

Review Article – Food Addiction: Fact or Fiction? – the NeuroFAST Project

Towards an Animal Model of Food Addiction

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Animal models • Food • Motivation • Psychiatric aspects • Obesity • Addiction

Abstract

The dramatically increasing prevalence of obesity, associated with potentially life-threatening health problems, including cardiovascular diseases and type II diabetes, poses an enormous public health problem. It has been proposed that the obesity epidemic can be explained by the concept of 'food addiction'. In this review we focus on possible similarities between binge eating disorder (BED), which is highly prevalent in the obese population, and drug addiction. Indeed, both behavioral and neural similarities between addiction and BED have been demonstrated. Behavioral similarities are reflected in the overlap in DSM-IV criteria for drug addiction with the (suggested) criteria for BED and by food addiction-like behavior in animals after prolonged intermittent access to palatable food. Neural similarities include the overlap in brain regions involved in food and drug craving. Decreased dopamine D2 receptor availability in the striatum has been found in animal models of binge eating, after cocaine self-administration in animals as well as in drug addiction and obesity in humans. To further explore the neurobiological basis of food addiction, it is essential to have an animal model to test the addictive potential of palatable food. A recently developed animal model for drug addiction involves three behavioral characteristics that are based on the DSM-IV criteria: i) extremely high motivation to obtain the drug, ii) difficulty in limiting drug seeking even in periods of explicit non-availability, iii) continuation of drug-seeking despite negative consequences. Indeed, it has been shown that a subgroup of rats, after prolonged cocaine self-administration, scores positive on these three criteria. If food possesses addictive properties, then food-addicted rats should also meet these criteria while searching for and consuming food. In this review we discuss evidence from literature regarding food addiction-like behavior. We also suggest future experiments that could further contribute to our understanding of behavioral and neural commonalities and differences between obesity and drug addiction.

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Introduction

The obesity epidemic has become a major threat to public health with 1 in 3 individuals being obese in the USA [1]. Obesity and its comorbidities that include cardiovascular disease, type 2 diabetes and several cancers are now the number one preventable cause of premature death in the USA [2]. The notion that food addiction may contribute to the high prevalence of obesity is gaining attention among scientists and mental health professionals [3–5]. To further investigate the addictive potential of food and its neurobehavioral underpinnings, an animal model of food addiction is essential. In this paper, we will briefly discuss behavioral and neurobiological similarities between overeating and drug addiction before we address the main question of this article: ‘What is a valid animal model to determine whether food addiction exists and if so, whether it resembles drug addiction on a neurobiological level?’ We will briefly highlight several useful, widely employed models from the drug addiction field on which we base our proposed model to study food addiction.

Although the overarching aim of our research is to understand the neural and behavioral mechanisms of obesity in general, we here focus on binge eating disorder (BED) because of its high prevalence (2.0% in males and 3.5% in females [6]) and possible behavioral resemblance to addiction. Clearly, similar arguments may be used to link addiction to other eating disorders or obesity in general [5]. We are, indeed, well aware of the fact that not all cases of obesity are caused by BED, that BED and obesity are not synonymous, and that BED and obesity have a distinct, if overlapping, neurobiological background [7].

Although it has become very prominent in recent years, the question whether overeating is a form of addiction is not new. Previously, several authors have theorized about whether food (or food components) can have addictive qualities, akin to drugs of abuse [3, 5, 8, 9]. Proponents point out that both obesity and addiction involve similar neurobiological substrates and that there are several clinical and behavioral similarities. Opponents, on the other hand, indicate that addiction and overeating have a distinct etiology and that their treatment requires different strategies. Should food indeed be able to induce addiction-like behavior in vulnerable individuals, then this can have far-reaching consequences for the prevention and treatment of obesity. Obesity prevention programs could, for example, benefit from the success achieved by anti-smoking campaigns in Europe and North America, and potential treatments for obesity could include addiction treatments such as pharmacological interventions, cognitive behavioral therapy, and 12-step programs (although a 12-step program for obesity can, of course, not aim for complete abstinence of food) [10].

