Overlaps in the Nosology of Substance Abuse and Overeating: The Translational Implications of "Food Addiction"

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Abstract: The obesity epidemic has led to the postulation that highly palatable foods may be "addictive" for some individuals. This idea is supported by the fact that there are overlaps in brain circuitry that underlie addictive behavior as well as overeating. In this paper, we discuss the utility of the concept of "food addiction" as it may relate to treating certain disordered eating behaviors. Using criteria set forth in the DSM-IV for substance-use disorders, we review data that have emerged from animal models suggesting that overeating, in the form of binge eating, fits some of the criteria for substance abuse. Further, we discuss preclinical data revealing that the addiction-like behavioral changes observed in response to overeating are concomitant with neurochemical changes that are similar to those observed in response to drugs of abuse. With this background and evidence in mind, we conclude this article with a discussion as to how "food addiction" research may translate into clinical strategies and pharmaceutical treatments useful in curtailing overeating.

Keywords: Binge eating, dopamine, hyperpalatable foods, obesity, rat, translational research.

INTRODUCTION

Chronic overeating of palatable foods has emerged as a contributing factor in the obesity epidemic [1, 2]. However, despite the efforts to educate the public on the deleterious effects that obesity can impart on medical, social and economic well-being, people are still overweight, both in the United States and abroad [3-7]. Moreover, among children, the trends are alarming, with presently one third of children characterized as being overweight or obese [8]; it is predicted that up to 80% of obese children will become obese adults [9].

Given the global and profound effects of obesity, it is of great importance to identify factors that are driving its observed increase, so that effective treatments and preventive strategies can be developed. Recent attention has been given to the idea of food addiction and how it might have a role in obesity and select eating disorders [2, 10-13]. In this context, the diagnostic criteria described in the Diagnostic and Statistical Manual (DSM-IV-TR) for substance dependence will be used to define and identify food addiction. Based on experimental and emerging experiential and clinical evidence [14-16], we will discuss how food addiction research may translate into clinical strategies for curtailing overeating. We should note that when we use the term food addiction, it is meant within the context of the consumption of highly palatable foods. These foods are often consumed in excess by humans, and in some cases this subsequently can lead to obesity.

CRITERIA FOR SUBSTANCE RELATED DISORDERS AND THE NEUROBIOLOGY OF ADDICTION

DSM Criteria

The literature on the neuroscience of drug use, abuse and addiction is vast [17-19], and it provides a theoretical framework within which we can study aspects of non-drug addictions. However, in order to compare classic drug dependence to conditions related to food intake, we first need to establish detailed criteria to identify and define "addiction." We can use the criteria set forth in the drug literature to describe these criteria. While the term addiction has not historically been used in previous versions of the DSM, it does appear in the proposed revision plan for the next version (DSM-V). These proposed revisions include changes to the definitions of substance abuse that have important implications for how we think about and classify addictions. First and foremost, in the upcoming edition of the DSM, "substance-related disorders" is slated to be re-titled "addiction and related disorders." This spectrum of diagnoses allows for the inclusion of non-substance addictions. For example, pathological gambling has been moved into this category, and there are other addiction-like behavioral disorders such as "Internet addiction" that will be considered as potential additions to this category as data accumulate [20].

Although the spectrum of disorders related to addiction is broadening to include non-substance addictions, substance-use disorder remains the best-characterized and defined disorder in the category. Thus, we will use the criteria for substance-use disorder as a framework for thinking about food addictions. In the DSM-V, it has been suggested that substance-use disorder should be characterized as "a maladaptive pattern of substance-use leading to clinically significant impairment or distress, as manifested by two (or more) of the listed criteria within a 12-month period" [20]. These criteria are listed in Table **1**. In brief, signs of tolerance, withdrawal, excessive intake, and persistent desire to obtain the substance are noted as symptoms that characterize substance-use disorder. As described in the sections that follow, many of these behaviors have also been noted in response to overeating some highly palatable foods.

