The Neurobiological Underpinnings of Obesity and Binge Eating: A Rationale for Adopting the Food Addiction Model

Dana G. Smith and Trevor W. Robbins

The food addiction model of overeating has been proposed to help explain the widespread advancement of obesity over the last 30 years. Parallels in neural substrates and neurochemistry, as well as corresponding motivational and behavioral traits, are increasingly coming to light; however, there are still key differences between the two disorders that must be acknowledged. We critically examine these common and divergent characteristics using the theoretical framework of prominent drug addiction models, investigating the neurobiological underpinnings of both behaviors in an attempt to justify whether classification of obesity and binge eating as an addictive disorder is merited.

Key Words: Addiction, binge eating, dopamine, drug abuse, obesity, opioid

There has been a surge in waistlines and weight gain around the world over the last 30 years, with up to two thirds of the population of some western nations classified as overweight or obese. Obesity-related maladies, such as type II diabetes, hypertension, and liver disease, have replaced smoking as the leading cause of preventable death in adults, reducing life expectancy by an estimated 6 to 7 years (1,2). The health and science communities have responded to this epidemic by working to discover the physiological and psychological underpinnings of obesity and excessive food consumption, in the hopes of understanding the multitude of factors that have contributed to our present state.

One plausible motivational approach is that overeating reflects an addiction analogous to drug abuse, with individuals becoming physically and psychologically dependent on foods high in fat and sugar. The case for classifying overeating as an addictive disorder is particularly strong in instances of binge eating, defined as "recurring episodes of eating, in a discrete period of time, an amount of food that is definitely larger than most people would eat during a similar period of time [with a]…lack of control during the episodes" (3). These criteria closely match those used to describe drug dependence (Table 1), and binge eating is currently being considered for classification as an addiction spectrum disorder in the upcoming DSM-V (www.dsm5.org/ProposedRevisions/Pages/proposedrevision.aspx?rid=372#). Specifically, addicted individuals experience a lack of control in the face of food or drugs of abuse; have a continuation of overuse despite severe health, social, legal, and financial problems; and are unsuccessful at attempts to cut back or reduce their consumption. These behaviors are typically accompanied by feelings of guilt, remorse, and distress.

In addition to analogous behavioral traits, there are also similarities in the brain structure and neurochemical profile of substance-dependent and obese individuals. These include abnormalities in the dopamine and opioid neurotransmitter systems, changes in fronto-striatal circuitry, and associated dysfunctional impulsive and compulsive behaviors. Individuals at risk for developing drug or food dependency show a decrease in striatal dopamine D2 receptor availability, potentially making them more vulnerable to the rewarding properties of pleasurable stimuli (4). Highly palatable food and drugs of abuse directly affect the mesolimbic dopamine and opioid pathways, with consumption of each type of substance increasing neurotransmitter levels (5–7). Additionally, cue-induced anticipation of these substances can elevate activity in the fronto-limbic circuitry, thought to correspond with striatal dopamine release (5,8–10). The reward deficiency hypothesis has been advanced to explain how a baseline hypofunctioning dopamine system might lead to compulsive consumption of drugs of abuse, as individuals attempt to self-medicate via direct manipulation of neurotransmitter levels (11). This theory has also been proposed for obese individuals, similarly self-medicating flattened baseline dopamine functioning by overconsumption of high-fat/high-sugar foods (11,12).

This review will investigate the neurobiological underpinnings of obesity and binge eating, taking direction from drug addiction literature, as a rationale for adopting a food addiction model. While this idea has been proposed previously, this review will synthesize the work from several labs in the fields of drug addiction and obesity in an attempt to provide a new perspective on the issue. We will incorporate in one comprehensive survey data from both preclinical and human research and will use the theoretical framework of prominent drug addiction hypotheses over the last 40 years to structure and direct the argument. We will discuss common and divergent neural substrates, neurochemistry, and behavioral characteristics existing between the two conditions in an attempt to justify classification as an addictive disorder.

