distinct, albeit often intersecting, neurobiological mechanisms.

In this review, we will first describe the different disorders of eating characterized by compulsivity, and then define the three elements of compulsive eating. Within each element, we first summarize original and review articles important to the conceptualization of that element of compulsivity in addiction (drugs of abuse as well as food). We then describe studies, first in humans, and then in animals, detailing the behavioral manifestations of that element in feeding- and eating-related disorders. Finally, we discuss the neurobiological substrates hypothesized to underlie these processes in feeding-related disorders in humans and animals. The overall goal of this review is to systematically breakdown the proposed elements of

Table 1 Diagnostic Criteria for Disorders Associated with Compulsive Overeating

Disorder	Diagnostic criteria	Reference
Obesity	BMI ⩾ 30 (BMI = body weight (kg)/height (m^2))	(WHO, 2000)
Binge eating disorder	1. Marked distress regarding binge eating is present 2. Recurrent episodes of binge eating characterized by (1) eating within a 2-h period of time an amount of food larger than what most people would eat in a similar period of time under similar circumstances and (2) a sense of lack of control overeating during the episode 3. Binge eating episodes are associated with three (or more) of the following cognitive symptoms i. Eating much more rapidly than normal ii. Eating until feeling uncomfortably full iii. Eating large amounts of food when not feeling physically hungry iv. Eating alone because of feeling embarrassed about how much one is eating v. Feeling disgusted with oneself, depressed, or very guilty afterward 4. Binge eating occurs, on average, at least once a week for 3 months 5. Binge eating is not associated with the recurrent use of inappropriate compensatory behaviors (eg, purging) and does not occur exclusively during the course of bulimia nervosa or anorexia nervosa.	A diagnosis of BED is given when these five criteria are met (American Psychiatric Association, 2013).
Food addiction[a]	Clinically significant impairment or distress AND (2 or more of the following criteria) 1. Consumed more (larger amount and for a longer period) than planned 2. Unable to cut down or stop 3. Great deal of time spent 4. Important activities given up or reduced 5. Use despite knowledge of physical/emotional consequences 6. Tolerance (increase in amount, decrease in effect) 7. Withdrawal (symptoms, substance taken to relieve withdrawal) 8. Craving or strong desire 9. Failure in role obligation 10. Use despite interpersonal/social consequences 11. Use in physically hazardous situations	A diagnosis is given when impairment or distress is met as well as 2+ other symptoms. A severity classification is given based on the number of criteria. (2–3 = mild, 4–5 = moderate, and 6+ = severe; Gearhardt *et al*, 2016).

[a]Food addiction is not yet accepted as a DSM-V disorder; these criteria were adapted by Gearhardt *et al* (2016) from the Substance-related and addictive disorders criteria within the DSM-V (APA, 2013).

compulsive eating within the heterogeneous disorders of feeding behavior.

COMPULSIVE EATING IN FORMS OF OBESITY AND EATING DISORDERS: PREVALENCE AND SIGNIFICANCE

Compulsive eating behavior is characteristic of multiple disorders of eating, including BED, certain forms of obesity, and the newly proposed construct of 'food addiction' (diagnostic criteria for these disorders can be found in Table 1; APA, 2013; Gearhardt *et al*, 2016; Volkow *et al*, 2008a). Although diagnoses for BED and food addiction necessitate compulsive eating behaviors, this is not a diagnostic criterion for obesity, and overweight/obesity is neither necessary nor sufficient to characterize compulsive eating (Davis, 2013).

Obesity is becoming increasingly prevalent: with more than one-third (35%) of the US population being obese, resulting in an estimated $147 billion cost per year (Finkelstein *et al*, 2009; Ogden *et al*, 2014). Although in the general population the prevalence of BED and food addiction are much lower (an estimated 2–5% and 5–15% for BED and food addiction, respectively; Davis *et al*, 2011; de Zwaan, 2001; Gearhardt *et al*, 2009; Kessler *et al*, 2013), these numbers increase 2–3 fold in obesity treatment-seeking populations (ie, Weight Watchers, low-energy diet, and bariatric surgery; de Zwaan, 2001; Pursey *et al*, 2014).

Individuals with BED and food addiction are much more likely to be overweight/obese (an estimated 40–70%, respectively; Dingemans and van Furth, 2012; Kessler *et al*, 2013; Pursey *et al*, 2014). Obesity and BED are associated with significant impairments in health-related quality of life, increased direct health-care costs, and higher prevalence of comorbid psychiatric conditions (Agh *et al*, 2016; Dickerson *et al*, 2011; Fontaine and Barofsky, 2001; Halfon *et al*, 2013; Kessler *et al*, 2013; Wolf and Colditz, 1998). Individuals with food addiction have self-reported impairment and distress due to symptoms, and in adults with obesity and/or BED, an additional diagnosis of food addiction is associated with

greater pathology and comorbid psychiatric disorders (Davis *et al*, 2011; Gearhardt *et al*, 2012). The high degree of comorbidity among these feeding and eating disorders may reflect shared etiologies and/or underlying mechanisms, manifesting in some cases through compulsive eating behaviors.

