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Modeling and testing compulsive eating behavior in animals

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MODELING AND TESTING COMPULSIVE EATING BEHAVIOR IN ANIMALS

by

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ABSTRACT

The study of compulsive eating has been swiftly gaining attention in both preclinical and clinical research. Compulsive eating behaviors characterize obesity and several eating disorders and can be conceptualized as being composed of three main elements: 1. *habitual overeating*, 2. *overeating to alleviate a negative emotional state*, and 3. *overeating despite negative consequences*. At a preclinical level, developing appropriate and clinically-relevant animal models and tests has been a barrier to investigating the neurobiological substrates of compulsive eating with the purpose of refining pharmacological interventions for forms of obesity and eating disorders. Throughout this review, we will describe the strategies used to develop animal models, first detailing experimental manipulations that are most commonly used to facilitate development of compulsive eating behavior and then we will focus on the tests used to measure compulsive eating as defined by the three aforementioned elements. Retuning the methodological approach towards compulsive eating behavior is essential to understand the complex mechanisms underlying the maladaptive food intake in forms of obesity and eating disorders.

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LIST OF ABBREVIATIONS

ANBP	Anorexia Nervosa Binge-Purge Subtype
BED	Binge Eating Disorder
BEP	Binge-Eating Prone
BER	Binge-Eating Resistant
BMI	Body Mass Index
BN	Bulimia Nervosa
CB(1)	Cannabinoid Type-1
Cyfip2	Cytoplasmic FMR1-interacting protein 2
DSM-V	Diagnostic and Statistical Manual of Mental Disorders
EPM	Elevated Plus Maze
FTO	Fat mass and obesity-associated
HFD	High-Fat Diet
HFSD	High-Fat and High-Sugar Diet
HSD	High-Sugar Diet
ICSS	Intracranial Self-Stimulation
MC4R	Melanocortin-4 Receptor
Ob(lep)	Leptin Gene
PR	Progressive Ratio
QTL	Quantitative Trait Loci
RDoC	Research Domain Criteria
YFAS	Yale Food Addiction Scale

INTRODUCTION

Compulsive eating is regarded as a strong, irresistible internal drive to consume food, typically contrary to one's will (Davis and Carter, 2009; Dalley et al., 2011; American Psychiatric Association, 2013), similar to the construct of compulsive drug use that characterizes drug addiction. Compulsive eating behaviors are characteristic of certain forms of eating disorders and obesity (Davis and Carter, 2009; Moore et al., 2017b). Compulsive eating has been garnering attention in part due to increasing rates of overweight and obesity (Meule, 2015). Compulsive eating has been proposed to consist largely of three main elements, which have been adapted from the drug addiction literature (Moore et al., 2017b): 1) *habitual overeating,* 2) *overeating to alleviate a negative emotional state,* and 3) *overeating despite negative consequences.*

The study of compulsive eating only recently has been gaining attention in both preclinical and clinical research (Figure 1). At a preclinical level, the development of appropriate animal models and tests, which allow the study of complex behavioral constructs, has been a barrier to both investigating the neurobiological substrates of compulsive eating and refining pharmacological interventions for various forms of obesity and eating disorders. Within the last half century of drug abuse research, a deeper understanding of the addiction process has been achieved through the development of elaborate animal models and tests, which mimic the multiple facets and stages of this chronic, relapsing disorder (Olmstead, 2006). Unfortunately, preclinical research in obesity and eating disorders has been classically hampered by a preferential focus on the energy-homeostatic and metabolic aspects of these disorders, at the expense of their motivational, emotional, and cognitive characteristics.

Animal models and tests of drug addiction have been refined across many decades of research, and are now providing invaluable insights into the approach and methodology needed to appropriately mimic other addiction-related behaviors, including compulsive eating. Thus, the purpose of this review is to describe the progress made in the last couple of decades in the development of animal models and tests that respectively mimic and measure compulsivity in the context of eating behavior.

In this review, we will first describe certain eating disorders and forms of obesity that are characterized by compulsive eating behaviors, as well as briefly describe the rationale and the evidence behind the three main elements of compulsive eating. We will then describe how to model and test for compulsive eating in preclinical research, including descriptions of the different variables that are typically manipulated to produce a compulsive eating phenotype.

COMPULSIVE EATING IN FORMS OF OBESITY AND EATING DISORDERS

Eating disorders are extremely heterogeneous, with symptomology varying largely by diagnosis, even within subtypes. Compulsive eating behavior is a transdiagnostic criteria of multiple eating disorders, including binge-eating disorder (BED), bulimia nervosa (BN), anorexia nervosa (binge/purge subtype; ANBP), ‘food addiction,' as well as certain forms of obesity (Volkow et al., 2008; Gearhardt et al., 2009; Gearhardt et al., 2016). While specifics of the presentation, symptomology, and etiology of these eating disorders differ, compulsive eating behavior has been observed in each, representing the potential for shared therapeutic targets.

BED is a psychiatric condition defined by uncontrolled, intermittent overconsumption of food in brief periods of time (for full diagnostic criteria see Table 1) (de Zwaan, 2001; Kessler et al., 2013; Kessler et al., 2016). Binge eating also characterizes BN and ANBP (American Psychiatric Association, 2013); however, as opposed to BED, bingeing in BN and ANBP is followed by inappropriate compensatory behaviors aimed to prevent weight gain (see Tables 2-3) (American Psychiatric Association, 2013). While ANBP is characterized by an abnormally low body weight, individuals with BN tend to have a normal or above normal body weight (American Psychiatric Association, 2013). Obesity is defined by a body mass index (BMI) of 30 or above (World Health Organization, , 2000). Importantly, while some obese individuals often also display compulsive eating behavior, compulsive eating behavior is not a diagnostic criterion for obesity, and overweight/obesity isn't necessary or sufficient to characterize compulsive eating (Davis, 2013). A recently proposed disorder characterized by compulsive eating is 'food addiction', which emerged largely from a multitude of research demonstrating the similarities between pathological forms of eating behaviors and addictions to drugs of abuse (Hernandez and Hoebel, 1988; Avena et al., 2004; Rada et al., 2005; Avena et al., 2008). In 2009, a diagnostic tool named the Yale Food Addiction Scale (YFAS) was created, and also recently updated, based on the substance use disorder diagnostic criteria in the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) (Gearhardt et al., 2009; American Psychiatric Association, 2013; Gearhardt et al., 2016). Using the YFAS, a diagnosis of food addiction is given when a patient displays clinically significant impairment or distress and meets criteria such as eating much more than intended and experiencing problems in ability to function because of food (Gearhardt et al., 2016). The most commonly reported YFAS symptom is an inability to reduce food consumption or discontinue eating (Eichen et al., 2013; Gearhardt et al., 2013; Meule et al., 2014). As currently most epidemiological data on food addiction are collected using the YFAS, in this review we will refer to food addiction in humans as the condition measured by this scale, even though it is important to emphasize that this emerging, not fully-established condition is different from the already well-recognized eating disorders, and that further validation is necessary (Long et al., 2015).

Comorbidity among the eating disorders mentioned in this review is extremely high, likely reflecting the shared characteristics of the disorders and their diagnostic criteria. Obesity has the highest prevalence, estimated to be 36.5% in the United States (Barry et al., 2009; Pedram et al., 2013; Ogden et al., 2015). Eating disorders are clinically diagnosed through a characterization of aberrant eating, dysregulated body weight, and overconcern for shape and weight, and will affect millions of women and men in their lifetime. Anorexia nervosa is estimated to affect less than 1% of the population, with a binge/purge subtype being more common, associated with longer illness duration and more severe outcomes (i.e. higher rates of relapse and mortality) (Zipfel et al., 2000; Eddy et al., 2002). BN is only slightly more common at a prevalence of 0.5-1.5% (Hudson et al., 2007), and has a high lifetime comorbidity with AN and BED, demonstrating high incidences of ‘crossover’ in these disorders (Eddy et al., 2008; Stice et al., 2013). Prevalence of BED and of food addiction in the general population are estimated to be 2-5% and 5–15%, respectively (de Zwaan, 2001; Gearhardt et al., 2009; Davis et al., 2011; Kessler et al., 2013). The prevalence of these disorders is 2–3 times higher in populations of obese individuals seeking treatment through weight-loss programs, dietary changes, and bariatric surgery (de Zwaan, 2001; Pursey et al., 2014).

There is a great amount of overlap among the above discussed disorders, and often this comorbidity is associated with greater symptom severity and lower quality of life. A YFAS-diagnosis of ‘food addiction’ is associated with obesity/overweight, BED, and/or BN (Gearhardt et al., 2012; Gearhardt et al., 2013; Mason et al., 2013; Pedram et al., 2013; Flint et al., 2014; Gearhardt et al., 2014; Meule and Gearhardt, 2014). Obese individuals with BED have more frequent binge eating episodes compared to non-obese individuals with BED (Dingemans and van Furth, 2012). Individuals with BED and obesity often report a poorer quality of life and higher health-care expenses, and have a higher prevalence of psychiatric comorbidities (Wolf and Colditz, 1998; Fontaine and Barofsky, 2001; Dickerson et al., 2011; Halfon et al., 2013; Kessler et al., 2013; Agh et al., 2016).