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Table 1. Overlaps in the Criteria for Substance Dependence and Overeating

DSM-IV Criteria for Substance Dependence	Preclinical Evidence for Food Dependence	Clinical Evidence for Food Dependence
Tolerance (marked increase in amount; marked decrease in effect)	Escalation of daily sugar intake [79] or vegetable shortening [95] over three week access period.	Clinical accounts of increased food consumption in each binge as the disorder becomes chronic [82], with higher body weight correlated with the frequency and severity of binge-eating episodes [96].
Characteristic withdrawal symptoms; substance taken to relieve withdrawal	Somatic signs (teeth-chattering, tremor), anxiety, aggression, ultrasonic distress vocalizations following sugar overeating [58, 59, 63, 64].	Clinical reporting of headaches, irritability, and flu-like symptoms when not overeating [82]. Clinical accounts in which self-identified food addicts use food to self-medicate, eating when they feel tired, anxious, depressed or irritable in order to escape a negative mood state [14].
Substance taken in larger amount and for longer period than intended	Enhanced sugar intake following an abstinence period [60].	This behavior is described in the DSM criteria for BED: eating, in a discrete period of time, an amount of food that is definitely larger than most people would eat in a similar period of time under similar circumstances, as well as eating much more rapidly than normal, eating until feeling uncomfortably full and eating large amounts of food when not feeling physically hungry [97].
Persistent desire or repeated unsuccessful attempts to quit	Higher progressive ratio breakpoint for fat [66].	Food cravings are reported at significantly higher rates in adults with BED than non-bingeing controls [82, 83].
Much time/activity to obtain, use, recover		
Important social, occupational, or recreational activities given up or reduced		
Use continues despite knowledge of adverse consequences (e.g., failure to fulfill role obligation, use when physically hazardous)		Distress and guilt about eating behavior, and difficulty controlling eating despite unhealthy weight gain and ensuing medical problems such as diabetes and hypertension [81, 98].

Neurobiological Mechanisms

Another lens through which we can assess food addiction is through consequential physiological and neurological maladaptation that may result from excessive intake of highly palatable foods. Drugs of abuse exert their reinforcing effects by influencing brain pathways that originally evolved to support survival-promoting behaviors, such as mating and feeding [21] and are known to usurp these neurobiological pathways, which are involved in, or help regulate, reward, motivation and decision making [22]. Although many different neurotransmitter systems are involved in this motivation and reward pathway [17, 19, 23-25], much attention has been given to the mesolimbic dopamine system, which interacts with opioid, GABAergic, cholinergic and serotonergic circuits that drive these survival-based behaviors [26-30]. In short, most drugs of abuse release mesolimbic dopamine [31-33]. Further, there are concomitant changes in dopamine receptor gene expression and availability that result from this repeated dopamine release [34-36]. During normal feeding as well as the ingestion of highly palatable foods, the mesolimbic dopamine system is also activated, with the release of dopamine driven by the novelty of a highly palatable food. However, when the food is no longer novel, dopamine release is attenuated [37, 38], except in situations where food deprivation is imposed [39]. Thus, when studying food addiction in laboratory animals or humans, the assessment of perturbations in the mesolimbic dopamine system can be helpful in differentiation of drug-like effects from those of normal food intake.

Likewise, brain opioid systems have a role in hedonic aspects of reward [40-42]. Abused opiates alter gene expression of endogenous opioid peptides in the nucleus accumbens (NAc) [43-45]. Ingestion of highly palatable foods can also affect endogenous opioids in a variety of sites [46, 47], and the injection of mu-opioid agonists or antagonists in the NAc can influence palatable food intake [48, 49]. While opioids are influenced, and can influence, ingestion of drugs of abuse and palatable foods in a similar manner, there are differences between them. The clearest example is that of opiate withdrawal, which is seen when opiates are removed or withdrawal is precipitated with an opioid antagonist. Opiate-like withdrawal is not normally seen in the context of food consumption, providing another benchmark that can differentiate the effect of food addiction from normal food intake.