ELEMENTS OF COMPULSIVE EATING BEHAVIOR

Compulsive eating behavior is posited to be a combination of one or more of the following elements: (1) habitual overeating, (2) overeating to relieve a negative emotional state, and (3) overeating despite aversive consequences. We propose that these elements emerge from dysfunctions of brain areas involved in reward learning, emotional processing, and inhibitory control. Although each of these processes involves multiple regions within interconnected circuits, for the purpose of this review, we will focus on three specific key areas implicated in the above discussed elements: the basal ganglia, the extended amygdala, and the prefrontal cortex (PFC; see Table 2 for a summary of features). Importantly, we acknowledge that these elements, although part of a unifying construct, are not mutually exclusive, nor would they all be necessary for the designation of a behavior as compulsive.

HABITUAL OVEREATING

Psychobehavioral Feature: Maladaptive Habit Formation

Maladaptive habit responding is hypothesized to begin with Pavlovian conditioning mechanisms (Belin and Everitt, 2008). Environmental food-associated stimuli, known as conditioned reinforcers, can robustly enhance the desire to eat even in absence of food *per se* or in absence of physiological needs (Everitt and Robbins, 2005; Robinson *et al*, 2015). With repeated pairings of a cue (conditioned stimulus) with food (unconditioned stimulus), the learned cue itself becomes salient (termed incentive salience), therefore triggering intense urges to obtain the associated reward, and also acts as a conditioned reinforcer able to maintain food seeking in the absence of food presentation (Giuliano *et al*, 2012; Velazquez-Sanchez *et al*, 2015; Giuliano and Cottone, 2015).

Habit formation is the end result of an adaptive learning process where voluntary actions become habitual through the reinforcement of these behaviors. It is hypothesized that compulsive behavior may reflect a maladaptive stimulus–response habit that was once a flexible and voluntary goal-directed behavior (Everitt and Robbins, 2005; Halbout *et al*, 2016; Lucantonio *et al*, 2014; Ostlund and Balleine, 2008). Habits are formed through repeated reinforced action until the stimulus–response association lapses the goal of the behavior (eg, the palatable food or drug) as the motivation to perform the action (Everitt and Robbins, 2013). Outcome devaluation procedures are often used to assess whether a response has become habitual, through the measurement of perseverative responding after the value of the outcome (ie, drug/food reward) has been reduced. Habits can be considered compulsive when they persist despite devaluation, or a reduction in reinforcer efficacy (Everitt and Robbins, 2005). Analogously to what is observed in drug addiction, in compulsive eating disorders, the inability to adapt eating behavior based on the motivational value of the outcome may reflect a compulsive habit (Corbit, 2016; Everitt and Robbins, 2005; Voon *et al*, 2015).

Some evidence suggests that obese individuals are less sensitive to devaluation, indicative of increased habitual control over food intake. Specifically, a study found that higher BMI was inversely related to sensitivity of a food-seeking response to earlier consumption of that reward (Horstmann *et al*, 2015). This may suggest difficulty in adapting behavior subsequently contributing to food seeking or overconsumption; however, differences in respect to habituation to food may confound assessments using specific satiety as a measure of devaluation in obese participants (Epstein *et al*, 2009). Another study indicated a bias for individuals with BED to engage in habit learning devices compared with other types of learning, also seen in individuals with methamphetamine addiction and obsessive-compulsive disorder (Voon *et al*, 2015). This favoring of habit learning may underlie the compulsive habit responding that is characteristic of these disorders and represent a dysfunction in a neurocomputational mechanism of learning. In addition, individuals with BED, food addiction, and obesity all show heightened sensitivity and attentional biases to food cues at a behavioral level (Meule *et al*, 2012; Schmitz *et al*, 2014; Shank *et al*, 2015; for review see Garcia-Garcia *et al*, 2013; Hendrikse *et al*, 2015). These measures of increased sensitivity are related to food seeking, eating

Table 2 A Summary of the Features of Each Element of Compulsive Eating Behavior

Elements of compulsive eating behavior	Neuropsychobiological mechanisms	Characteristic behavior	Most implicated brain area	Selected references
Habitual overeating	Aberrant reward learning	Inability to reduce eating or seeking behavior following a decrease in food value or contingency	Basal ganglia	Horstmann *et al*, 2015; Furlong *et al*, 2014; Corbit, 2016
Overeating to relieve a negative emotional state	Affective habituation	Eating to cope with decreased sensitivity to reward	Basal ganglia	Johnson and Kenny, 2010
	Affective withdrawal	Eating to cope with negative affect (eg, anxiety and stress)	Extended amygdala	Cottone *et al*, 2009a; Parylak *et al*, 2011
Overeating despite negative consequences	Decreased inhibitory control	Eating persists in conditions where it would normally be suppressed	Prefrontal cortices	Heyne *et al*, 2009; Balodis *et al*, 2013b; Cottone *et al*, 2012

(Lawrence *et al*, 2012), BMI (Shank *et al*, 2015), and severity of self-reported symptoms (Schmitz *et al*, 2014).