High comorbidity among these disorders suggest there are similarities in etiologies and/or underlying mechanisms, which could arise through compulsive eating. As highlighted in Figure 2, DSM-V diagnosed eating disorders are distinct by design, though there are instances of lifetime comorbidities (Eddy et al., 2008; Stice et al., 2013).

In contrast, food addiction measured by the YFAS has a high degree of comorbidity with obesity as well as already recognized eating disorders. Thus, this review focuses on the transdiagnostic construct of compulsive eating, encouraged by the implementation of the Research Domain Criteria (RDoC) framework by the National Institute of Mental Health, which calls for the classification of high-level domains that are common to multiple mental disorders (The National Institute of Mental Health, 2013).

The concept of food addiction has been met with criticism for several reasons, perhaps the most evident being the lack of direct, overlapping analogies between some of the diagnostic criteria of drug addiction. Specifically, whether the "existence" of food addiction would require the presence of diagnostic criteria such as tolerance and withdrawal ("dependence" in the traditional sense) is under debate. Indeed, despite evidence that excessive consumption of foods rich in sugars and fat has been demonstrated to have similar powerful effects of abused drugs on the brain reward and antireward systems (Cottone et al., 2009a; Johnson and Kenny, 2010; Koob, 2013; Volkow et al., 2013), arguing that food can produce effects comparable to drugs of abuse is controversial (Ziauddeen et al., 2012; Salamone and Correa, 2013). In addition, behavioral addictions (i.e. non-substance related addictions), have also been argued to not share tolerance and withdrawal criteria with substance use disorders (Holden, 2010; Ziauddeen et al., 2012). For example, pathological gambling, a disorder comprised of feelings of a loss of control over gambling with an emphasis on life disruptions and damage (Fauth-Buhler et al., 2016), is built upon the evidence that engagement in a behavior can become compulsive in absence of substance-induced, pharmacological effects in the brain. However, these criticisms reflect more the misunderstanding of tolerance and withdrawal in drug addiction than differences between drugs and behavioral addictions and/or food addiction. Tolerance occurs in all behavioral addictions as there is increased reward seeking and taking to produce the same effect, and dependence, as defined as a motivational withdrawal syndrome, when the reward sought is not available, is also observed in all behavioral addictions. Similarly, tolerance is observed in compulsive eating and food addiction where individuals ingest more and more to produce the same hedonic effect and where dysphoria, depression, and irritability (motivational withdrawal symptoms) occur in the absence of food ingestion. Recognizing the evolving understanding of addictive disorders, the newest edition of the DSM (5th ed) (American Psychiatric Association, 2013) has placed more emphasis on behavioral aspects to avoid the old physical dependence construct and shifted terminology from “substance dependence” to “substance use disorders”, which reflects the redirection of focus from dependence qualifiers to behavioral dimensions that reflect the underlying neurobiology including the adding of “craving” as a criterion (Gearhardt et al., 2011; O'Brien, 2011; Hasin et al., 2013; Badiani, 2014). Therefore, we argue that, using old physical definitions of tolerance and withdrawal, rather than behavioral measures of tolerance and withdrawal, is a red herring in the overall conceptual framework of addiction, and food addiction should be accepted as an addictive disorder, as it shares similar neurobiology, risk factors, etiologies, and behavioral manifestations as other, currently recognized behavioral and drug addictions (Carlier et al., 2015; Schulte et al., 2016). Additionally, understanding the unique characteristics of food addiction can inform current research tools, including the necessity to move away from diagnostic questions involving physiological symptoms that allegedly only apply to abused drugs (e.g. physical withdrawal and dependence). The utility of a food addiction diagnosis separate from, or in the absence of, these other conditions is not yet known; however, it holds potential for increasingly personalized treatment approaches for these disorders (Davis et al., 2011).

ELEMENTS OF COMPULSIVE EATING BEHAVIOR

Habitual Overeating

Feeding can eventually become maladaptive and habitual through a shift in the instrumental learning mechanisms that drive behavior. Energy-dense foods are powerful reinforcers; thus, the pleasant outcomes of their consumption lead to an increased probability of their ingestion. After repeated pairings, environmental cues associated with food can eventually drive and reinforce behavior on their own (i.e. become conditioned reinforcers) (Giuliano and Cottone, 2015; Corbit, 2016). Habits are regarded as compulsive once the reinforced behavior is performed even when the primary reinforcer (e.g. food) is lowered in value or removed (Robbins and Everitt, 1999; Everitt and Robbins, 2005; Everitt et al., 2008; Redish et al., 2008; Halbout et al., 2016). Studies have shown that individuals with obesity (Horstmann et al., 2015; Watson et al., 2017) and/or BED (Voon et al., 2015; Reiter et al., 2017) tend to engage in habitual, or stimulus-driven, behavior.

Overeating to alleviate a negative emotional state

An important element of compulsive eating behavior involves overeating food for the purpose of alleviating a negative emotional state. Adapted from drug addiction and obsessive-compulsive disorder literature, compulsive eating can be characterized by anxiety and stress before committing a behavior (i.e. eating), followed by relief from that stress after performing that behavior (Koob and Volkow, 2010; Koob, 2015). While ingesting energy-dense food is initially positively reinforced (i.e. the increased probability of a behavioral response produced by obtaining a positive stimulus) (Hagan et al., 2002; Corwin, 2006; Avena, 2007), it can acquire negatively reinforcing properties (i.e. the increased probability of a behavioral response produced by the removal of a negative stimulus) (Bale et al., 2003; Cottone et al., 2009a; Parylak et al., 2011), where overeating serves to paradoxically medicate the negative emotional state. Two distinct, but overlapping, processes are hypothesized to underlie this element of compulsive behavior: decreased reward function and withdrawal-induced negative affect, both thought to result from repeated over-stimulation of the brain's reward systems (Koob and Le Moal, 2001). Individuals with obesity and/or eating disorders have greater rates of psychiatric comorbidities involving negative emotional states (i.e. anxiety and depression) (Peterson et al., 2005; Zeller and Modi, 2006; Baumeister and Harter, 2007), which can further trigger binge eating (Rosenberg et al., 2013; Klatzkin et al., 2015). Furthermore, there is evidence that eating energy-dense food may be a way to 'self-medicate' through alleviating negative emotional states temporarily (Pecoraro et al., 2004; Macht, 2008; Tomiyama et al., 2011).

Overeating despite negative consequences

Loss of control over eating behaviors is regarded as persistent overconsumption despite harmful consequences that would typically suppress feeding (Cottone et al., 2012; Rossetti et al., 2014; Velazquez-Sanchez et al., 2015). Most clearly, overeating of energy-dense food is a significant causative factor of obesity (Ruhm, 2012), which in turn causes a multitude of health complications including diabetes mellitus, myocardial infarction, stroke, hypertension, and arteriosclerosis (World Health Organization, 2000; McGee, 2005; Klatzkin et al., 2015). Beyond physical conditions, overeating is associated with social problems, emotional problems, and other psychiatric disorders (World Health Organization, 2000; Warschburger, 2005). Although people experience negative outcomes due to their overeating, many feel unable to stop (Davis and Carter, 2009). Loss of control over eating behavior is associated with deficits in ‘top-down’ inhibitory control mechanisms that suppress inappropriate actions. Individuals who compulsively overeat show poor performance on tasks of inhibitory control related to food (Batterink et al., 2010; Svaldi et al., 2014; Hege et al., 2015), and these deficits predict poorer outcomes, such as further weight gain (Seeyave et al., 2009; Pauli-Pott et al., 2010) and resistance to weight loss treatment (Murdaugh et al., 2012).

MODELING AND TESTING COMPULSIVE EATING

While they are often used interchangeably in neuropsychopharmacological preclinical research, “model” and “test” represent two different aspects of the study of animal behavior (Charney et al., 2018). A model is a nonhuman subject that exhibits a specific phenotype, reminiscent of a physiological or pathological human condition, as a result of an experimental manipulation. A test is an experimental setup that enables the measurement of a specific behavior in the experimental nonhuman subject (i.e. readout), relevant for a physiological or pathological human condition. Therefore, in the next sections we will first review the experimental manipulations that are most commonly used to make animals behave as compulsive eaters, and then we will focus on the tests used to measure compulsive eating as defined by the three aforementioned elements. This review will not be exhaustive in the description of the specific animal models, thus, a discussion on the different validities (e.g. face, construct, predictive, convergent, etc.) in each specific model, is outside the scope of this paper.

MODELING COMPULSIVE EATING

As mentioned earlier, a model is a nonhuman subject that exhibits a specific phenotype, reminiscent of a physiological or pathological human condition, as a result of an experimental manipulation. While the scientific literature offers several strategies to develop models of aberrant forms of eating behavior in animals, in the specific context of compulsive eating, the research is still in its infancy. Some clarification of the terminology is necessary at this point. Compulsive eating can encompass overeating and binge eating, but overeating and binge eating are not necessarily compulsive in their nature. Overeating is a very general term and most often defined as consuming an excess amount of food relative to energy expended, while binge eating is consuming an excess of what most people would eat in a discrete period of time (typically 1 to 2 hours)

(American Psychiatric Association, 2013). Though arguably maladaptive, overeating or binge eating alone are neither necessary nor sufficient to be considered compulsive eating behavior. Compulsive eating is regarded as a strong, irresistible internal drive to consume food, typically contrary to one's will, and it represents a more nuanced and complex construct, defined most appropriately and accurately by its three main elements.