Similarities between BED and Addiction in Humans

BED is an eating disorder characterized by recurrent episodes of uncontrolled eating (binges). It is highly prevalent in obese individuals [11]. BED differs from other eating disorders in that no effort is made to compensate for the excess of energy intake by purging or intense exercise [12]. BED is currently not described in the DSM-IV itself, but in its appendix B which deals with possible new diagnostic categories. Suggested diagnostic criteria for BED are listed in table 1. An analysis of the DSM-IV criteria reveals similarity with drug addiction (which is termed substance dependence in the DSM-IV). Note, however, that the potential DSM criteria for BED remain subject to debate [13, 14].

According to DSM-IV [12], substance dependence is diagnosed when 3 of 7 criteria listed in table 1 have been met. The occurrence of either withdrawal symptoms or tolerance is indicative of physical dependence to drugs. Although physical dependence may not be a useful concept in the context of obesity, since all animals are physically dependent on food,

Table 1. Diagnostic criteria for addiction (as defined in the DSM-IV) and the corresponding diagnostic criteria for BED

Substance dependence (addiction)	BED
Withdrawal symptoms	
Tolerance	
Taken larger amount and longer than intended	During episodes: a sense of lack of control Eating until uncomfortably full Eating large amounts of food when not feeling hungry Eating larger than normal amounts in a short period of time
Persistent desire, repeated unsuccessful attempts to quit	
Much time spend to obtain, use and recover from use	Binge eating occurs at least two days per week
Social, occupational or recreational activities given up in favor of use	Eating alone because being embarrassed by how much one is eating
Continued use despite knowledge of adverse consequences	Marked distress regarding binge eating is present Feeling disgusted with oneself, depressed or very guilty after overeating The binges are not associated with any type of compensatory mechanism such as purging

it has been shown in animal experiments that tolerance and withdrawal may arise after extended intermittent access to palatable food, as will be discussed in the following sections [15–18]. The remaining five DSM-IV criteria for substance dependence relate to loss of control over drug intake. As can be seen in table 1, some of the criteria for BED markedly overlap with criteria for addiction, and loss of control over food intake is also a major element in BED. For one, in both drug addiction and BED the subject persists in destructive food- or drug-directed behavior while consciously aware of its deleterious consequences [12].

Table 1 lists the diagnostic criteria for addiction (according to DSM-IV) and the corresponding diagnostic criteria for BED. This approach is based on Volkow and O'Brien [5], who designed a similar table comparing addiction to obesity in general.

Behavioral Similarities

As can be gleaned from table 1, addiction shares several behavioral characteristics with overeating, and especially with BED. In both drug addiction and BED, subjects lose control over intake [19]. Gearhardt et al. [20] have recently developed a questionnaire, the Yale Food Addiction Scale (YFAS), to assess food addiction. The group of individuals that scored high on the YFAS also scored high on measures for BED, childhood attention deficit/hyperactivity disorder (ADHD), and severe depression [21]. It is interesting to note that ADHD and depression have also been associated with substance dependence [22–26].

Not all individuals exposed to drugs of abuse (or palatable food) lose control over behavior. Highly addictive drugs like cocaine are used on a regular basis in certain environments, but not all involved individuals become addicted [27, 28]. The same is, of course, true

for palatable food. The entire western population is exposed to an environment where palatable (energy-dense) food is constantly available, but only a subgroup of individuals will lose control over food intake and become obese and/or develop BED. Several risk factors for addiction have been identified, including genetic factors (reviewed in [29]), and impulsivity.