In animal models of addiction, habitual responding is measured through the persistence of responding following a devaluation of the reward outcome, such as the addition of bitter-tasting quinine, lithium–chloride-induced post-ingestive malaise, or specific satiety, where free access to the reward is given prior to the test. Similar to extended drug self-administration, prolonged intermittent access to palatable food was shown to accelerate the shift from voluntary to habitual food seeking (Furlong *et al*, 2014). Analogous to drugs of abuse, highly palatable food consumption can influence habitual responding, cognitive control, and learning to a greater degree than food with lower palatability (Smith *et al*, 2015; Velazquez-Sanchez *et al*, 2015).

Drug- and food-associated stimuli are able to elicit and maintain compulsive seeking behavior associated with drug or food craving (Everitt and Robbins, 2016). A classical experimental procedure used to discern seeking behavior from intake, is using a second-order schedule of reinforcement, where responding on a seeking lever is maintained not only by the self-administered drug/food, but also by contingent presentation of reinforcer-paired stimuli that serve as conditioned reinforcers of instrumental behavior (Everitt and Robbins, 2000; Velazquez-Sanchez *et al*, 2015). In this procedure, the first interval acquires particular relevance, as it is not influenced by the presence of the reinforcer (Everitt and Robbins, 2000). In drug addiction, seeking responses become resistant to devaluation through extinction or through the introduction of unpredictable shock over time in compulsive-like animals (Belin *et al*, 2008; Zapata *et al*, 2010). However, studies have not yet shown resistance to devaluation on food-seeking behavior under this schedule. In addition, related compulsive-like food-seeking behaviors seen in animals include continued responding on a food-paired lever during a period of signaled nonavailability (Mancino *et al*, 2015), and cue-induced reinstatement of responding following extinction (Nair *et al*, 2009).

Neurobiological Substrate: The Basal Ganglia

Structures of the basal ganglia, including the nucleus accumbens (NAc) and the dorsal striatum, are highly involved in the rewarding/reinforcing effects of food/drugs and in instrumental/habitual learning, respectively (Everitt and Robbins, 2005). One of the neurochemical similarities of food and drugs of abuse is the increase in extracellular dopamine in the NAc following exposure to associated cues (Day *et al*, 2007; Stuber *et al*, 2008). This potentiated dopaminergic neurotransmission to cues is hypothesized to result in increased incentive salience, and may similarly enhance habit learning (Everitt and Robbins, 2016), contributing to the emergence of compulsive-like behavior (dopamine system further discussed in the 'overeating to relieve a negative emotional state,' below; Peciña and Berridge, 2005; Robinson *et al*, 2015). In a study that used functional magnetic resonance imaging (fMRI), researchers found decreased activation in the caudate nucleus of the striatum (involved in goal-directed actions) and increased activity of the putamen (involved in habit responding) to palatable food taste in obese subjects as compared with healthy weight controls (Babbs *et al*, 2013). Thus, certain functional differences may exist in response to palatable food in habit-driven regions of the brain in obese individuals. There is also some evidence for associated structural differences in these habit learning systems. A study by Voon *et al* (2015) found obese subjects with BED displayed an increased tendency to engage in habit-based responding, associated decreases in ventral and dorsal striatal gray matter volume, and corresponding prefrontal projection areas compared with those without BED. This study suggests that impaired goal-directed learning in individuals with BED may be reflected in accelerated habit formation and structural abnormalities in areas responsible for action–outcome associations.

The habit learning processes implicated in the shift to addiction are accompanied by a ventral to dorsal striatal shift in the basal ganglia in control over behavior. Although the NAc is critical for the acquisition of drug or food self-administration (goal-directed responding), the dorsal striatum is necessary for habitual behavior (Belin and Everitt, 2008; Corbit *et al*, 2012). Rats exposed to intermittent access to palatable food display a loss of goal-directed actions for food reward coupled with greater activation of the dorsolateral striatum (Furlong *et al*, 2014). Habitual behaviors are also influenced by indirect amygdalar projections to the dorsolateral striatum (Lingawi and Balleine, 2012) and prefronto-cortical control of flexible, goal-directed actions per its executive-inhibitory control functions. Thus pre-existing vulnerabilities and/or modulation of frontal areas by palatable food are hypothesized to contribute to or exacerbate predominance of the shift to dorsal striatal control over habitual behavior (Everitt and Robbins, 2016). Therefore, both the amygdaloid anti-reward system and the prefronto-cortical system influence the dorsal striatal-mediated facilitation of habit formation. This evidence is one demonstration that the different elements of compulsivity are not mutually exclusive and are based on overlapping neurobiological substrates.