Food type

The increased availability of energy dense food is proposed to be a risk factor for eating disorders and obesity (Hill et al., 2003). Moreover, episodes of binge eating most often occur with foods high in sugar and/or fat (Yanovski et al., 1992). In this review, a palatable diet is defined as food that is uniformly preferred by animals over the standard laboratory chow. Notably, while preferred food is typically called ‘palatable’ by researchers in the preclinical literature, this is loose and anthropomorphic terminology, with the more precise term being ‘preferred.’

Palatable diets can refer to a high-sugar diet (HSD), a high-fat diet (HFD), or a combination of the two, referred to here as a high-fat and high-sugar diet (HFSD). HFSDs can be a formulation of rodent chow that is high in both fat and sugar, or a so-called ‘cafeteria diet’/‘junk-food diet,’ typically consisting of multiple types of human-food that is high in sugar and fat (e.g. Oreo’s, lard, peanut butter) (Heyne et al., 2009; Martire et al., 2015).

The highly palatable diet can be provided with or without concurrent standard chow access in a free-choice, or forced-choice paradigm, respectively. However, a highly palatable diet is supposed to be preferred to a large extent over the standard chow diet. Under conditions of concurrent, free-choice access, the palatable diet intake typically consists of >90% of the total caloric intake (Cottone et al., 2008b; Cottone et al., 2008a; Johnson and Kenny, 2010). For this reason, the palatable diet is most often provided as the only option during scheduled access, and can be assumed to be the case unless otherwise noted in this review. While food type is varied across models to different degrees, there does not seem to be any particular diet formulation (HSD vs. HFD vs. HFSD) that results in any more or less compulsive eating behavior apart from its level of preferredness/palatability.

Schedule of access to palatable food

Often individuals attempt to lose body weight by controlling the quality of foods consumed and by limiting their intake of energy-dense, highly palatable, “forbidden” foods and consuming only low-palatability, “safe” foods (Laessle et al., 1989; de Castro, 1995; Mela, 2001). Inevitably, restrained intake of safe foods is ultimately associated with later disinhibited eating of forbidden foods (Herman and Polivy, 1990). Thus, in humans who display disordered eating behaviors, there is often a pattern of discrete alternations in intake of foods with different palatability.

In animal models, palatable diet access is either given continuously (i.e. *ad libitum*), or intermittently. Intermittent access periods can range from daily 10 minute periods (Cottone et al., 2008b) to multiple days (Cottone et al., 2009a). In this review, we consider intermittent access lasting less than 12 hours a short access period, with long access lasting 12 hours or longer. Importantly, these designations are not equivalent to long and short-access models of drug addiction, where short-access conditions are meant to mimic recreational drug use, while long-access conditions result in compulsive drug use (Ahmed and Koob, 1998; Ahmed et al., 2000). Indeed, compulsive and binge eating behaviors are often readily observed in animal models that give as short as 10 minute daily access to a palatable diet (Cottone et al., 2008b; Cottone et al., 2012; Velazquez-Sanchez et al., 2015; Ferragud et al., 2016).

These variations of access to palatable food result in certain reproducible phenotypes related to food consumption patterns. Intermittent access models consistently show an *escalation of intake* over time (Parylak et al., 2012; Dore et al., 2014; Velazquez-Sanchez et al., 2015), a feature that is considered a hallmark of addictive-like behavior (Ahmed and Koob, 1998; Ahmed et al., 2000). Intermittency appears to be critical to this pattern of intake, likely due to a hypervaluation of the palatable diet when unavailable. Additionally, overeating of the palatable food progressively shifts towards the beginning of the renewed access (Avena et al., 2005; Cottone et al., 2008a), a pattern resembling ‘deprivation effects’ seen in models of intermittent drug or alcohol access (Wise, 1973; Rodd et al., 2004; George et al., 2007; Sabino et al., 2009).

In continuous access models, animals show overconsumption of the palatable diet, though this overeating occurs in a steadier and more continuous pattern, with no distinct binge periods. Intermittent palatable diet access enables binge-like consumption of palatable food, creating a distinct phenotype from continuous access (Corwin, 2006).

However, continuous access is still able to produce compulsive eating behavior and brain deficits paralleling those seen in drug addiction (Johnson and Kenny, 2010).

In intermittent short access conditions, when animals are allowed to self-administer palatable food in 1-hour operant conditioning sessions, they display higher rates of responding to obtain palatable food compared to controls' responses to acquire standard chow (Cottone et al., 2012). Daily caloric intake escalates over time, resulting in up to 4x higher consumption in animals responding for palatable food compared to chow, and these animals show multiple characteristics of compulsive eating behaviors (Velazquez-Sanchez et al., 2014; Smith et al., 2015).

In intermittent long access conditions, a model of compulsive eating is obtained by providing rats with standard chow for 5 days per week and a high-sucrose, palatable food for 2 days per week (Cottone et al., 2009a; Cottone et al., 2009b). Following repeated cycles of access to the palatable diet and chow, intake of palatable food upon the 1st hour of renewed access escalates over time, and animals show compulsive-like eating behavior of the palatable diet, as well as withdrawal-dependent hypophagia of standard chow, and anxiety-like behavior diet (Cottone et al., 2009a; Cottone et al., 2009b).

Food restriction/deprivation

Dieting, which typically consists of limiting daily caloric intake, promotes binge and compulsive eating behavior, and is regarded as a risk factor for obesity (Herman and Polivy, 1990; Stice et al., 2008; Lowe et al., 2013; Dulloo and Montani, 2015). In animals, forced, experimental food restriction/deprivation is used to mimic the voluntary caloric restriction observed in human dieters. Food restriction limits animals' daily food intake to a fixed amount that is significantly lower than that of *ad libitum* fed controls, whereas food deprivation prevents animals from accessing any food for a set period of time (Bi et al., 2003). Food restriction can be chronic (i.e. throughout the duration of the study) (Pankevich et al., 2010) or given acutely in cycles of restriction and refeeding (Hagan and Moss, 1997).

It is important to note that while caloric restriction and exposure to highly palatable food can both induce neuroadaptations promoting forms of compulsive-like behavior (Shalev et al., 2001; Carr, 2016), the underlying mechanisms are likely different (Cottone et al., 2009b; Cottone et al., 2012; Smith et al., 2015). Caloric restriction causes deficits in energy intake, which leads to greater than normal consumption of food as an energy-homeostatic response. This energy-homeostatic motivation behind hyperphagia of palatable food imposes a limitation on how accurately the hedonic mechanisms of palatable food overconsumption can be assessed.

A model of binge-like sucrose consumption involves 12-hour food deprivation followed by *ad libitum* access to chow and 25% glucose (Colantuoni et al., 2002; Avena et al., 2005; Rada et al., 2005). In this animal model, compulsive eating may result from a negative emotional state as emotional and physical withdrawal can be pharmacologically precipitated by treatment with the opioid receptor antagonist, naloxone (Avena et al., 2008).

Stress

While stress can affect feeding behavior bidirectionally, most individuals tend to overeat following a stressful condition (Adam and Epel, 2007). In individuals with eating disorders, stress is known to trigger binge and compulsive eating (Heatherton et al., 1991; Greeno and Wing, 1994). In animals, stress generally exerts an anorectic action (Hotta et al., 1999; Valles et al., 2000). However, in animals that have underwent experimental manipulations to induce aberrant feeding behavior, stress can induce binge-like and compulsive-like eating behavior (Hagan et al., 2002; Micioni Di Bonaventura et al., 2014; Calvez and Timofeeva, 2016). The consumption of palatable food has been shown to dampen down the physiological stress response, compared to stressed animals with access to only standard chow (Pecoraro et al., 2004). Almost all of the animal models using stress couple this consumption with periods of caloric restriction, as stress and caloric restriction have been shown to have a synergistic effect on food intake. For example, Hagan et al. (2002) found that a history of restriction (4 days of 66% of mean daily chow) and refeeding (6 days of *ad libitum* chow) followed by a footshock stressor induced greater overeating than no-stress and no-restriction groups. Other types of acute stress used include a forced-swim stress (Consoli et al., 2009), chronic variable stress (e.g. restraint, predator odor, etc.) (Pankevich et al., 2010), and a frustration-stress induced by physical separation from the palatable food during a restriction period (Micioni Di Bonaventura et al., 2014).