FOOD ADDICTION IN PRACTICE

The Diagnostic Utility of the Concept of Food Addiction

With this behavioral and neurochemical definition of addiction in mind, we can begin to develop ideas regarding how food intake may come to have aspects of addiction. Food addiction could be important in both assessing and

treating several different conditions that involve disordered eating. Many obese individuals exhibit signs similar to those seen in addiction as described in Table **1**, such as the need for increasing amounts of food to maintain satiety, distress during dieting, and maintenance of overeating despite knowledge of adverse physiological and psychological consequences [50]. Clinical reports of "addiction" to certain foods have been documented, particularly in the context of foods rich in carbohydrates, and often in individuals who are overweight [14]. Further, several overlaps have been identified between those with eating disorders and drug use [51], with high rates of drug use among those with eating disorders and high rates of disordered eating among substance dependent individuals, potentially linking the underlying substrate of the two disorders. Similarly, some drug addicts engage in binge eating early in recovery and report using food as a substitute "drug" in order to satisfy drug cravings [52]. Also, binge eating disorder (BED), which affects 6% of the population [53], may also include aspects of addiction. In one study, 94% of adults with diagnosed BED described themselves as either "food addicts" or "compulsive overeaters" and simultaneously met DSM-IV criteria for substance-dependence disorder when the term "substance" referred to "binge eating" [54]. Food addiction may also be important in studies of bulimia nervosa, an eating disorder that is characterized by episodic binge eating coupled with caloric purging, which affects 2% of the population [53]. Bulimic patients show scores on the Addiction Scale of the Eysenck Personality Questionnaire that are similar to those reported for drug addicts and alcoholics [55].

EVIDENCE OF FOOD ADDICTION

Preclinical Data: Behavioral Signs of Addiction

We and others have taken the behavioral criteria for substance-use disorder and applied them to the study of food addiction using a laboratory animal model. These data have been discussed in detail in previous reviews [11, 12, 56]. In brief, in our model, developed in Bart Hoebel's laboratory, rats are given 12-h daily access to an aqueous 10% sucrose solution (25% glucose in some experiments) and lab chow, followed by 12 h of deprivation, for three or more weeks [57]. This feeding schedule induces spontaneous binge eating. These rats are compared with control groups offered *ad libitum* access to sucrose and lab chow, *ad libitum* access to lab chow, or 12-h access to lab chow. We find that the rats maintained on 12-h sucrose and lab chow enter a state that resembles drug dependence in several dimensions. They escalate their sugar intake and increase their intake during the first hour of daily access, which we define as a "binge." In addition to first hour binges, spontaneous binge episodes occur throughout the access period [11]. Signs of opioid withdrawal have been noted after daily intermittent access to sugar, and are seen when withdrawal is precipitated with an opioid antagonist, or when food and sugar are removed [58, 59]. Rats with 12-h daily access to sucrose also lever press for more sugar compared to a control group following a 2-wk sugar abstinence period indicating an increased motivation to obtain the substance [60], and they also show locomotor cross-sensitization to amphetamine and enhanced intake of alcohol [61, 62].

It is important to note that it is not simply the composition of the diet, but an interaction between diet and availability that leads to these addiction-like alterations. Specifically, in our model free access to the highly palatable food does not result in signs of dependence; a limited access schedule is needed in order to see these behaviors emerge. Data from other research groups also suggest aspects of addiction using animal models of overeating, and many incorporate patterns of restrictive eating of highly palatable foods. Other groups have shown that rats with limited access to sucrose show signs of aggressive behavior [63], withdrawal [64], and cross-sensitization to cocaine [65]. When offered binge access to fat, rats show increased progressive ratio breakpoints compared with non-binge groups, again indicating enhanced motivation to obtain the food [66]. Binge access to sugar/fat combinations results in stress-induced hyperphagia [67], and rats prone to binge eat will more readily endure shock to obtain a highly palatable food [68]. These studies collectively support the idea that behaviors associated with addiction are apparent when animals overeat highly palatable foods under select binge conditions.