OVEREATING TO RELIEVE A NEGATIVE EMOTIONAL STATE

Psychobehavioral Feature: Emergence of a Negative Affect

Performing a behavior such as taking a drug or ingesting palatable food for the purpose of alleviating a negative emotional state is another important element that defines compulsive behavior (Koob, 2009; Koob and Volkow, 2010; Parylak *et al*, 2011). This element of compulsivity is rooted in the conceptual framework underlying obsessive-compulsive disorder, which is characterized by anxiety and stress before committing a compulsive behavior, and relief from that stress by performing the behavior (Koob and Le Moal, 2008). Two distinct, but overlapping, processes are hypothesized to underlie this withdrawal-induced negative affect: decreased reward and increased stress. Decreased reward function is characterized by affective habituation and loss of motivation for ordinary rewards (Koob, 1996; Parylak *et al*, 2011). Negative affect also derives from recruitment of the brain stress systems, which are hypothesized to be repeatedly engaged during drug or palatable food withdrawal (Cottone

et al, 2009a; Koob, 1999), leading to irritability and anxiety. Thus, as drug taking/eating becomes compulsive, the factors motivating behavior are hypothesized to shift: although at first the behavior is positively reinforced, later compulsivity would arise from negatively reinforcing mechanisms such as the relief of the negative emotional symptoms of withdrawal (Cottone *et al*, 2009a; Iemolo *et al*, 2012; Koob and Le Moal, 2001; Parylak *et al*, 2011; Teegarden and Bale, 2007). It should be noted that withdrawal in this context is separate from classically defined, purely 'physical' symptoms that occur upon removal of the substance (O'Brien, 2011). Instead, a motivational withdrawal syndrome, characterized by dysphoria, anxiety, and irritability when the reward sought is not available (Koob *et al*, 1997), is present in disorders of feeding and can drive compulsive eating behavior (Tao *et al*, 2010; Wray and Dickerson, 1981).

The concept of 'withdrawal' is very different in compulsive eating compared with drug addiction. Indeed, although drug users may quit drugs, abstinence from certain foods is achieved by dieting, reflected by a reduction in calories ingested and/or a shift from energy-dense, highly palatable 'forbidden' foods to energy-diffuse, less palatable 'safe' foods (Gonzalez and Vitousek, 2004; Stirling and Yeomans, 2004). In support of this, many reports have shown that obese people who started a dieting regimen report not only irritability and nervousness, but also intense anxiety (Keys *et al*, 1950; Silverstone and Lascelles, 1966; Stunkard, 1957). Furthermore, there is evidence that switching from a high-to low-fat diet can have adverse effects on mood (Wells *et al*, 1998). Indeed, dietary restraint is known to correlate with stress and depressive symptoms (Eldredge *et al*, 1990; Kagan and Squires, 1983; Rosen *et al*, 1990; Rosen *et al*, 1987), and these correlate with overeating in response to stress (Greeno and Wing, 1994; Heatherton *et al*, 1991), perhaps reflecting an attempt to self-soothe or self-medicate with 'comfort' foods (Macht, 2008; Tomiyama *et al*, 2011) as this eating can effectively dampen down the body's stress response (Pecoraro *et al*, 2004). Furthermore, the Kaplan and Kaplan theory proposes that obese people overeat when anxious and that eating reduces this anxiety (Kaplan and Kaplan, 1957). Similarly, Bruch's theory proposes that overeating occurs in response to 'emotional tension' and 'uncomfortable sensations and feelings' (Bruch, 1973). Taken together, these studies support the hypothesis that dieting may precipitate a negative emotional state, or an 'affective withdrawal,' and that compulsive eating may be maintained through a negatively reinforced mechanism (for further review, see Parylak *et al*, 2011).

Although withdrawal from palatable food is responsible for the emergence of negative affect and, in turn, hypothesized to drive compulsive eating through a negative reinforcement mechanism, abstaining from calorie-dense food also often implicates caloric restriction, which has well-known effects on rebound binge eating and weight gain (Stice *et al*, 2008; Mann *et al*, 2007). A potential mechanism for this phenomenon is that food restriction itself causes neuroadaptations that promote certain compulsive behaviors, which includes compulsive-like eating as well as increased drug seeking in animals (Carr, 2016; Sedki *et al*, 2015; Shalev, 2012). However, it is important to distinguish that although food restriction and exposure to highly palatable food may produce similar behavioral outcomes, differential neuropsychopharmacological mechanisms likely mediate their effect (Cottone *et al*, 2009b; Cottone *et al*, 2012; Smith *et al*, 2015).

Notably, in addition to a perpetuation of compulsive eating, negative affective states that include symptoms associated with depression and anxiety may also confer vulnerability to (ie, predate) eating disorders and some forms of obesity, just as in addiction to drugs (Dallman *et al*, 2003; Rosenbaum and White, 2015). For example, individuals with BED have greater rates of psychiatric comorbidities involving negative emotional states compared with the general population and to weight matched controls (Galanti *et al*, 2007; Peterson *et al*, 2005). These negative emotional states are associated with greater binge eating behavior (Wilfley *et al*, 2000) and predict poorer treatment outcomes (Clark *et al*, 1996; Linde *et al*, 2004; McGuire *et al*, 1999). In drug addiction, it has been hypothesized that this vulnerability may reflect some degree of an already constituted state of allostasis; or a deviation from a 'normal' range of reward function (Koob and Le Moal, 2001).