A history of trauma or chronic stress early in life (e.g. childhood physical/sexual abuse or bullying) can also be a risk factor for developing eating disorders, such as BED (Striegel-Moore et al., 2002). Maternal separation is an example of a chronic, early-life stressor used in laboratory animals to model childhood stress/trauma (Plotsky and Meaney, 1993). In these paradigms, neonatal rats are separated from their maternal dams for 3h daily for the first few weeks of life (Ryu et al., 2008; Jahng, 2011). Pups that experience maternal separation stress demonstrate greater hyperphagia when paired with chronic food restriction/refeeding (Iwasaki et al., 2000). A similar early-life stress is a low amount of maternal care (licking and grooming) received in the neonatal phase. When paired with chronic restriction and refeeding, a lack of maternal care has been shown to exhibit greater binge eating in response to stress (Hancock et al., 2005).

Unpredictable footshocks can also be used to induce compulsive-like drinking of sucrose (Calvez and Timofeeva, 2016). The recruitment of brain stress systems is a key feature of compulsive eating models, and through blocking the neuropeptide corticotropin-releasing factor-1 receptor within these brain areas, you can also block stress-induced overeating (Micioni Di Bonaventura et al., 2014), among other behaviors associated with compulsive eating (Cottone et al., 2009a; Iemolo et al., 2013).

Genes and Phenotypes

Eating disorders are extremely heritable (Bulik et al., 1998), and genetics can interact with environmental factors, such as the availability of highly palatable food, to influence compulsive eating behaviors (Davis, 2015). A large number of genes have been identified to contribute to hyperphagia. Historically, focus has been on genes regulating homeostatic food intake (e.g. polymorphisms in the fat mass and obesity-associated (*FTO*) gene, melanocortin-4 receptor (MC4R) gene, leptin gene Ob(lep)) that lead to hyperphagia and obesity (Chen et al., 1996; Church et al., 2009; Srisai et al., 2011). Recently, discovery-based genetic approaches, such as quantitative trait loci (QTL) mapping, have been applied to finding novel mechanisms of hedonic eating. One such study used QTL mapping to identify Cytoplasmic FMR1-interacting protein 2 (*Cyfip2*) as a determinant in binge eating and compulsive eating behavior (Kirkpatrick et al., 2017).

Innate individual phenotypic differences may also be used to study models of compulsive eating behavior (Velazquez-Sanchez et al., 2014; Calvez and Timofeeva, 2016). Binge-eating prone (BEP) and binge-eating resistant (BER) feeding phenotypes are commonly used to study innate individual differences in compulsive eating behavior. BEP rats model human eating behaviors that align with the DSM-V diagnostic criteria for BED, including high food consumption in short intervals of time and faster consumption than normal (Calvez and Timofeeva, 2016). BEP/BER studies classify test animals according to their general consumption of palatable food in a period of 1-4 hours, under stressful or non-stressful conditions (Boggiano et al., 2007; Oswald et al., 2011; Calvez and Timofeeva, 2016). BEP animals display stable and behaviorally distinct phenotypes, consistently exhibiting greater consumption of intermittent palatable food, altered stress-like responses, and compulsive-like eating (Oswald et al., 2011; Calvez and Timofeeva, 2016). Another study classified animals by trait impulsive action, and found that high trait impulsivity was associated with increased susceptibility to binge-like eating, high motivation, and compulsive-like eating (Velazquez-Sanchez et al., 2014).

The elements of compulsive eating were first adapted from the drug addiction literature (Moore et al., 2017b), where compulsivity has previously been argued to be a critical factor of disease manifestation (Koob, 2013; Piazza and Deroche-Gamonet, 2013; Everitt, 2014; Hopf and Lesscher, 2014; Belin-Rauscent et al., 2015). Compared to compulsive drug use, the field of compulsive eating behavior is still emerging, and little work has been done to systematically define and investigate compulsive eating behavior (Figure 1). Just as the elements have been adapted from the drug addiction literature, many of the behavioral tests used to study compulsive eating behavior in rodents are modified tests of compulsive drug use, using food as a primary reinforcer/reward instead of a drug of abuse. While discussing the tests used to measure compulsive eating, we will also acknowledge behaviors that have been exhibited by animal models of compulsive drug use in these same tests in order to draw certain parallels between these two compulsive behaviors. It is important to note that while we are able to differentiate between the elements of compulsive eating via different methods of testing, these elements are not mutually exclusive.

Habitual Overeating

Compulsive, habitual eating behavior can emerge after a history of palatable food consumption, and is accelerated with food of higher palatability. Habitual behavior refers to a shift from voluntary, goal-directed responding (action-outcome), to more stimulus-driven responding (stimulus-response) that is resistant to devaluation of the expected reward. Habitual eating behavior can be assessed through multiple methods of outcome devaluation.

Outcome Devaluation

In an outcome devaluation test, instrumental responding for an outcome (i.e. seeking behavior) is evaluated after the value of that outcome has been reduced. If an animal is using a goal-directed strategy, relying on the action-outcome contingency, then responding for a devalued outcome should decrease. However, maintaining levels of responding for a devalued outcome suggests habitual, or stimulus-driven, behavior.

Currently, the three most popular methods of inducing outcome devaluation to test for habitual behavior in animal models of drug addiction are: outcome-specific satiety, taste aversion learning, and contingency degradation (Ostlund and Balleine, 2008). Outcome-specific satiety lowers a palatable food’s rewarding properties by allowing animals to become sated with that food during a period of ad libitum access. An alternate method of outcome devaluation is taste aversion learning, or pairing the reward repeatedly with injections of lithium chloride, inducing nausea (Balleine, 1992; Loy and Hall, 2002). Contingency degradation refers to the devaluation of a reward through reducing the probability that it will be presented upon the performance of a response, and simultaneously increasing the probability that it will be presented non-contingently (Ostlund and Balleine, 2008). At this time and to the best of our knowledge, only outcome-specific satiety has been applied to animal studies of compulsive eating.

Outcome-specific satiety

In outcome-specific satiety, animals are trained to respond (e.g. lever press) for food rewards. On test days, the value of that reward is reduced by giving the animals *ad libitum* access to the specific reward, inducing satiety prior to the operant sessions (de Jong et al., 2013; Furlong et al., 2014). In animal models of drug addiction, chronic long-access to drugs results in resistance to devaluation (i.e. persistence in responding for the drug) (Miles et al., 2003; Corbit et al., 2012).

Habitual responding for food developed under intermittent-short, but not continuous, HFSD access conditions (Furlong et al., 2014). In this experiment, three groups of animals (Control diet, Intermittent HFSD, Continuous HFSD) were trained to lever press for grain pellets or 10% sucrose solutions. On the test day, animals were given 1h *ad libitum* access to their instrumental outcome. In the test session, animals responded for food under extinction conditions (i.e. no reward presentations) (Furlong et al., 2014). Only the intermittent-short HFSD group displayed resistance to devaluation (i.e. their test performance remained high), while continuous HFSD and control rats maintained action-outcome responding (Furlong et al., 2014). Thus, intermittent-short access to a HFSD significantly decreased sensitivity to devaluation and accelerated development of habitual food-seeking.

In a similar procedure by Reichelt et al. (2014), continuous access to a HFSD resulted in habitual responding in two devaluation tasks. In a Pavlovian-conditioned approach procedure, rats were first trained to discriminate two discrete audio cues that were paired with the delivery of two sucrose solutions from opposite magazines (e.g.

noise → grape-maltodextrin, tone → cherry-sucrose). On test days, animals were allowed to self-administer one of the two solutions for 20 minutes prior to a test session where cues were presented with no delivery of the solutions. The cue-outcome devaluation test measured approach behavior (i.e. magazine head entries) during the cue presentation that signaled availability of one of the two reward solutions. Rats with prior continuous access did not devalue or respond less for the solution they had previously consumed *ad libitum* (Reichelt et al., 2014). In another test of sensory-specific satiety, animals were given access to both solutions in the home cage. Pre-exposure to one solution *ad libitum* prior to testing did not cause a reduction in the consumption of the devalued outcome. Thus, this finding suggests that continuous access can also result in similar compulsive and habitual eating behavior as seen under intermittent-short access conditions.

Contexts paired with palatable-food eating have been shown to impair goal-directed responding, triggering increased habitual eating (Kendig et al., 2016). A study by Kendig et al. (2016) found that a single pairing of HFSD access with a specific context caused resistance to specific satiety devaluation in that context, but not in a context paired with standard chow. Interestingly, the habitual eating brought on by the palatable food-paired context could be ameliorated by the presentation of a chow-associated cue, suggesting the ability of cues to not only impair, but also potentially restore, decision-making processes (Kendig et al., 2016). This study demonstrates the potential influence of environments paired with palatable food to impair goal-directed control over eating behavior.

Overeating to alleviate a negative emotional state

Overeating to alleviate a negative emotional state has been behaviorally well characterized in animal models of compulsive eating (Cottone et al., 2009a; Cottone et al., 2009b; Iemolo et al., 2012; Blasio et al., 2013). This element of compulsive eating is twofold: decreased reward and the emergence of a negative emotional state (Koob, 2015; Moore et al., 2017b). Results from the tests described below show reliable and reproducible evidence of decreased reward (increased anhedonia, depressive-like behavior, and reduced reward system functioning) and the emergence of a negative emotional state (increased anxiety-like behavior) in animal models of compulsive eating.