Preclinical Data: Neurochemical Signs of Addiction

As with the behaviors associated with addiction, we have discussed the neurochemical similarities between overeating and drugs of abuse in previous reviews [11, 12]. We will briefly summarize data on two key neurotransmitters that have been shown to result in changes that are consistent with the changes seen in response to many drugs of abuse.

Dopamine. In animal models, a variety of foods have been shown to release dopamine in the NAc, including standard rodent chow, sucrose, saccharin, and corn oil [37, 38, 69-71]. In satiated animals, this dopamine release appears to be contingent on novelty since it wanes with repeated access, even when the food is highly palatable [37, 38]. However, when rats binge on sucrose, the pattern of release of dopamine is more like that of a drug of abuse than a food, where dopamine is consistently released in response to binges [37, 72]. Control rats fed sugar or chow *ad libitum,* rats with intermittent access to just chow, or rats that taste sugar only two times, develop a blunted dopamine response that is typical of food as it loses its novelty. These results are supported by findings, from both our groups and others, of alterations in accumbens dopamine turnover and dopamine transporter, as well as gene expression of dopamine receptors in rats maintained on an intermittent sugar-feeding schedule [73, 74]. Likewise, rats that overeat a cafeteria-style diet show changes in accumbens dopamine receptors that are akin to the effects seen when rats are drug dependent [75], and rats that become obese from this diet show deficits in dopaminergic activity that are ameliorated by highly palatable food, but not plain lab chow [76]. This suggests that overeating that leads to obesity in this animal model can produce a state in which there is a reward deficit. One can extrapolate that this is much like the reward deficit seen in drug dependence, but in the case of obesity the highly palatable food appears to be the object of abuse. It will be important to further dissociate the reward-related effects that binge eating and obesity have, both compounded and independently. Recent research suggests that in the absence

of obesity, alterations in dopamine in reward-related brain regions are better correlated with binge incidence than body mass index in patients with BED [77].

Opioids. In our animal model, sugar bingeing has been shown to alter enkephalin receptor-binding and gene expression. These rats have a significant decrease in enkephalin mRNA [73], similar to rats with limited daily access to a liquid, sweet-fat diet [78]. Mu-opioid receptor binding is also significantly enhanced in sugar-bingeing rats compared with chow-fed controls, perhaps in response to decreased enkephalin production [79]. In addition to these changes in the brain, it is particularly telling that rats with binge access to sugar show signs of opiate-like withdrawal (anxiety, somatic behaviors, and alterations in accumbens dopamine/acetylcholine balance) in response to the opioid antagonist naloxone [59]. Thus, brain opioid systems are activated by overeating in a way that is similar to classic signs of drug dependence.

TRANSLATIONAL IMPLICATIONS OF FOOD ADDICTION: WHAT CAN IT MEAN FOR DISORDERED EATING IN HUMANS?

Up until this point, the study of food addiction has been conducted mostly in preclinical laboratory animal models. However, many studies have begun to assess aspects of food addiction in clinical populations, with findings that are consistent with, and give further validity to, the work that has been conducted in laboratory animals. Food addiction may be a component of disordered eating that can occur in some eating disorders, as well as obesity. It is important to note that aspects of addiction would not explain all incidences of eating disorders, and we are not refuting the contributions of cultural and societal perceptions, or other biological factors, on the development of eating disorders. Nonetheless, the overlaps that have been shown between the *behaviors* and neurochemistry that are seen in some eating disorders (e.g., the act of binge eating—which is seen in cases of bulimia nervosa, BED, and even obesity) and those seen in substance dependence in animal models are well documented. We will now consider the clinical implications of these findings, within the framework of emerging clinical research of food addiction in humans.

Previously clinical researchers relied on self-identification to discern "food addicts." However, the recent development of the Yale Food Addiction Scale [15] has allowed for further identification and operationalization of this state. The scale is the first psychometrically validated measure used to target food addiction by identifying feeding behaviors that are paramount to addiction, and provides a behavioral standard by which clinical food addiction can be further explored.