In animal models, repeated, intermittent access to palatable food leads to spontaneous (Cottone *et al*, 2008, 2009b; Iemolo *et al*, 2012; Sharma *et al*, 2013) or pharmacologically precipitated (Avena *et al*, 2008a; Blasio *et al*, 2013; Colantuoni *et al*, 2002) emotional signs of withdrawal, such as anxiety- and depressive-like behavior, and enhanced stress-responsiveness. Following exposure to a high-fat diet, rats show elevated brain stimulation reward thresholds (decreased reward; Johnson and Kenny, 2010). A similar decreased reward system functioning is also observed in obesity-prone rats, prior to the development of obesity (Valenza *et al*, 2015), indicating that the decreased reward system functioning is both a vulnerability factor (Valenza *et al*, 2015) as well as a consequence of the overconsumption of palatable food (Johnson and Kenny, 2010). Renewing access to palatable food following abstinence induces overconsumption of palatable food (Avena *et al*, 2008a; Colantuoni *et al*, 2002; Cottone *et al*, 2009b; Rossetti *et al*, 2014), and this renewed access is able to relieve withdrawal-induced depressive and anxiety-like behaviors (Iemolo *et al*, 2012). Thus, evidence from animal models strongly suggests that pathological eating can contribute to the emergence of a negative emotional state, and that relief of anxiety or stress can drive compulsive eating behavior.

Neurobiological Substrates: The Basal Ganglia and Extended Amygdala

The neurobiological substrates that underlie this element of compulsivity are dual: within-system neuroadaptations, which refer to the downregulation of reward neurotransmission (Koob and Bloom, 1988), and between-system neuroadaptations, which refer to the recruitment of the brain 'antireward' stress systems during food withdrawal (Parylak *et al*, 2011).

Consumption of palatable food is hypothesized to result in within-system neuroadaptations through repeated stimulation, during which a form of sensitization of incentive salience initially occurs (Robinson and Berridge, 1993), and eventually desensitization of the mesolimbic dopamine system, therefore creating deficiencies in reward signaling. In populations with BED and obesity, there is evidence to

support a hypofunctioning of the midbrain dopamine system (described below); however, no research has focused on directly linking this phenomenon to compulsive eating as opposed to bingeing. Balodis *et al* (2013a) found that binge eating individuals had lower striatal and prefrontal activation to anticipation of a monetary reward, and this decrease was associated with increased incidence of binge eating (Balodis *et al*, 2014). In animal models, high-fat and high-sugar diets induce alterations in dopaminergic system, such as down-regulated dopamine 2 receptors (D2DRs) in the striatum (Colantuoni *et al*, 2001; Johnson and Kenny, 2010), reduced basal levels of dopamine in the NAc (Rada *et al*, 2010), and alterations in dopamine transport and turnover (Bello *et al*, 2003; Hajnal and Norgren, 2002). Over time, the once rewarding properties of the palatable food are diminished, reflecting a decrease in dopaminergic transmission in the ventral striatum (Bello *et al*, 2002; Bello *et al*, 2003; Hajnal and Norgren, 2002). Overeating may, therefore, reflect the need to reactivate a hypofunctional reward circuit (Geiger *et al*, 2009; Wang *et al*, 2001). However, it is important to note that dopaminergic signaling within striatal areas may be dynamic, where under certain experimental conditions, dopamine signaling in response to food bingeing-related cues remains high (Avena *et al*, 2008b; Corwin *et al*, 2011; Rada *et al*, 2005), resulting in a persistence of sensitization of incentive salience (Robinson and Berridge, 1993), despite a compromised reward system.

A key between-system neuroadaptation implicated in the emergence of a negative emotional withdrawal state is the recruitment of the stress systems in the extended amygdala. Although neuroimaging studies in humans have demonstrated increased amygdalar activation in response to high-calorie food-cues compared with low-calorie food cues (measured using fMRI; Stoeckel *et al*, 2008) and altered resting functional connectivity with cortical areas (Lips *et al*, 2014) in obese compared with lean subjects, much of what is known in its role in compulsive eating is from preclinical research. Specifically, animal studies have demonstrated neuroplasticity in these circuits including the recruitment of corticotropin-releasing factor (CRF) and its type-1 receptor (CRFR1) in the extended amygdala. The CRF–CRFR1 system is a key player in mediating responses to stressors and it contributes to the maintenance and resumption of addictive behaviors (Koob *et al*, 2014; Koob and Zorrilla, 2010; Shalev *et al*, 2010). Extended access to drugs and palatable food engages the CRF–CRFR1 system (Cottone *et al*, 2009a; Iemolo *et al*, 2013; Koob and Zorrilla, 2010). During palatable food withdrawal, CRF expression and CRFR1 electrophysiological responsiveness is increased in the central amygdala (CeA), which are accompanied by withdrawal-dependent arousal and anxiety-like behavior. (Cottone *et al*, 2009a; Iemolo *et al*, 2013; Teegarden and Bale, 2007, 2008). Furthermore, selective CRFR1 antagonists block anxiety-like behavior seen during withdrawal from palatable food when directly administered into the CeA (Cottone *et al*, 2009a; Iemolo *et al*, 2013), and block stress-induced binge-like eating when administered into the bed nucleus of the stria terminalis (BNST; Micioni Di Bonaventura *et al*, 2014).