Decreased Reward

The shift from positive to negative reinforcement mechanisms in part involves a depressive-like state, characterized by decreased reward function and loss of motivation for ordinary life stimuli (i.e. anhedonia), as well as behavioral despair. Sucrose consumption (preference for a natural reward), hypophagia of less palatable food alternatives, progressive ratio responding (motivation) for lesser rewards, and intracranial self-stimulation (reward system functioning) are common assessments of anhedonia in animals. Two common tests of depressive-like behavior: the forced swim test (rats and mice) and the tail suspension test (mice), rely on the same principle of measuring behavioral despair when faced with inescapable situations (Castagne et al., 2011).

Sucrose Consumption Test

A classical test of anhedonia is the sucrose consumption test, where sucrose consumption is used as a measure of responsiveness to natural rewards. Low consumption of and preference for sucrose is thought to represent a deficit in the reward system's response to a natural reward and is used as the operational definition of anhedonia. Withdrawal from drugs of abuse, including amphetamine, cocaine, and heroin, has been shown to reduce motivation for natural rewards like sucrose in rats (Der-Avakian and Markou, 2010). Intermittent-long HSD access resulted in reduced sucrose preference compared to control rats when tested during palatable food withdrawal (Iemolo et al., 2012). Renewed access to the HSD reduced this anhedonic-like behavior (Iemolo et al., 2012). Models utilizing continuous HFD access consistently display decreased sucrose preference in obese experimental animals (Yamada et al., 2011; Sharma et al., 2013; Dutheil et al., 2016). These results suggest that withdrawal from palatable food and/or an obese phenotype (resulting from continuous HFD access) can result in anhedonic-like behaviors, likely indicating reward deficits.

Maternally separated rats showed decreased sucrose intake in preference tests; however access to a palatable diet alleviated this anhedonic-like effect (Maniam and Morris, 2010b; Maniam and Morris, 2010a), suggesting consumption of highly palatable food may be protective against anhedonia elicited by an early-life stress.

Hypophagia of Food with Lower Palatability

Interruption of palatable food access consistently results in hypophagia of the standard chow, when this becomes the only food available (Colantuoni et al., 2002; Levin and Dunn-Meynell, 2002; Cottone et al., 2008a; Cottone et al., 2009b; Blasio et al., 2014; Dore et al., 2014; Rossetti et al., 2014). While the decrease in food consumption occurs even after a single shift to a less palatable diet in intermittent access paradigms, the hypophagia increases in magnitude with each additional palatable diet access cycle (Cottone et al., 2008a; Cottone et al., 2009b; Blasio et al., 2014).

Hypophagia was originally proposed as an energy-homeostatic compensatory response to previous hyperphagia and body weight gain induced by access to a highly palatable diet. Indeed, in animals shifting to a less palatable diet, hypophagia is accompanied by body weight loss (Levin and Dunn-Meynell, 2002).

While this phenomenon could be an energy-homeostatic mechanism, hedonic mechanisms are also implicated in hypophagia of less palatable food (Cottone et al., 2008a). The most striking evidence of this is when hypophagia was observed without overeating of a more preferred food (compared to controls) (Cottone et al., 2008a). In this instance, the alternating diets were similar in energy density and were both preferred over standard chow (Cottone et al., 2008a). However, following the removal of the more preferred food, rats signficantly and progressively reduced their intake of the less preferred diet, suggesting that intermittent access to rewards, such as palatable food, can affect the reinforcing efficacy of otherwise satisfactory alternatives (Cottone et al., 2008a). Hypophagia is hypothesized to arise from a phenomenon called successive negative contrast (Flaherty and Rowan, 1986; Flaherty et al., 1995), a reduction in reward consumption following previous experience of another reward of higher magnitude

(Austen et al., 2016), implicating hedonic rather than energy-homeostatic mechanisms (Flaherty and Rowan, 1986; Flaherty et al., 1995).

Hypophagia may be also explained by the opponent process theory of motivation, which proposes progressively increasing habituation to a rewarding stimulus followed by a progressively increasing intensity of hedonic withdrawal with each exposure to that stimulus (Solomon and Corbit, 1974). Animals may become increasingly habituated to the palatable diet, leading to progressively increasing hyperphagia of this diet, and exhibit increasing hypophagia of the less palatable diet caused by an increasingly powerful withdrawal state. Importantly, hypophagia is specific to models of disordered eating, and no equivalent exists in drug addiction models.

Progressive Ratio Responding for Food

Similar to hypophagia, during withdrawal from a palatable diet, animals also exhibit lower motivation to seek less palatable alternatives (e.g. standard chow) in progressive ratio (PR) operant task procedures. This procedure assesses animals' sensitivity to different food rewards by having them perform an exponentially increasing number of instrumental responses (e.g. button/lever press) to obtain a self-administered food reward in operant chambers (Cottone et al., 2008b). In these procedures, the breakpoint (i.e. last ratio completed) is used as a measure of motivation (Velazquez-Sanchez et al., 2014). In drug addiction studies that used sucrose as a lesser reward, withdrawal from drugs of abuse resulted in lower breakpoints (i.e. decreased motivation) for rewards of lower magnitude than drugs of abuse (Hoefer et al., 2006; Zhang et al., 2007). During withdrawal from intermittent-long HSD access, rats exhibited a lower total number of PR responses and lower breakpoints for the less palatable food reward, compared to controls, showing lower motivation for the less palatable diet (Cottone et al., 2008b).

Intracranial Self-Stimulation (ICSS)

Intracranial Self-Stimulation (ICSS) is a procedure used to assess brain reward function. Implanted bipolar stimulating electrodes (in the medial forebrain bundle at the level of the lateral hypothalamus) deliver electrical stimulation in animals when they successfully perform an action (i.e. lever press or wheel turn) (Johnson and Kenny, 2010; Iemolo et al., 2012). Brain reward function is measured as the animal’s reward threshold, which is the minimum current intensity stimulus, or minimum frequency of stimulation, able to maintain self-stimulation behavior (Carlezon and Chartoff, 2007; Johnson and Kenny, 2010; Iemolo et al., 2012). Reward threshold increases and decreases throughout the trials are operationalized as lowered reward function and elevated reward function, respectively (Johnson and Kenny, 2010; Iemolo et al., 2012). ICSS has been used to study the effects of drugs of abuse on reward system function. Reward thresholds are increased in animal models of cocaine, amphetamine, and heroin addiction (Kokkinidis and McCarter, 1990; Markou and Koob, 1991; Ahmed et al., 2002; Kenny et al., 2006).

There are two main procedures used to assess the brain reward threshold: a rate-independent, discrete-trial current intensity paradigm (Esposito and Kornetsky, 1977) and a response-rate frequency paradigm (Gallistel and Freyd, 1987; Carlezon and Chartoff, 2007). In the discrete-trial current intensity protocol, there are a series of trials beginning with a non-contingent electrical stimulation (varying current), after which animals have a limited time to perform a response to self-stimulate that same level of electrical current (Johnson and Kenny, 2010; Iemolo et al., 2012). In the response-rate frequency paradigm, animals initially receive a non-contingent electrical stimulation (varying frequencies) and are then given a limited time to perform as many self-stimulating responses as desired (Carlezon and Chartoff, 2007).

Continuous HFSD access was found to elevate ICSS reward thresholds in rats compared to intermittent-short HFSD access and control animals (Johnson and Kenny, 2010). These findings suggest continuous palatable food access decreases brain reward function. Furthermore, these results show shorter periods of daily palatable food access are insufficient to induce the same behavioral effects (Johnson and Kenny, 2010). In a study using diet-induced obesity rats, continuous HFD access resulted in reduced reward system functioning, evidenced by decreased sensitivity to dextroamphetamine’s ability to potentiate decreased ICSS thresholds (Valenza et al., 2015).

Intermittent-long HSD access did not result in changes in the brain reward threshold when tested during both palatable diet access and withdrawal conditions (Iemolo et al., 2012). There are several reasons why reward threshold changes were not observed in this study, including the type or schedule of access to palatable diet (Iemolo et al., 2012). Reward dysfunction may also be more easily observed in an obese phenotype, which developed after continuous palatable diet access (Johnson and Kenny, 2010), but not in intermittent-long HSD (Iemolo et al., 2012) or intermittent-short HFSD access conditions (Johnson and Kenny, 2010). Alternately, pharmacological precipitation of withdrawal may be necessary to observe changes in the brain reward threshold in rats with intermittent access to palatable diets.

Forced-Swim Test

The forced-swim test measures time animals spend immobile in water to assess depressive-like behavior. Depressive-like behavior is defined by increased immobility time compared to controls when placed in a pool of water. Animal models of cocaine (Hall et al., 2010), opiate (Anraku et al., 2001), and amphetamine (Cryan et al., 2003) addiction have displayed quicker onset of immobility and longer immobility times during withdrawal. Intermittent-long HSD access resulted in longer immobility times during a period of withdrawal from palatable food, indicating depressive-like behavior (Iemolo et al., 2012). Restoring access to the palatable diet reversed these depressive-like behaviors, with immobility time becoming similar to controls (Iemolo et al., 2012). Continuous HFD access resulted in similar overall depressive-like behavior during access to the HFD (Yamada et al., 2011) as well as after a withdrawal period (Sharma et al., 2013). Yamada et al. (2011) also tested animals after 3 weeks of withdrawal from the HFD, a period sufficient to decrease body weight to control levels and normalize markers of obesity (i.e. plasma levels of glucose, insulin, and leptin). At this time point, immobility time was no different from controls (Yamada et al., 2011), suggesting that the obese phenotype is associated with depressive-like behavior, or at the very least, that a 3-week withdrawal period was long enough to ameliorate, and not potentiate, the depressive-like behavior.