In addition to being components of the Yale Food Addiction Scale, some of the DSM-IV criteria for dependence have been identified in eating disorders and obesity. The first disordered eating behavior we will consider is binge eating. Drug dependence and binge eating behaviorally share common processes in terms of loss of control, tolerance, withdrawal and craving [80]. Of these, loss of control is a hallmark of dependence and a cornerstone of binge eating, describing the compulsive use of food, despite adverse consequences (such as health concerns and social ramifications). BED may presently have the most direct link to food addiction, as many of the preclinical models described above use binge eating to stimulate overeating, resulting in behavioral and neurochemical indications of an addiction-like state. As noted before, BED patients often describe themselves as "food addicts" or "compulsive overeaters" [54]. BED patients report distress and guilt after binges and difficulty controlling binge behavior, despite weight gain and the associated medical problems such as diabetes and hypertension [81]. Further, tolerance and withdrawal in humans have been documented, mostly from clinical observations and self-report [82]. Craving has been demonstrated in the human literature with BED patients reporting more food cravings than non-bingeing individuals [83]. While further scientific examination is warranted, there appears to be significant mounting clinical data linking binge eating and addiction that are also well supported by the laboratory animal literature.

As previously stated, there are links between binge eating and obesity [84]. It has been suggested that BED may be a biologically-based subtype of obesity [85]. However, some patients with BED show enhanced preference for sweet and fatty foods compared with obese non-bingers [86]. This supports the idea that there are important differences between BED and obesity. Given this, one must consider and study binge eating and obesity both as integrated disorders and as independent conditions.

Evidence from brain imaging studies suggests similarities between obesity and drug addiction with regard to reward-related neurofunctioning [22, 87]. Thus, it is plausible that behavioral indications of food addiction may also be seen in certain individuals who are obese, and this could impact the way that we develop novel treatment approaches. Medications that have been shown to be effective in treating drug abuse might also be effective as weight loss treatments. In potentially simultaneously targeting a variety of reward mediated systems, such as the opioid and dopamine systems, pharmaceuticals can be added to the toolbox available to health providers in combating extreme obesity. In addition, it is important to acknowledge the contributions that other elements driving the malfunctioning of the reward system would also provide important targets for drug development.

We noted earlier that the data on food addiction could inform studies of a variety of eating disorders. It has been suggested that eating disorders, such as bulimia nervosa, may have properties of an "addiction" [55, 88, 89]. For example, in bulimia nervosa, appetite dysfunction in the form of binge eating and self-starvation can stimulate endogenous opioid activity [90]. Further, there is a known comorbidity between bulimia nervosa and substance abuse, again suggesting potential overlapping pathways of activity [51, 91]. Atypical reward-related brain activation has been seen *via* imaging studies in patients afflicted with bulimia nervosa [92]. These clinical links between eating disorders and addictive symptomology would greatly benefit from the further study of food addiction.

The knowledge ascertained from laboratory animal studies can inform the next steps to be taken in clinical studies of humans. For example, from preclinical studies we

have determined that "addiction" may not manifest in the same way for all types of highly palatable foods [12]. More specifically, our research in animal models indicates that unlike in sugar bingeing rats, animals that binge eat sweet-fat combinations do not show clear signs of opiate-like withdrawal. From this we conclude that binge consumption of different nutrients can induce behaviors associated with addiction in different ways. Further, the behaviors that could characterize food addiction may be subtyped based on the nutritional composition of the abused food. In clinical populations this might call for different treatment paradigms in patients that prefer varying highly palatable foods. This too has been reflected in the laboratory animal literature, with different classes of drugs proving to be more effective in ceasing binge eating of specific macronutrients [93, 94]. This research into macronutrient specific drug approach could soon translate into nutrient-specific pharmaceutical approaches toward curtailing overeating.