The recruitment of the brain stress systems in the extended amygdala is also accompanied by compensatory mechanisms to oppose these effects. The endocannabinoid system is considered one of several 'buffer systems', which acts to restore homeostasis to amygdalar circuits (Hillard *et al*, 2012; Koob, 2015; Sidhpura and Parsons, 2011). Withdrawal from palatable food increases the endocannabinoid 2-arachidonoylglycerol and cannabinoid receptor 1 (CB1R) levels in the CeA (Blasio *et al*, 2013). Infusion of the CB1R inverse agonist rimonabant into the CeA precipitates anxiety-like behavior and anorexia during palatable food withdrawal (Blasio *et al*, 2013; Blasio *et al*, 2014a). We therefore hypothesize that the endocannabinoid system of the amygdala is recruited during withdrawal from palatable food as a compensatory mechanism to dampen anxiety. Thus, compelling evidence exists to argue that plasticity in the brain stress systems, a heretofore largely neglected component of addiction, is triggered by acute excessive drug/palatable food intake, is sensitized during repeated withdrawal, persists into protracted abstinence, and contributes to the development and persistence of addiction (Koob, 2013).

OVEREATING DESPITE AVERSIVE CONSEQUENCES

Psychobehavioral Feature: Failure of Inhibitory Control

Loss of control over food and drug seeking and taking behavior is considered an intractable aspect of addiction, resulting in continued use despite many incurring negative consequences under which behaviors would typically be suppressed (Deroche-Gamonet *et al*, 2004; Hopf and Lesscher, 2014; Rossetti *et al*, 2014; Vanderschuren and Everitt, 2004; Velazquez-Sanchez *et al*, 2014). Maladaptive eating behavior can result in medical conditions associated with weight gain as well as social impairment, emotional problems, and psychiatric disorders (Klatzkin *et al*, 2015; WHO, 2000; Warschburger, 2005). However, despite the many resulting negative consequences of the behavior, the individual finds it very difficult to stop. 'Loss of control' is thought to result from deficits in inhibitory control mechanisms responsible for the suppression of inappropriate actions. These deficits likely confer vulnerability to addictive behavior and/or emerge from persistent and prolonged drug use or palatable food overconsumption (Chen *et al*, 2013; Lubman *et al*, 2004; Volkow *et al*, 2013).

Individuals with disorders of compulsive eating behavior show poor performance on tasks of executive function and inhibitory control related to food, such as limiting responses, inhibiting cravings, or delay discounting (Batterink *et al*, 2010; Hege *et al*, 2015; Svaldi *et al*, 2014; Wu *et al*, 2013). These deficits are associated with further weight gain (Pauli-Pott *et al*, 2010; Seeyave *et al*, 2009) and poorer response to weight loss treatment (Murdaugh *et al*, 2012). This loss of control overeating often persists despite the multitude of adverse events encompassing physical, psychological, and social problems that arise or are exacerbated by overeating. Individuals who compulsively overeat are, indeed, often plagued with distress following overeating, citing reactions of shame, denial, rationalization, and blaming, as well as feelings of a loss of control (Lyons, 1998). When these negative emotional and physical consequences outweigh the desirable effects of palatable food, people often attempt to diet and to avoid triggering foods (Curtis and Davis, 2014), even though most relapse into unhealthy eating habits (Halmi, 2013).

Under this theoretical framework, compulsive-like behavior is operationalized in preclinical research as the obtainment of the search for a reward in spite of adverse conditions or consequences (Barnea-Ygael *et al*, 2012; Belin *et al*, 2008; Cottone *et al*, 2012; Smith *et al*, 2015; Vanderschuren and Everitt, 2004). Multiple paradigms have suggested that compulsive-like eating behavior can become evident following a history of palatable food consumption (ie, high in fat and/or sugar; Di Segni *et al*, 2014). For instance, animals display compulsive-like behavior such as continuing to consume palatable food even in the presence of mild electric shock (Rossetti *et al*, 2014) or a conditioned stimulus that signals an electric shock (Latagliata *et al*, 2010; Nieh *et al*, 2015; Velazquez-Sanchez *et al*, 2015). Animals will also continue to eat palatable food even when they must endure an aversive condition (ie, crossing a novel, bright, and potentially dangerous environment to obtain it; Calvez and Timofeeva, 2016; Cottone *et al*, 2012; Dore *et al*, 2014; Oswald *et al*, 2011) or working through a progressive ratio procedure where the cost of responding increases with each reward (Velazquez-Sanchez *et al*, 2014).

Neurobiological Substrates: The Prefrontal Cortex

Dysfunctions in multiple prefronto-striatal circuitries are hypothesized to underlie compulsive behaviors, and specifically loss of control. Within the PFC, two opposing systems are postulated: one which drives craving and re-engages habits (a 'GO' system; dorsolateral PFC (dlPFC), anterior cingulate, and orbitofrontal cortex), and one which instead inhibits this drive through the assessment of the incentive value of choices and suppression of emotional responses to stimuli (a 'STOP' system; ventromedial PFC (vmPFC); Koob and Volkow, 2016). In addictive disorders, these systems become unbalanced such that on one side PFC areas are hyperresponsive to food cues, whereas on the other side a general hypoactivation of prefrontal circuits involved in inhibitory control results in the disinhibition of the basal ganglia and stress systems of the amygdala (Koob and Volkow, 2016).