A highly palatable diet may alleviate the depressive-like state emerging from the stress of early-life maternal separation. Following prolonged maternal separation and access to a highly palatable diet, rats exhibited significantly lower immobility times in forced swimming tests (Maniam and Morris, 2010a; Kim et al., 2015) than controls, suggesting consumption of highly palatable food may be helpful to alleviate depressive-like states that arise from stressful experiences.

Tail suspension test

Similar to the forced swim test, the tail suspension test can be used in mice to assess depressive-like behavior through analysis of time spent immobile when suspended upside down by the tail (Cryan et al., 2002). Rats have exhibited increased immobility in this test during withdrawal from amphetamine (Cryan et al., 2003). Increased immobility time was used as an index of depressive-like behavior. Continuous HSD access resulted in increased immobility in the tail suspension test after 1 week of withdrawal from the palatable food (Kim et al., 2018). However, in a group of ‘reinstated’ mice that were also given 1 week of withdrawal from the HSD (10% sucrose solution), but then allowed access to a 2% sucrose solution for 2 days, there was no evidence of a depressive-like state (Kim et al., 2018).

Emergence of a negative affect

Withdrawal from a palatable diet is associated with the emergence of a negative emotional state; and compulsive eating may reflect an attempt to reduce anxiety and improve mood (Parylak et al., 2011; Moore et al., 2017b). To assess the emergence of a negative emotional state in animals, tests for anxiety-like behavior can be performed, and in intermittent access conditions, be compared across phases of palatable food access and withdrawal. There are many iterations of unconditioned anxiety tests assessed in animal models of compulsive eating. All anxiety tests described here are exploration-based, simulate conditions that occur in nature, and create a conflict of rodents' innate desire to explore novel environments with their innate aversion to bright and open environments (Campos et al., 2013). The elevated plus-maze, light/dark box, defensive withdrawal, and open field tests all assess anxiety through placing animals in an illuminated open space that usually contains a dark and/or enclosed area for animals to retreat to in order to avoid the bright and open environment.

Elevated-Plus Maze

The elevated plus-maze (EPM) is a plus-shaped apparatus with two "open" (no walls and brightly lit) arms and two "closed arms" (walled and dimly lit). In the EPM test, increased anxiety-like behavior is operationalized as lower amounts of time spent in the open arms. In models of drug addiction, rats with a history of chronic drug exposure spent less time in the open arms (i.e. higher anxiety-like behavior) while in withdrawal from alcohol (Bhattacharya et al., 1995; Knapp et al., 2004), methamphetamine (Nawata et al., 2012), cocaine (Sarnyai et al., 1995; Hall et al., 2010), opiates (Schulteis et al., 1998; Zhang and Schulteis, 2008), nicotine (Bhattacharya et al., 1995), and benzodiazepines (File et al., 1987; Bhattacharya et al., 1995). Rats in withdrawal from intermittent-long HSD access (Cottone et al., 2008b; Cottone et al., 2009a; Cottone et al., 2009b) or continuous HFSD access (Sharma et al., 2013) display decreased open-arm time in the EPM (i.e. increased anxiety-like behavior). Furthermore, upon restored access to palatable food, open-arm time increased to control levels, suggesting palatable food can relieve the negative emotional state brought on by withdrawal (Iemolo et al., 2012; Sharma et al., 2013). There is evidence that after protracted withdrawal (4 days), rats with prior intermittent-long HSD access no longer show spontaneous anxiety-like behavior in the EPM (Blasio et al., 2013).

Other studies using intermittent-long HSD (Blasio et al., 2014) and HFD (Rossetti et al., 2014) access models did not find increased anxiety-like behavior as assessed by the EPM. This could be explained by protocol differences, where Blasio et al. (2014) used a schedule of intermittent access that may not be sufficient to induce a spontaneous negative emotional state in female rats (cycles of 2 days of standard chow, 1 day of palatable food). While Rossetti et al. (2014) attributed these negative results to a potential floor effect, in Blasio et al. (2014), anxiety-like behavior was precipitated by systemic administration of rimonabant, an antagonist/inverse agonist of cannabinoid type-1 (CB(1)) receptor.

An animal model of intermittent HSD access and food restriction (12h access, 12h food deprivation) exhibited a pharmacologically-precipitated anxiety-like state, shown by decreased open-arm time (Colantuoni et al., 2002). In another experiment with intermittent-short HSD access that occurred for only 10 minutes daily (Cottone et al., 2008b), rats showed decreased open-arm time (increased anxiety-like behavior) that negatively correlated with the amount of palatable food eaten (Cottone et al., 2008b).

In rats that underwent maternal separation stress during early life, access to a highly palatable diet resulted in greater time spent in the open arms of an EPM compared to stressed controls with only access to a chow diet (Maniam and Morris, 2010b; Maniam and Morris, 2010a; Marcolin Mde et al., 2012; Lalanza et al., 2014; Kim et al., 2015). Thus, the consumption of a highly palatable diet effectively reduced anxiety-like behavior elicited by an early-life stressor.

Light/Dark Box

The light/dark box test utilizes a two-compartment chamber divided into “light” (illuminated) and “dark” compartments. Longer latencies to enter the light compartment, and lower amounts of total time spent in the light compartment reflect increased anxiety-like behavior. Withdrawal from chronic drug use in mice has been shown to increase latency to enter the light compartment and decrease the time spent in the light compartment (Singh et al., 1992; Timpl et al., 1998). Intermittent-long HSD access rats in withdrawal spent significantly less time in the light compartment than controls, providing further evidence that withdrawal from intermittent HSD access can induce anxiety (Iemolo et al., 2013).

Defensive Withdrawal

Anxiety-like behavior in the defensive withdrawal test is defined by 1) longer latencies to emerge from an opaque withdrawal chamber located in an illuminated open field and 2) shorter durations of time spent in the open field, outside of the chamber (Cottone et al., 2009b). Rats exhibited both components of anxiety-like behavior following precipitated withdrawal from benzodiazepines (Skelton et al., 2007). Withdrawal from intermittent HSD access resulted in longer latencies and shorter time spent outside the chamber compared to controls, indicating greater anxiety-like behavior (Cottone et al., 2009b). Another study using intermittent-long HSD access found no spontaneous anxiety-like behavior, in protracted withdrawal (Blasio et al., 2013). However, in the same study, anxiety-like behavior in the defensive withdrawal test could be pharmacologically precipitated by either systemic administration or site-specific microinfusion of rimonabant into the central nucleus of the amygdala, in rats protractedly withdrawn from palatable food (Blasio et al., 2013).

Open Field Test

In an open field test, rodents are placed in the center of an illuminated box where decreased time spent in the center of the field and increased fecal boli production during the test are used to measure anxiety-like behavior (Teegarden and Bale, 2007; Sharma and Fulton, 2013). Decreased fecal boli production has been observed in rats in withdrawal from chronic amphetamine exposure (Lynch and Leonard, 1978). Mice in withdrawal from continuous HFD or HFSD access exhibited anxiety-like behavior, which was displayed as less time spent in the center (HFD) (Sharma and Fulton, 2013) or higher fecal boli production (HFSD) (Teegarden and Bale, 2007) compared to groups fed only standard chow. A modified version of the open-field test, in which a novel object is placed in the center following a habituation period, can also be used to assess anxiety-like behavior. Intermittent-long HSD access rats showed a reduced time in the open field, and a reduced, but not significant, amount of time spent exploring the novel object (both considered measures of anxiety-like behavior) (Rossetti et al., 2014).

There is also some evidence that palatable food may ameliorate anxiety-like behavior, as assessed by the open field test. Rats with a history of early-life maternal separation exhibit less center-time in the open field compared to non-stressed controls. However, if rats were given access to a highly palatable diet, they spent more time in the center of open fields compared to chow-fed controls with similar separation (Marcolin Mde et al., 2012; Lalanza et al., 2014). This suggests the consumption of highly palatable food can reverse anxiety-like behavior arising from early-life stress.

Overeating despite negative consequences

Animal models of compulsive eating, similar to models of drug addiction, show persistent and enduring palatable food-seeking and eating in the face of aversive conditions, or the threat of aversive conditions (Belin et al., 2008; Heyne et al., 2009; Oswald et al., 2011; Di Segni et al., 2014). Animals will continue to consume palatable food in the presence of either a conditioned or an unconditioned aversive stimulus. The light/dark conflict test, conditioned suppression of feeding procedure, punishment-induced suppression of intake procedure, and footshock maze require animals to experience an aversive physical environment or stimulus, or a cue that signals an aversive stimulus, in order to acquire the palatable food reward.