CONCLUSION

As seen in Table **1**, there are data from multiple research groups supporting the idea that there are aspects of addiction that arise in response to overeating certain highly palatable foods. Nonetheless, there are blanks in the table that warrant further study, both in laboratory animals and in humans. For example, studies are needed to understand if people have disruptions in their societal or occupational lives, as a result of being preoccupied with food. While there is certainly anecdotal evidence, more empirical work is needed in this area.

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Future Research Questions:

- Understanding the neurobiological substrates of "food addiction" may allow for direct and novel pharmaceutical treatments that could be used in treating overeating and/or obesity. For example, medications that have been shown to be effective in treating drug abuse might also be effective as weight-loss treatments.
- Preclinical evidence indicates that "food addiction" to different macronutrients may not manifest in the same ways. It is important to understand macronutrient-specific traits in clinical populations in order to better inform potential pharmaceutical treatments.
- Lastly, much of the research on "food addiction" still resides in the preclinical realm. It is crucial to expand these studies effectively into clinical populations, to aptly apply it to treatment options.

Key Learning Objectives:

- The idea of "food addiction" can be explored through the lens of substance use disorder. The DSM-IV suggests that substance use disorder is "a maladaptive pattern of substance-use leading to clinically significant impairment or distress, as manifested by two (or more) of the listed criteria within a 12-month period." In order to apply diagnosis to "food addiction," an operational definition of the criteria for substance-use disorder must be established. Behaviorally, substance dependence can manifests as signs of excessive intake, tolerance, withdrawal, and persistent desire to obtain the substance. Neurochemically, drugs of abuse act on and interfere with the brain's mesolimbic dopamine system, which further interacts with opioid, GABAergic, cholinergic and serotonergic circuits. These behavioral and neurochemical hallmarks of substance dependence can be used to study the concept of "food addiction."
- Preclinical evidence shows that certain eating patterns (specifically binge eating) can lead to behaviors similar to those seen during drug dependence. In our rat model, animals escalate their sugar intake over time and show signs of opiate-like withdrawal when administered an opioid antagonist, or when food and sugar are removed. These rats also lever press for more sugar compared to a control group following a 2-wk sugar abstinence period, indicating an increased motivation to obtain the substance. They also show locomotor cross-sensitization to amphetamine and enhanced intake of alcohol. Data from other research groups also suggest aspects of addiction using animal models of overeating, and many of them incorporate patterns of restrictive eating of highly palatable foods.
- Preclinical evidence also shows neurochemical indicators in overeating and obesity that mimic those seen in drug abuse. Specifically, mesolimbic dopamine release in response to sugar binge eating resembles that seen in drug use rather than normal food consumption. Further, rats that overeat a cafeteria-style diet show changes in accumbens dopamine receptors that are akin to the effects seen when rats are drug dependent, and rats that become obese from this diet show deficits in dopaminergic activity that are ameliorated by highly-palatable food, but not plain laboratory chow. In addition to changes in dopamine, the opioid system is affected by both overeating and drug use. For example, sugar bingeing has been shown to alter enkephalin receptor-binding and gene expression. Thus, brain opioid systems are activated by overeating in ways that are similar to classic signs of drug dependence.
- While most of the evidence for supporting the concept of "food addiction" has come from the preclinical realm, studies have begun to assess clinical populations. The development of scales, such as the Yale Food Addiction Scale, allows for "food addiction" to be psychometrically assessed in patients.
- Overeating, specifically in the form of binge eating, and drug dependence behaviorally share common processes in terms of loss of control, tolerance, withdrawal and craving. Further, many obese individuals exhibit signs similar to those seen in addiction, such as the need for increasing amounts of food to maintain satiety, distress during dieting, and maintenance of overeating despite knowledge of adverse physiological and psychological consequences. Further, evidence from brain imaging studies suggests similarities between obesity and drug addiction with regard to reward-related neurofunctioning. These behavioral and neurochemical findings are consistent with, and give further validity to, the emerging work investigating the concept of "food addiction."

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