Opponent-Process Theory: A Binge-Eating Model of Food Addiction

Withdrawal is one of the primary instigators of relapse in drug-dependent individuals, particularly opiate users, negatively reinforcing drug administration in an opponent-process model (13,14). Positive reinforcers that produce affective or hedonic experiences are followed by disparate processes producing contrasting negative effects in a simple dynamic control system (13). These withdrawal symptoms typically manifest as opposing physiological and psychological reactions to those experienced

From the Behavioural and Clinical Neuroscience Institute and Department of Psychology, University of Cambridge, Cambridge, United Kingdom.
Address correspondence to Dana G. Smith, B.A., University of Cambridge Behavioural and Clinical Neuroscience Institute, Department of Psychology, Downing Street, Cambridge CB2 3EB, United Kingdom; E-mail: ds555@cam.ac.uk.

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Table 1. DSM-IV-TR Definitions of Substance Dependence and Binge Eating Disorder

Comorbid Symptom	Substance Dependence	Binge Eating Disorder
Escalation of Use	The substance is taken in larger amounts or over a longer period than intended.	Eating large amounts of food when not feeling physically hungry.
Loss of Control	There is a persistent desire or unsuccessful effort to cut down or control substance use.	A sense of lack of control during the episodes, e.g., a feeling that one can't stop eating or control what or how much one is eating.
Social Consequences	Important social, occupational, or recreational activities are given up or reduced because of use.	Eating alone because of being embarrassed by how much one is eating.
Personal Distress	The substance use is continued despite knowledge of having a persistent physical or psychological problem that is likely to have been caused or exacerbated by the substance.	Feeling disgusted with oneself, depressed, or feeling very guilty after overeating; marked distress regarding binge eating; eating until feeling uncomfortably full.

A categorical comparison of the DSM-IV-TR definitions of substance dependence and binge eating criteria for both bulimia nervosa and binge eating disorder (3).

during the initial high, motivating drug users to take more of the drug to alleviate the unpleasant symptoms. Withdrawal can be initiated through drug deprivation or administration of opioid receptor antagonists, systemically or into the striatum (15). Both manipulations result in a depletion of dopamine and an upregulation of acetylcholine in the nucleus accumbens, resulting in shivering, sweating, vomiting, anhedonia, and negative affect (16). In rodents, withdrawal symptoms present as anxiety, behavioral depression, and somatic responses such as tremor, teeth chattering, and head shaking.

Similar to opiate dependence, rats raised on a binge model of sucrose consumption show withdrawal-like symptoms when sucrose access is removed or after administration of an opioid antagonist (17–20). Following a 12-hour intermittent food deprivation availability cycle, Avena, Hoebel, and colleagues (18) were able to initiate binge-like tendencies for a high-sucrose solution in rats. Self-administration of food or drugs in a binge manner is consistent with the behavior of dependent users, who take copious amounts when the drug is first available and sporadically increase their dosage as tolerance builds. When highly palatable food is intermittently made available, particularly following a fast, animals display similar tendencies, consuming up to 58% of their daily calories within the first hour of access (18,21). These behaviors are in contrast to animals to which sucrose and food chow have been made readily available, suggesting it is the intermittent access and fast-feast model that prompts the binges. After several weeks of these consummatory patterns, bingeing rats display evidence of withdrawal, suggesting physical dependence has developed via changes in neurotransmitter systems, similar to drugs of abuse. While physical withdrawal symptoms from highly palatable foods have not been reported in humans, dysphoria has been anecdotally described after removing sugar from the diet, potentially indicating psychological withdrawal (22). The overlap of psychological symptoms in humans is notable, suggesting a common pathway involving affect and motivation in food and drugs of abuse. However, physical withdrawal presents only with opiate use, indicating an additional effect from the more potent direct manipulation of the opioid system, likely acting on autonomic pathways (23). Elucidating the distinction between physiological and psychological withdrawal could be a target for future research, parsing out possible underlying differences in these affective and autonomic opioid pathways and the unique effects that food and drugs of abuse have on them.