Light/Dark Conflict Test

In the light/dark conflict test, animals are placed in the light compartment of a light/dark box, which contains a cup of palatable food (Cottone et al., 2012; Dore et al., 2014; Velazquez-Sanchez et al., 2014). Under normal circumstances, eating would be suppressed in the brightly lit, aversive compartment; thus palatable food consumption in this context is defined as compulsive-like eating behavior. This test was specifically developed to measure compulsive eating, rather than having been adapted from a test of compulsive drug use, thus no light/dark conflict tests have been performed on models of drug addiction at this time.

In animal models with intermittent-long and intermittent-short HSD access, rats show increased compulsive-like eating in the light/dark conflict test (Cottone et al., 2012; Dore et al., 2014; Smith et al., 2015). Rats with intermittent-short HSD access that were found to be more impulsive ate signficantly more palatable food than low-impulsive rats with intermittent-short HSD access history (Velazquez-Sanchez et al., 2014). This suggests that palatable food can interact with underlying impulsive traits to potentiate compulsive-like eating (Velazquez-Sanchez et al., 2014). In a model of intermittent HSD access, proneness to binge eating was associated with significantly higher palatable food consumption in the light/dark conflict test than resistance to binge eating in rats (Calvez and Timofeeva, 2016). Lastly, in an investigation into the *Cyfip2* gene’s influence on compulsive-like eating, *Cyfip2* heterozygous knockout (1 copy of the *Cyfip2* allele) and wild-type mice were tested in the light/dark conflict test (Kirkpatrick et al., 2017). Wild-type mice with prior access to a HSD ate more palatable food compared to wild type controls with only access to standard chow; however, heterozygous *Cyfip2* knockout mice with a history of HSD access did not show compulsive-like eating (Kirkpatrick et al., 2017). This finding suggests that compulsive eating behaviors arise from interactions between genetic factors and palatable diet exposure.

Footshock Maze

A novel paradigm created by Oswald et al. (2011) assessed motivation for palatable food despite punishment using a footshock maze. Similarly to the light/dark conflict test, the footshock maze was developed to investigate compulsive eating specifically; thus, it has not been used in any animal studies of drug addiction. In this procedure, a sated rat is placed in an apparatus with two arms, one containing standard chow without footshocks, and the other arm containing palatable food with footshocks (Oswald et al., 2011). Palatable food consumption and tolerance of increasing footshock intensities were used as measures of compulsive-like eating (Oswald et al., 2011). BEP rats with intermittent-short HFSD access showed significantly higher HFSD consumption and tolerated higher intensities of footshock compared to BER rats with similar diet access history (Oswald et al., 2011). This suggests individual differences in binge-eating tendencies, not history of diet access, can affect compulsive-like eating (Oswald et al., 2011).

Punishment-induced Suppression of Intake

Punishment-induced suppression of intake tests pair an aversive unconditioned stimulus (e.g. footshock) with a self-administered food reward (Rossetti et al., 2014). Food intake is considered to be suppressed when animals consume less of the palatable diet in the presence of the aversive stimulus, compared to their palatable diet consumption without this punishment. Cocaine intake remained unchanged despite punishment with footshocks in rats with a history of chronic cocaine self-administration (Pelloux et al., 2007; Belin and Everitt, 2008). Rats with prior intermittent-long access to a palatable diet continued food-seeking behavior (i.e. lever presses) in spite of footshocks, whereas food-seeking behavior was suppressed in controls (Rossetti et al., 2014). This persistent behavior demonstrates that intermittent exposure to a highly palatable diet can promote compulsive-like eating behavior.

The addition of quinine to the palatable diet to adulterate its taste has also been used as a punishment to suppress intake (Heyne et al., 2009). Animal studies of drug and alcohol addiction have used quinine adulteration to assess compulsive drug use. Addiction to opiates, dextroamphetamine, or alcohol in rats has been shown to cause similar consumption of their quinine-adulterated drug of addiction compared to their unadulterated drug consumption (Wolffgramm and Heyne, 1991; Heyne, 1996; Heyne and Wolffgramm, 1998). Obese rats with 8 weeks of continuous HFSD access showed either one of two distinct feeding behaviors when given standard chow and quinine-adulterated HFSD (Heyne et al., 2009). Rats either consumed amounts of quinine-adulterated HFSD similar to their unadulterated HFSD consumption or did not eat any of the presented diets (Heyne et al., 2009). This finding suggests that compulsive-like eating behaviors may be related to the taste of palatable food and/or to the fat/carbohydrate content of palatable food (Heyne et al., 2009).

Conditioned Suppression of Feeding Behavior

Conditioned suppression of feeding behavior tests pair an aversive/punishing unconditioned stimulus (e.g. footshock) with a harmless conditioned stimulus (e.g. light, noise) (Di Segni et al., 2014). Compulsive-like eating behavior is operationally defined as continued food seeking and/or consumption in the presence of the conditioned stimulus in this test (de Jong et al., 2013; Di Segni et al., 2014; Rossetti et al., 2014). Long-access to cocaine has been shown to cause resistance to the suppression of cocaine seeking compared to short-access controls (Vanderschuren and Everitt, 2004).

Johnson and Kenny (2010) found rats with continuous HFSD access, but not intermittent-short HFSD access, displayed resistance to conditioned suppression of food intake. Velazquez-Sanchez et al. (2015) found intermittent-short HSD access produced compulsive-like responding in a conditioned suppression test. One potential explanation for these discrepant findings could be the type of diet used in the procedure (HSD vs. HFSD) or the differences in procedures used for palatable food access (home-cage vs. operant self-administration). Self-administration under a fixed-ratio schedule has been shown to promote habitual responding (Dickinson et al., 1983), which could contribute to the development of other kinds of compulsive-like eating, including resistance to conditioned suppression of intake seen by Velazquez-Sanchez et al. (2015).

DISCUSSION AND CONCLUSIONS

A systematic investigation of the construct of compulsivity in the context of feeding behavior has started only recently (Figure 1), leaving a gap in knowledge and missed opportunities to better understand the neurobiological mechanisms of aberrant feeding behaviors (Cottone et al., 2009a; Cottone et al., 2012; Moore et al., 2017b; Moore et al., 2017a; Moore et al., 2018). At a preclinical level, this gap has been particularly profound, given that historically the motivational, emotional, and cognitive aspects related to eating behavior have been depreciated in favor of a biased energy-homeostatic view of feeding-related disorders. The scientific community has already paid a high cost for this oversight. Only a decade ago, the antagonist of the cannabinoid receptor 1, rimonabant, was introduced in the market as a highly promising anti-obesity drug, because of its ability to reduce homeostatic feeding and food reward centrally, as well as metabolism and energy expenditure peripherally (Matias and Di Marzo, 2007). However, rimonabant was swiftly removed from the market following evidence of adverse psychiatric effects, including depression, anxiety, and suicidality (Christensen et al., 2007; Blasio et al., 2013). After a decade, the lesson learned from rimonabant’s failure is that dissociating energy-homeostatic feeding from higher order emotional, motivational, and cognitive constructs can be risky. In this process, animal research plays a critical role. At the preclinical level, the battle against the epidemics of obesity and eating disorders needs to be brought to the next level through the integration of measures of complex behavioral constructs (e.g. negatively reinforced feeding, food craving, salience of food-related cues, food seeking, eating in spite of negative consequences, habitual/inflexible feeding/responding, stress/cues/primed food relapse). Retuning the methodological approach will be essential to understand the complex mechanisms underlying the maladaptive forms of food intake in obesity and eating disorders.

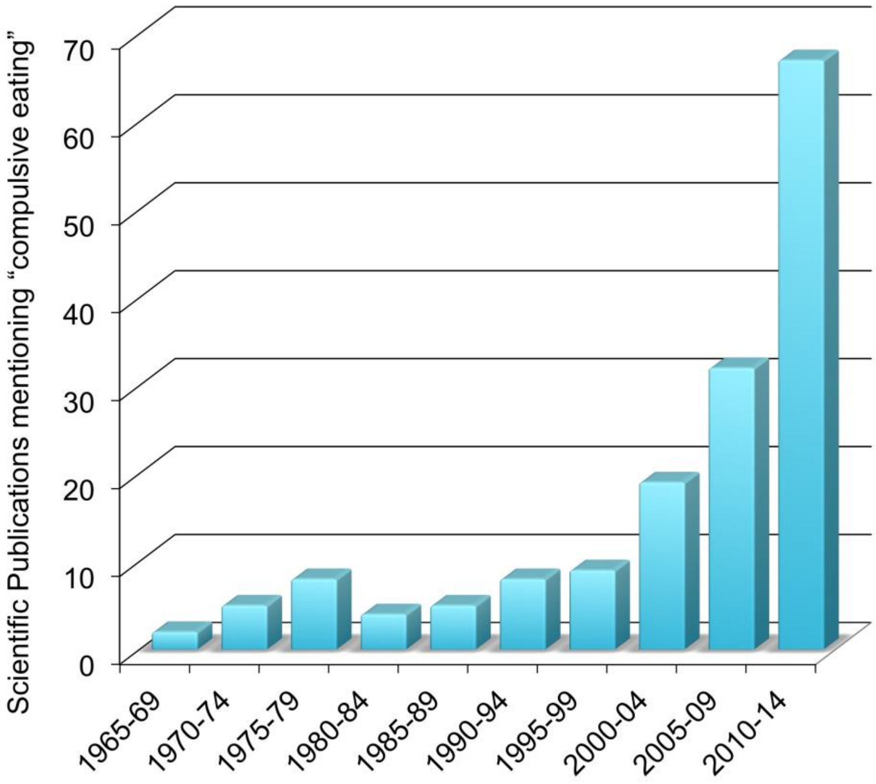

Figure 1: Number of scientific publications on "compulsive eating" during the years 1965-2014. Values obtained by a Web of Science search for each 5-year block, beginning with 1965, which is the earliest year included in the Web of Science Core Collections. Searches used the search term "compulsive eating" and selecting "topic" (which searches the title, abstract, and keywords within a record).