Individuals displaying high levels of impulsivity have an increased risk to become addicted to drugs and to develop obesity [30–35]. Interestingly, the relationship between addiction and impulsivity is bidirectional, as indicated by the fact that prolonged exposure to drugs results in impaired impulse control [32, 36]. It has been shown that impulsivity is a predictor of the treatment outcome in obese children [34, 35, 37, 38] and in addiction [39–43]. One potential behavioral mechanism underlying the relationship between impulsivity and addiction is the fact that impulsive individuals can be more sensitive to immediate gratification (in fact, intolerance to delay of reward is a prominent form of impulsivity) and less sensitive to long-term adverse consequences of behavior, which may contribute to losing control over food and/or drug intake.

Neurobiological Similarities

Both food and drugs can be the subject of intense craving. Below, we discuss several examples of functional neuroimaging studies investigating food and drug craving, the neural substrates of which display remarkable overlap. For an extensive review on the neurocircuitry of drug craving and addiction see [44, 45].

In studies of food and drug craving, measures of brain activity have been obtained using either positron emission tomography (PET) [46] or functional magnetic resonance imaging (fMRI) [47, 48]. In these studies, craving was provoked using a visual presentation of the craved substance [48], a tactile drug cue (e.g. a marijuana pipe, as used by Filbey et al. [47]), or a verbal recount of a drug-related experience of the participant (Kilts et al. [46]).

Several studies have shown involvement of the orbital frontal cortex (OFC), prefrontal cortex (PFC), anterior cingulate, nucleus accumbens, amygdala, and insula in drug craving [46–49]. These regions involved in drug craving likely also mediate craving for natural rewards, including sex [50] and food [48]. Indeed, there is striking overlap between the regions activated during drug and food craving, since the insula, nucleus accumbens, anterior cingulate, amygdala, and OFC have also been implicated in food craving. When craving was self-induced by subjects, increased activity was found in the hippocampus, caudate, and insula [51]. Craving for chocolate (using pictures of chocolate or letting participants taste chocolate) has been associated with increased activity in the ventral striatum, subgenual cingulate, and OFC [52].

Suppression of craving, which will aid in remaining in control over intake, involves the dorsolateral PFC (DLPFC), which has been widely implicated in cognitive control over behavior [53]. When subjects were asked to suppress food or tobacco craving, activity in the accumbens, VTA, amygdala, and cingulate cortex decreased while activity in the DLPFC increased [48]. Interestingly, both the fMRI data and the behavioral (craving) data from this study showed striking similarities in the modulation of craving for drugs and food. The DLPFC was implicated in food addiction in a study by Gearhardt et al. [54] that investigated the neural correlates of food addiction as measured with the recently developed YFAS scale (see above). This study found increased activation in the DLPFC as well as in the caudate in individuals with a high food addiction score, during the anticipation of the receipt of palatable food. The role of the DLPFC in eating disorders has been explored in a clinical study in which participants with bulimic disorders were exposed to repetitive transcranial stimulation (TMS) of the DLPFC. These patients reported decreased craving immediately after TMS and fewer binge eating episodes in the 24 h following TMS, as compared to patients who received sham TMS [55]. Thus, craving for food and drugs appears to involve comparable neural substrates [56].

Table 2. Measuring addiction-like behavior

What to measure?	How to measure?
Tolerance	cross-tolerance with opioids, increased self-stimulation threshold Drugs: [97, 99] (among many others) Food: [19, 93, 98]
Withdrawal	observing withdrawal symptoms, e.g. teeth chattering and increased anxiety drugs: [126] (among many others) food: [16,18]
Extremely high motivation	progressive ratio schedule, in which animals have to exert increasingly more work to obtain a reward drugs: [76, 112–114] food: [117, 118]
Difficulty limiting intake	limited access paradigm, in which seeking responses during signaled non-availability are measured drugs: [71] food: [119]
Continued use despite harmful consequences	reward seeking associated with (conditioned) punishment drugs: [70, 71, 74] food: [98, 122–124]