Cue-induced activation of PFC regions drives craving through functional connections with the striatum (Tomasi and Volkow, 2013). Both drug addicted and obese individuals show abnormal activation of PFC regions following cue-exposure, and this activation correlates with levels of elicited craving for drugs or food (Tomasi and Volkow, 2013; Volkow and Fowler, 2000; Volkow *et al*, 1993; Volkow *et al*, 2008b). In compulsive eating, this increased activation is thought to re-engage the basal ganglia circuitry involved in habitual overeating. Consistent with the above, a treatment approach directly targeting the dlPFC with transcranial direct current stimulation (tDCS) was shown to be effective in reducing craving for palatable food in binge eating women (anode right/cathode left, excitatory and inhibitory, respectively; Kekic *et al*, 2014). This effect of tDCS may be effectively attenuating the 'cue-induced craving' circuit modulated by the dorsolateral PFC, or alternatively, through boosting inhibitory control systems by its connectivity to the vmPFC (Hare *et al*, 2014).

In BED, PFC dysregulation is associated with deficits in inhibitory control (Balodis *et al*, 2013b; Boeka and Lokken, 2011; Hege *et al*, 2015). In addition, diminished activation of vmPFC during an inhibitory control task was associated with impaired dietary restraint in obese individuals with BED, but not in obese controls (Balodis *et al*, 2013b). A study using positron emission topography observed decreased glucose metabolism in prefrontal areas of obese populations, which correlated with lower D2DR striatal levels (Volkow *et al*, 2008b). As lower amounts of D2DRs in the striatum are associated with lower inhibitory control (ie, higher impulsivity; Klein *et al*, 2007), it is hypothesized that these deficits in PFC activity may cause disinhibition of impulsivity circuits in the ventral striatum (Volkow *et al*, 2008b; for further review see (Kessler *et al*, 2016).

Modulation of the mPFC glutamatergic projections (both the 'GO' and 'STOP' systems) is a promising therapeutic target for compulsive eating. For example, μ-opioid antagonists have been shown to reduce attentional biases for food cues (Chamberlain *et al*, 2012). Memantine (an N-methyl-D-aspartate glutamate receptor (NMDAR) uncompetitive antagonist) was found to reduce binge eating as well as 'disinhibition' of eating behaviors (Brennan *et al*, 2008). Memantine has also been shown to reduce impulsivity and enhance cognitive control in compulsive shoppers (Grant *et al*, 2012), a proposed behavioral addiction. Furthermore, Sigma 1-receptors, though not yet tested in humans, are regarded as a promising target for addiction, among other psychiatric disorders, and are known to modulate the PFC glutamatergic system (Alonso *et al*, 2000; Dong *et al*, 2007; Hayashi *et al*, 2011).

Animal models have demonstrated the involvement of prefrontal μ-opioid receptors, Sig1Rs, NMDARs, and recently the trace amine-associated receptor-1 (TAAR1) in compulsive-like eating behavior (Blasio *et al*, 2014b; Ferragud *et al*, 2016; Selleck *et al*, 2015; Smith *et al*, 2015; Velazquez-Sanchez *et al*, 2014). Specifically, using a model of compulsive-like eating (Cottone *et al*, 2012), limited access to a highly palatable diet increased levels of the gene coding for the opioid peptide pro-opiomelanocortin and suppressed the expression of the pro-dynorphin gene in the mPFC; and administration of the opioid antagonist naltrexone directly into the mPFC-reduced binge-like eating (Blasio *et al*, 2014b). These effects are thought to be driven by modulation of inhibitory control, likely through effects of PFC opioids on glutamatergic signaling to NAc targets (Mena *et al*, 2011; Mena *et al*, 2013; Selleck *et al*, 2015).

Sig1Rs, known to modulate alcohol and drug reinforcement (Blasio *et al*, 2015; Robson *et al*, 2012; Sabino *et al*, 2011; Sabino *et al*, 2009a; Sabino *et al*, 2009b), also appear to mediate compulsive-like eating in animal models. Limited access to palatable food increases Sig1R expression levels in prefronto-cortical regions of the brain, and systemic administration of BD-1063, a Sig1R antagonist, decreased compulsive-like eating (Cottone *et al*, 2012). Similarly, TAAR1 receptors, a system associated with inhibitory control and cognitive functioning (Espinoza *et al*, 2015a), were downregulated in the mPFC following binge-like eating, and TAAR1 agonist infusion into the infralimbic cortex blocked compulsive-like, binge eating (Ferragud *et al*, 2016). Both the Sig1R and TAAR1 systems in the mPFC may, therefore, influence glutamatergic signaling in cortico-striatal pathways, each contributing to compulsive-like behavior (Cottone *et al*, 2012; Dong *et al*, 2007; Espinoza *et al*, 2015b; Kalivas and Volkow, 2005). Accordingly, systemic treatment

with NMDAR uncompetitive antagonist memantine blocks compulsive-like eating and microinfusion of memantine directly into the NAc reduces binge-like eating (Smith *et al*, 2015).

Thus, it is likely that two mechanisms intersect in the frontal cortex to contribute to compulsive eating: prefrontal circuits re-engage striatal regions to activate craving (see habitual overeating section above), and dysregulation of prefrontal circuits produces disinhibition of both impulsive acts (via the basal ganglia) and stress reactions (via the extended amygdala; see overeating to relieve an negative emotional state section above).