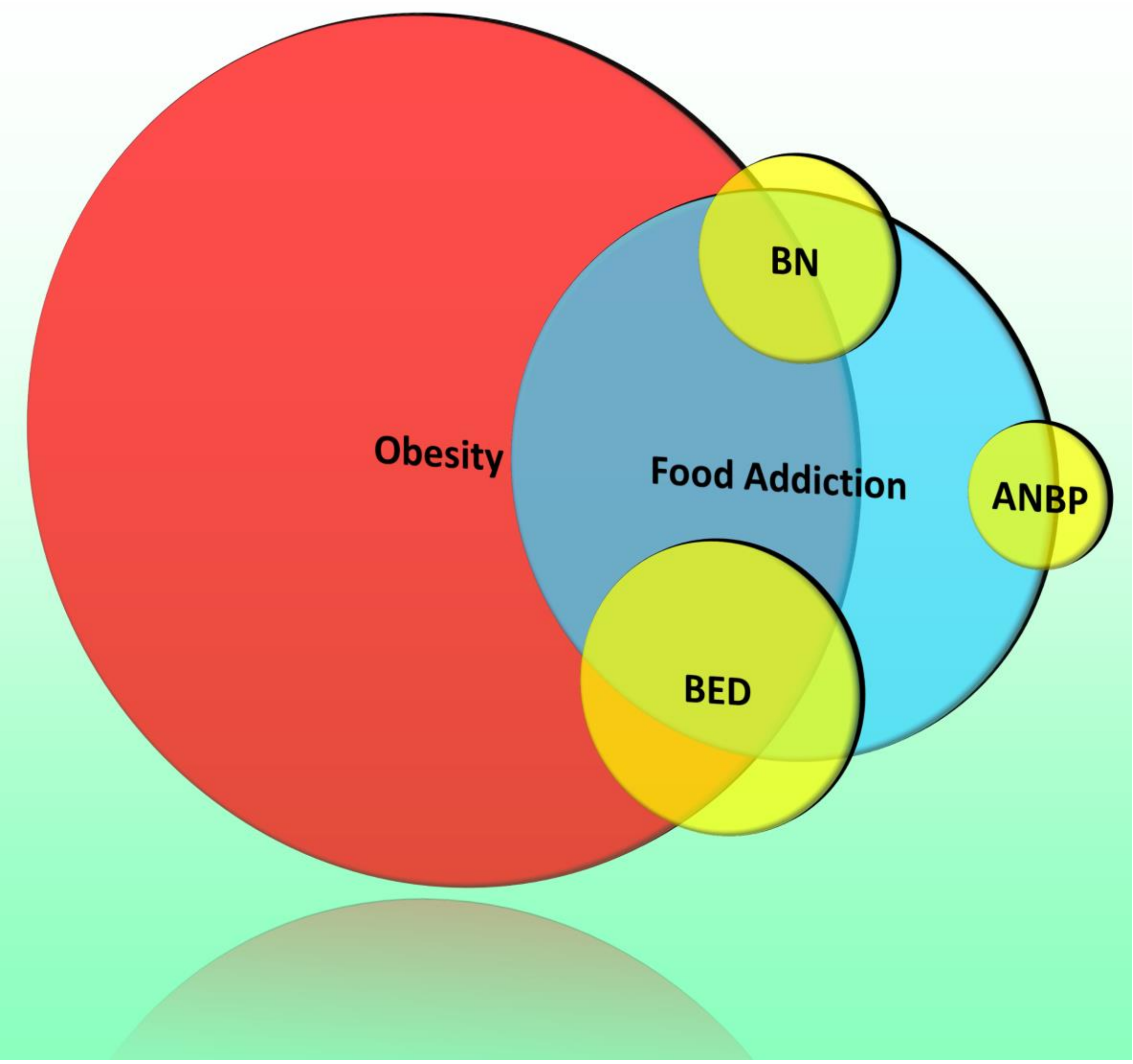

Figure 2: Comorbidity among obesity and the following eating disorders: Food Addiction, Binge-Eating Disorder (BED), Anorexia Nervosa Binge/Purge Subtype (ANBP), and Bulimia Nervosa (BN).

Diagnostic Criteria	Reference
A. Recurrent episodes of binge eating. a. An episode of binge eating is characterized by both of the following: i. Eating, in a discrete period of time (e.g., within any 2-hour period), an amount of food larger than what most people would eat under similar circumstances. ii. Lack of control over eating (e.g., a feeling of being unable to stop eating or control what or how much one is eating). B. Binge-eating episodes are associated with ≥ 3 of the following: a. Eating much more rapidly than normal. b. Eating until feeling uncomfortably full. c. Eating large amounts of food when not feeling physically hungry. d. Eating alone because of feeling embarrassed by how much one is eating. e. Feeling disgusted with oneself, depressed, or very guilty afterward. C. Marked distress regarding binge eating is present. D. On average, binge eating occurs at least weekly for 3 months. E. Binge eating is not associated with recurrent inappropriate compensatory behavior as in bulimia nervosa and does not occur exclusively during either bulimia nervosa or anorexia nervosa.	Diagnosis of BED requires all 5 criteria to be met (APA, 2013)

Table 1: Diagnostic Criteria for BED (DSM-V)

Diagnostic Criteria	Reference
A. Recurrent episodes of binge eating. a. An episode of binge eating is characterized by both of the following: i. Eating, in a discrete period of time (e.g., within any 2-hour period), an amount of food that is definitely larger than what most individuals would eat in a similar period of time under similar circumstances. ii. Lack of control over eating during the episode (e.g., a feeling that one cannot stop eating or control what or how much one is eating).	Diagnosis of BN requires all 5 criteria to be met (American Psychiatric Association, 2013)
B. Recurrent inappropriate compensatory behaviors to prevent weight gain, such as self-induced vomiting; misuse of laxatives, diuretics, or other medications; fasting; or excessive exercise.	
C. Binge eating and inappropriate compensatory behaviors both occur, on average, at least once a week for 3 months.	
D. Self-evaluation is unduly influenced by body shape and weight.	
E. The disturbance does not occur exclusively during episodes of anorexia nervosa.	

Table 2: Diagnostic Criteria for BN (DSM-V)

Diagnostic Criteria	Reference
A. Restriction of energy intake relative to requirements, leading to a significantly low body weight in the context of age, sex, developmental trajectory, and physical health. a. *Significantly low weight*: weight that is less than minimally normal for adults, or less than minimally expected for children and adolescents. B. Intense fear of gaining weight or of becoming fat, or persistent behavior that interferes with weight gain, even though at a significantly low weight. C. Disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or persistent lack of recognition of the seriousness of the current low body weight. D. Binge-eating/Purging Type: a. Recurrent episodes of binge eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas) within the past 3 months.	Diagnosis of ANBP requires all 4 criteria to be met (American Psychiatric Association, 2013)

Table 3: Diagnostic Criteria for ANBP (DSM-V)

Type	Diagnostic Criteria	Reference
Adult Obesity	A. Class 1 (Moderate Risk): $30 \leq BMI < 35$ B. Class 2 (Severe Risk): $35 \leq BMI < 40$ C. Class 3 (Very Severe Risk): $BMI \geq 40$	Class corresponds to risk of developing adverse health conditions from fat accumulation (Pi-Sunyer et al., 1998; Deurenberg and Yap, 1999).

Table 4: Diagnostic Criteria for Obesity

Diagnostic Criteria	Reference
A. Consumed more food than planned B. Unable to cut down or stop C. Great deal of time spent D. Important activities given up E. Use despite physical/emotional consequences F. Tolerance G. Withdrawal H. Craving I. Failure in role obligation J. Use despite interpersonal/social consequences K. Use in physically hazardous situations L. Impairment or distress	‘Mild’ = 2-3 symptoms ‘Moderate’ = 4-5 symptoms ‘Severe’ = ≥ 6 symptoms (Gearhardt et al., 2016)

Table 5: Diagnostic Criteria for Food Addiction (YFAS Version 2.0)

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CURRICULUM VITAE

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