Regarding similarities in the neurobiological background of food and drug addiction, dopamine D2 receptor (D2R) availability may play a role in both [10]. Indeed, PET studies have shown decreased D2R availability in the striatum in both drug-addicted individuals and morbidly obese patients [10, 57–59]. An explanation for these findings is that decreased D2R availability results in a hypofunctioning reward system, and ‘addicted’ individuals compensate for this effect by consuming large amounts of rewarding substances such as food and drugs. The question remains whether this decreased D2R availability is an effect or the cause of addiction. Apart from the animal studies investigating this question (discussed in the following sections), there is some human data correlating genetic predisposition with decreased D2R availability and reward hypofunction in obesity [60] and addiction [61], but not necessarily with BED [7]. There is also evidence to suggest that decreased D2R density in the striatum both contributes to the development of addictive behavior [62–65], and is a consequence of prolonged drug use [66, 67]. Human studies have shown that decreased D2R availability in the striatum can be a predictor of self-reported ‘liking’ of an intravenous injection of methylphenidate [64, 65]. Conversely, decreased D2R availability was shown to be a consequence of prolonged drug use in studies investigating cocaine self-administration in non-human primates [66, 67].

Brain opioid neurotransmission is also involved in drug addiction and BED. Opioids play an important role in hedonic appreciation (‘liking’) of food, and they have particularly been implicated in the intake of palatable food [68, 69]. The opioid receptor antagonist naloxone reduces appetite, in particular in patients with a history of bingeing [70, 71]. In addition, there is an increased prevalence of the A118G polymorphism of the μ -opioid receptor in BED patients [7]. This indicates an important role for the opioid system in BED, mimicking its

role in drug addiction, where the μ -opioid receptor has been shown to mediate the rewarding aspects of opioids, ethanol, nicotine, and probably psychostimulants (as reviewed in [72]). Furthermore, the opioid system has been implicated in withdrawal for both drugs and food, as discussed in the following sections.

Animal Models of Drug Addiction

There has been a plethora of experiments investigating several aspects of drug addiction, including the motivation to obtain a drug and the process of relapse to drug seeking after extinction of self-administration [73, 74]. This has tremendously contributed to our understanding of the neural and behavioral underpinnings of drug seeking and taking [44, 45, 75]. In this review, we focus on recently developed animal models that incorporate multiple DSM-IV criteria to identify animals that express addiction-like behavior.

Animals will readily self-administer and respond at high levels for food or drugs of abuse [74, 76], but being extremely motivated to obtain a reward is only one aspect of the addiction syndrome [12]. Experimental approaches of addiction, or loss of control over intake (see below), also involve setups in which seeking and/or taking rewards is met with aversive consequences. Examples of such approaches include punishing reward seeking with mild electric shock [77, 78], adulterating an ingested reward with the bitter-tasting quinine [79–81], or exposing the animal to a cue that has previously been associated with electric shock [82]. In addition, models for compulsive drug use usually take two more points into account. First, addiction develops after chronic drug use. Although a drug may be rewarding and evoke motivated behavior on initial contact, loss of control and compulsive behavior only arises after prolonged excessive drug use [79–83]. Second, there is substantial variability in the susceptibility to addictive behavior in animals and humans. Thus, even after extended access to a reward, only a subgroup of the exposed individuals (humans or animals) will lose control over intake [28, 77, 78, 84, 85]. Several studies have tried to identify neural or behavioral traits that predict whether or not an individual is likely to lose control over intake and become addicted.