DISCUSSION

As described above, compulsive eating behavior is a pathological form of feeding that phenotypically, neurobiologically, and conceptually resembles compulsive behavior associated with both drugs of abuse and behavioral addictions. Preclinical research on feeding, represented largely by studies on obesity, has been hampered by the predominant classical view of eating as a mere energy-homeostatic behavior, ignoring forms of overeating that are compulsive in nature. This limited view has hindered methodological advances on more complex behavioral expressions of pathological feeding and, in turn, on our understanding of the underlying neurobiological substrates. However, it should be noted that eating behavior is under control of multiple mechanisms (often compartmentalized in homeostatic and hedonic components), which are far from independent, and thus cannot be studied without consideration of the other. Although the study of the interaction of these two components in relation to the study of basic eating processes has been rapidly increasing in the scientific community, a bigger effort will be needed to investigate it in the context of compulsive eating.

The parallels drawn between drugs of abuse and food have led to the question of whether forms of compulsive eating in human and animal subjects may predispose to compulsive drug use and vice versa. Few studies have suggested significant overlap between compulsive drug use and disorders characterized by compulsive eating; for example, there is data of an increased prevalence of substance abuse disorders in individuals with BED (Javaras *et al*, 2008). Evidence in obesity is instead mixed, with some studies showing positive associations (Arif and Rohrer, 2005; Petry *et al*, 2008) and others negative associations (John *et al*, 2005; Simon *et al*, 2006) between alcohol use disorders and obesity. This discrepancy could be explained by the heterogeneity of obesity populations, such that only certain subgroups are at risk (Sansone and Sansone, 2013). Preclinical research in this context is still in its infancy, and studies have mostly focused on the effects of overeating or obesity induced by exposure to highly palatable foods (rather than compulsive-like eating *per se*) on drug-related behavior (rather than compulsive-like drug use *per se*). Indeed, in animal models of obesity and/or binge eating there is some evidence of vulnerability factors for the development of compulsive drug taking in the form of brain reward deficits (Valenza *et al*, 2015) that increased alcohol self-administration (Avena *et al*, 2004), and greater cocaine craving (Barnea *et al*, 2015). However, much more research is needed to understand the relationship between compulsive drug use and compulsive eating.

Investigations into the neurobiology of drugs of abuse and highly palatable foods have lent a solid theoretical foundation for how reward, stress, and cognitive function neurocircuitries may be disrupted and ultimately drive compulsive eating behavior. The evidence described here supports the hypothesis that palatable food consumption may initially activate the mesolimbic dopamine incentive salience pathways, and then, repeated, over-stimulations may lead to a cascade of neurobehavioral adaptations, including a shift to dorsal striatal-mediated habitual behavior, desensitization of the reward system, recruitment of the amygdaloid stress systems, and loss of prefronto-cortical control over behavior. However, these neurobiological mechanisms have many further complexities (eg, diet effects on dopamine systems; Baladi *et al*, 2012) that framed in the context of compulsive eating could serve as the topic of a future review.

It is necessary to further our understanding of the interactions of these maladaptive circuits and how compulsive eating behavior differs from non-pathological eating. Functionally anchored animal models of compulsive eating behaviors are also needed to bring the field to this next level through the integration of these elements (ie, habitual/inflexible feeding responding, negatively reinforced feeding, and eating in spite of negative consequences). One caveat is that the use of animal models has intrinsic limitations, especially when complex psychiatric disorders are modeled; for example, the utilization of specific controlled environmental conditions such as differential access to experimental diets (eg, intermittent *vs* continuous). Many factors (history and schedule of diet access, composition of diet, behavioral assessments of compulsivity) contribute to the percentages of animals that reliably display compulsive-like eating behavior (de Jong *et al*, 2013; Heyne *et al*, 2009; Parylak *et al,* 2012). The details of experimental conditions associated with compulsive-like eating behavior are extensive, and could serve its own topic in a future review. Despite some inherent limitations, innovative animal models of functionally anchored behaviors reflecting specific endophenotypes of psychiatric syndromes will prove indispensable to understand the neurobiological underpinnings of a disorder, and for the discovery of novel pharmacological treatments.

A deeper understanding of the mechanisms behind each of the elements can shed light on the underlying pathology of compulsive eating behavior, and can also explain its pathogenesis. Currently, there are substantial gaps in the knowledge of the emergence and time course of these elements of compulsive eating, which hold potential for providing essential information for preventative measures and therapeutic targets for these conditions. Furthermore, by focusing on all of the elements, as opposed to each separately, we can start to understand the interactions of these areas and related neurocircuitries, identifying how the elements may influence each other (eg, relationships between depression/stress on learning and decision-making processes). Such an approach will provide the evidence-based data for understanding individual differences and resonate well with the spirit of new initiatives in precision medicine. Retuning both conceptual and the methodological approaches to compulsive eating will be essential to gain a

better understanding diagnosis, prevention, and treatment of pathological eating.

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DISCLAIMER

The contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Institutes of Health.

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