The pioneering work by Piazza et al. [86] identified so-called ‘high’ and ‘low’ responders to novelty, in which high responders showed a stronger psychomotor response to a novel environment. High responders acquired amphetamine self-administration faster than low responders and showed enhanced cocaine self-administration in a subsequent study [87]. Studies in recent years have focused on impulsivity as a predictive factor for addictive behavior (reviewed in [36, 88]). Thus, Dalley et al. [63] used the five-choice serial reaction time task to identify impulsive rats. They showed that impulsivity in this task predicts escalation of cocaine intake (but not heroin intake [89]). High impulsive rats also displayed decreased D2R availability in the ventral striatum. Belin et al. [85] subsequently showed that impulsive rats in the five-choice serial reaction time task were more prone to develop addiction-like behavior for cocaine when addiction criteria based on DSM-IV were used (see below). Interestingly, impulsivity did predict addiction-like behavior, but not acquisition of cocaine self-administration, whereas the locomotor response to novelty (which did not correlate with impulsivity) predicted the acquisition of cocaine self-administration, but not addiction-like behavior [85, 90]. Together, these studies [63, 85] also indicate that low D2R availability is a predictor of escalated cocaine use ultimately culminating in addictive behavior [67]. The predictive value of impulsivity for addictive behavior is supported by other studies demonstrating that enhanced impulsive behavior is associated with different aspects of cocaine, nicotine, and ethanol (but not heroin) self-administration [91–94]. Another approach to identify an addiction-susceptible subgroup of animals has been

developed by Ahmed and colleagues [84, 95]. These researchers used a choice paradigm to show that, even after chronic exposure to cocaine, 90% of all Wistar rats prefer a sweet saccharin solution over a cocaine infusion [84, 95, 96]. This appears in contrast to the behavior of addicted individuals who (by definition) sacrifice non-drug rewards (like palatable food or social interaction) in favor of drug-related activities [12]. Interestingly, about 10% of the animals in these studies did express a preference for cocaine over saccharin, which is comparable to the proportion of human cocaine users who will go on to meet the criteria for addiction. It remains to be demonstrated, of course, whether the 10% cocaine-preferring animals will also show ‘addiction-like’ behavior for cocaine.

Based on the DSM-IV criteria for substance dependence [12] and the research previously described, three criteria, that relate to escalated drug intake and the failure to exert control over intake [78], have been proposed for addiction-like behavior in animals. First: an extremely high motivation to seek the drug. Second: difficulty limiting drug intake. Third: continuation of drug seeking despite aversive consequences. Deroche-Gamonet et al. [78] showed that a subgroup of rats, after chronic cocaine self-administration, scored positive on these three criteria. These animals differ from addiction-resistant animals in that they are highly impulsive [85] and have a persistent impairment in NMDAR-mediated long-term depression in the nucleus accumbens [97]. In order to assess the functional similarity in drug and food addiction, a similar group of ‘food addiction-like behavior’-expressing animals should be identified. Subsequently, this group of ‘food-addicted’ animals can be compared to drug-addicted animals to evaluate whether or not the biochemical and cellular changes in food and drug addiction-like behavior are similar.

Models for Aspects of Food Addiction-Like Behavior and Neurochemical Changes Resembling Addiction

There is ample evidence from animal studies to suggest that addiction-like behavior for food exists. Here, we briefly review experimental models that can be used to capture food addiction-like behavior. We will first discuss the seven DSM-IV criteria for addiction. Five of these relate to loss of control over drug intake. Loss of control can be studied in animals using the, previously described, 3-criteria model designed by Deroche-Gamonet et al. [78]. We will therefore also discuss these 3 criteria and how they can be assessed.

Tolerance

In the context of drug addiction, tolerance refers to the fact that after repeated drug use a larger quantity of the drug is needed to obtain the desired subjective effect or that the (positive) effect of a given drug dose decreases with repeated drug use. Interestingly, after extended access to a palatable diet, it has been shown that rats indeed increase their food intake [98], although mechanisms other than tolerance could also explain this finding. There is also data to suggest the existence of cross-tolerance between sweet solutions and opioids [18, 99]. Reward tolerance has also been studied measuring reward thresholds in an intracranial self-stimulation setup. This reward threshold is defined as the minimum electrical current needed to maintain stable self-stimulation [100, 101]. Acute treatment with drugs of abuse lowers the reward threshold, indicative of the rewarding properties of drugs [102]. However, the reward threshold is increased during withdrawal after extended drug treatment, likely as a result of desensitization of brain reward pathways [101, 103]. A similar effect on self-stimulation thresholds has been demonstrated after withdrawal from a highly palatable ‘cafeteria style diet’ [104]. The increase in self-stimulation threshold after withdrawal from palatable food or drugs has been associated with decreased D2R activity [104, 105].

Withdrawal

Pioneering work of Hoebel and colleagues [16, 106] provided evidence for withdrawal phenomena in rats that were exposed to 12 h / 12 h cycles of food deprivation and access to a sweet solution. When denied access to sucrose, rats exposed to these diet cycles, will binge and display signs of withdrawal such as increased anxiety (as assessed in an elevated plus maze) and increased teeth chattering [15]. These withdrawal symptoms were shown to be inducible by treatment with the opioid receptor antagonist naloxone and to be associated with an increase in D1R and μ -opioid receptor binding and a decrease in D2R binding [15, 107]. A decrease in D2R binding following intermittent sucrose administration was also observed by others [108].

Withdrawal from drugs of abuse and the associated changes in behavior have been suggested to depend on activation of brain stress mechanisms [109]. Conversely, stress can play an important role in the development of overeating [110, 111]. Indeed, there is an important interaction between food binging and stress. Binge eating can be triggered by foot shock stress [112, 113] or the frustrating presence of an unreachable (but easily visible) palatable treat [114]. Food restriction itself is also stressful and this may promote binge eating [115]. In addition, animals withdrawn from intermittent access to palatable food show withdrawal signs (increased anxiety and motivational deficits) that are attenuated by treatment with a CRF receptor antagonist [17]. Stress is also widely used to reinstate extinguished drug seeking in an animal model of relapse to drug use [116, 117]. Intriguingly, in these models stress does not reinstate chow or sucrose seeking. This may indicate that mere sucrose self-administration does not result in the same behavioral changes as drug self-administration or intermittent palatable food intake coupled with food restriction does.

Extremely High Motivation to Obtain the Reward

A widely used method to measure the motivation to obtain food or drugs is the so-called progressive ratio schedule of reinforcement, in which animals have to make an increasing number of operant responses for every subsequent reward [76]. Indeed, after prolonged cocaine or heroin self-administration, the motivation for drugs under a progressive ratio schedule of reinforcement has been shown to increase [78, 118–120] (but see [121, 122]). Likewise, it has been shown that rats show an increased motivation to obtain a sucrose reward under a progressive ratio schedule after chronic exposure to a high-fat, high-sucrose (HFHS) choice diet [123]. Other studies have shown that limited (1 h, 3 days a week) access to fat also increases the motivation for food [124].

Difficulty Stopping Use or Limiting Intake

This aspect of addictive behavior can be investigated using a so-called ‘time-out’ model. In this paradigm, seeking responses are measured in a designated period of an operant self-administration session when the non-availability of a reward is explicitly signaled to the animals. It has been shown that rats, after extended access to cocaine, continue to seek cocaine when this is not available [78]. Likewise, Ghitza et al. [125] demonstrated that, with prolonged training, animals exposed to a palatable diet increase their food seeking responses during time-out periods, indicating that they develop a ‘difficulty limiting’ food seeking.

Continued Use Despite Adverse Consequences

Recent studies have demonstrated that this characteristic of addictive behavior also occurs in laboratory animals. Vanderschuren et al. [82] showed that, after prolonged (but not limited) cocaine self-administration, rats will continue to seek cocaine in the presence of an aversive conditioned stimulus (a tone previously paired with foot shock). However,

after prolonged sucrose self-administration, suppression of sucrose seeking by the foot shock conditioned stimulus still occurred. Comparable results were obtained in devaluation experiments (in which an ingested reward is paired with lithium chloride-induced illness). In these studies, sucrose seeking was sensitive to lithium chloride-induced devaluation, whereas responding to alcohol [126] or cocaine was not [127]. Again, these data show that self-administered sucrose does not have the same addictive potential as drugs of abuse. Comparable conditioned aversion paradigms have, however, been used on several occasions to show that seeking palatable food (usually a combination of fat and sugar, instead of just sugar) can become resistant to punishment [104, 128]. For example, Johnson and Kenny [104] showed that after extended access to a 'cafeteria style diet', food seeking in rats became insensitive to presentation of a conditioned aversive stimulus. Using a conditioned suppression paradigm akin to that used by Vanderschuren et al. [82], Latagliata et al. [128] showed that food restricted animals continue to seek food regardless of its aversive consequences. Interestingly, they showed that noradrenaline depletion of the medial PFC prevented the occurrence of food seeking despite aversive consequences, i.e. restored conditioned suppression. These data are consistent with the notion that the PFC mediates 'top-down' inhibitory influence over maladaptive, addictive behavior [48].

In addition to conditioned aversion, several models have been developed that measure sensitivity to unconditioned punishment. Pelloux et al. [77] showed that a subgroup of rats, after chronic cocaine self-administration, continue to seek cocaine whilst taking the risk of receiving a foot shock as a consequence. Oswald et al. [129] designed a model in which animals have a choice between standard chow and palatable food paired with foot shock. It appeared that rats that easily binge when exposed to palatable food (binge eating-prone rats) were significantly less sensitive to the aversive effect of foot shock and continued to consume the palatable food as compared to binge eating-resistant rats.

Using a related punishment setup, Heyne et al. [130] showed that inflexible intake of palatable food occurs after lengthy intake of a choice diet. In these experiments, rats were given the choice between a 'cafeteria diet' (consisting of bacon, sausage, cheesecake, pound cake, frosting, and chocolate) and standard chow. After several weeks, a subgroup of animals continued to ingest the cafeteria diet even when it was adulterated with quinine (a bitter-tasting substance). This can be interpreted as inflexible behavior [79, 131], which is a defining characteristic of addictive behavior, in the sense that subjects are unable to shift their thoughts and behavior away from drugs but continue to seek the drug despite knowledge of aversive consequences [12]. Interestingly, the animals that did cease to eat the cafeteria diet after quinine adulteration displayed another form of, perhaps, inflexible behavior in that they did not compensate for decreased energy intake by taking more of the standard chow. This 'inflexible' behavior is not indicative of 'addictive' behavior, but it is a form of 'inflexible behavior' in that these animals do not adequately respond to a changing environment (i.e. the adulteration of their preferred food), by acquiring their daily caloric ration from another source.

Relapse and Cue-Induced Feeding

Addiction is a chronic, relapsing disorder. In fact, the high risk of relapse to addictive behavior that former drug addicts run and that remains present after years of abstinence is perhaps the most insidious aspects of addiction. Animals cannot, in the strict sense relapse since they are not consciously aware of the disadvantages of drug seeking and taking. They can, however, reinstate responding for food or drugs, which is widely employed as an animal model for relapse [73]. Food seeking can be reinstated by non-contingent presentation of food, or response-contingent presentation of food-associated conditioned stimuli. Although reinstatement to food or drug seeking does not equate to addiction-like behavior, it has been

shown that animals that had lost control over cocaine intake (as assessed using the 3-criteria model), were more prone to reinstatement of cocaine seeking [78], and the neural substrates of reinstatement of food and drug seeking overlap to some degree [133].

Besides provoking reinstatement of food seeking, food-associated cues can promote food intake itself. In so-called cue-induced feeding models, sated animals ingest chow following exposure to a food-associated conditioned cue. This was first demonstrated by Weingarten [134], who showed that sated rats resumed eating when exposed to a stimulus previously associated with meal delivery during food restriction. Another possibility involves exposing the animals to cues associated with palatable food or a tiny morsel of the palatable food itself [135]. It has been suggested that overeating in a western society may be mediated by a similar process caused by conditioned craving in response to food cues in our environment [136, 137].

Conclusion and Future Perspectives

The data from animal studies discussed above support the notion of addiction-like behavior directed at food. Both neurobiological (e.g. D2R down-regulation) and behavioral (increased intake, loss of control) similarities with drug addiction have been demonstrated.

Chronic ingestion of (large quantities of) palatable food may result in addiction-like behavior, as it occurs with drugs. Clearly, food addiction-like behavior may be dependent on the type of diet and the type of food reward the animals obtain. Especially relevant are limited access models, including the one used by Hoebel et al. [15] to show withdrawal and the one by Corwin et al. [124] to show both withdrawal and increased motivation for food. When rats are exposed to cycles of alternating periods of food restriction (dieting) and periods of exposure to (palatable) food, they will start to display binges on palatable food [138]. Indeed, alternating periods of dieting and binging on palatable food are highly prevalent in humans with BED [139]. Hagan et al. [112, 113] have suggested that a diet cycle model has face and construct validity for BED. The binges are characterized by increased intake of palatable food, but not standard chow intake. Therefore, they may be mediated by hedonic, but not homeostatic, control. Cifani et al. [114] provided support for the predictive validity of the diet cycle model by showing that several psychoactive drugs (sibutramine, fluoxetine, topiramate, and midazolam) have similar effects in the model and in patients with BED.

We propose that animals, after extended access to a limited-access paradigm, should be tested on the three criteria for addiction-like behavior comparable to the procedure employed for cocaine addiction by Deroche-Gamonet et al. [78]. If a subgroup of animals that is more likely to lose control over intake (based on these three criteria) can be identified, these animals can then be characterized to see whether or not their neural and behavioral makeup resembles drug addiction-prone animals. Several behavioral aspects should be taken into account to test whether food addiction-prone animals express the same altered behavior that drug addiction-prone animals do. For instance, in rats, impulsivity is a predictor for cocaine intake and addiction-like behavior [63, 85, 88, 92], nicotine and ethanol self-administration [91, 93], and sucrose seeking [140]. Is impulsivity also predictive of addiction-like behavior for food? Also, addiction-prone rats have a distinct pattern of drug intake when the drug is freely available, even before they display clear-cut signs of addiction-like behavior [141]. It would be of interest to see if this is also the case for food intake. Last, the expression of addiction-like behavior for cocaine has also been associated with increased reinstatement of cocaine seeking after extinction. It would therefore also be relevant to test if 'food addiction' is associated with augmented reinstatement of food seeking [125, 142].

In this review we briefly alluded to neurobiological changes in (food) addiction, including differences in D1R, D2R, and μ -opioid receptor expression. Once animals that express food addiction-like behavior have been identified, these systems can be further studied in the context of food addiction. As an example, neuronal activity following palatable food administration or anticipation to a palatable diet can be measured using immunohistochemistry for immediate early genes [143] or using (in- vivo) electrophysiology. Using these techniques, it can be investigated whether food-addicted animals rely on different neural networks for the expression of food-oriented behavior compared to addiction-resistant animals. Indeed, there is human data that indicates that food addicts rely differently on the dorsal lateral PFC and the caudate during anticipation of food [54]. Moreover, studies in non-human primates have shown that the brains of primates with a long history of cocaine administration respond differently to cocaine than animals with only limited experience with cocaine. One prominent neural change that has been identified is a shift in metabolic activity from the ventral to the dorsolateral striatum during cocaine self-administration in animals that self-administered cocaine for 1.5 years as compared to animals with limited self-administration experience [66, 144]. Likewise, it has been shown that the neural response to a methylphenidate challenge differs between cocaine addicts and control subjects [145]. Since the development of addictive behavior relies on concerted neural changes in the VTA, the striatum, the amygdala, and the PFC [44, 146], these circuits should be investigated accordingly.

In conclusion, the behavioral and neurobiological similarities between addiction and overeating (in particular BED) warrant further investigation. Of particular interest is the question whether the 'loss of control' over intake for both food and drugs involves comparable behavioral and neurobiological processes. To do this, applying pertinent models from the drug addiction field to the eating disorder field may provide vital information.

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