Craving for drugs is another common contributor to relapse, causing individuals to seek drugs despite a goal to remain abstinent. In animal models, drug seeking is demonstrated via compulsive lever pressing to obtain the substance, despite attempts at extinction and devaluation of the behavior through aversive consequences (24,25). Analogous tendencies have been demonstrated in response to sugar removal in rats, with enhanced motivation to obtain a sucrose solution after a period of abstinence (26). Similar experiences of craving, particularly for carbohydrates, are reported in human dieting literature (22). Former opiate-dependent individuals also often report cravings and binges on sweets, as well as food-hoarding behaviors (27,28).

This cross-substitutability of preference is also seen between highly palatable foods and stimulant drugs (18). Known as consummatory cross-sensitization, or the gateway effect, prolonged intake and sensitization with one substance can lead to increased consumption of another. For example, animals that preferred the taste of sucrose exhibited greater self-administration of cocaine (29). This could be due to an overall greater preference for hedonic substances or could stem from a hypothetical sensitizing or priming effect on shared receptors.

Opioid System Involvement in Drug and Food Addiction

Opioid pathways are crucially implicated in the hedonic properties of pleasurable stimuli (30), and both endogenous analgesics and synthetic opiate-based drugs have a long history of abuse due to their euphoria-inducing properties. The rewarding effects of opioids are thought to stem both from their direct activation of the opioid system in the striatum, as well as an indirect excitation of the mesolimbic dopamine pathway via gamma-aminobutyric acid receptor inhibition (30,31). The dopamine and opioid systems can therefore work in tandem to reinforce the pleasurable and rewarding properties of a stimulus.

Opioids are also implicated in eating, particularly of palatable foods (see [30,32] for review), and injection of opioid agonists into the striatum increases preferential intake of high-fat/high-sugar items, even in previously sated animals (33,34). Opioid agonists increase pleasurable taste reactivity (32,35), as well as willingness to work for a food reward, increasing the breakpoint in a progressive ratio schedule (30,36). Conversely, opioid receptor antagonists will selectively reduce ingestion of high-fat/high-sugar items (20,37,38) and self-report pleasantness ratings (37,39). As such, opioid receptor antagonists, currently used to treat opiate and alcohol dependency, can decrease food

consumption, particularly during a binge, and are suggested as possible treatments for overeating (40). Intake of palatable foods can also directly increase endorphin release in the hypothalamus, as well as gene expression involving the opioid peptide enkephalin in the striatum (41). This modulation of the opioid system from high-fat/high-sugar consumption is believed to underlie the anecdotal reports of sugar binges and craving in former opiate-dependent individuals (27,28).

Dopamine System Involvement in Appetitive and Consummatory Behaviors

Delving further into the neurochemical structures involved in addiction, the mesolimbic dopamine system has long been implicated in reward-related responding (42–44). Briefly, dopaminergic activity is believed to underlie the positive reinforcing properties of both intrinsically rewarding and conditioned stimuli (43). Dopamine agonists increase responding with conditioned reinforcement (45) and enhance Pavlovian-instrumental transfer (46) and certain forms of conditioning (43). Conversely, dopamine antagonists diminish incentive-motivation and may impede conditioning (43,44,47).

Drugs of abuse directly affect this system, artificially elevating dopamine levels in the striatum and creating associations between drug cues and the feeling of high experienced upon administration. This enhances the substance's abuse potential, magnifying its rewarding qualities and reinforcing relevant stimulus-reward associations, such that the anticipation of receiving the drug will cause similar increases in dopamine release, even before the drug's excitatory properties are experienced (47). Foods high in fat or sugar can have similar effects on the dopamine system, causing a release into the striatum and enhancing behavior associated with reward.

However, the overall contribution of dopamine to eating and food-related appetitive behaviors is less clear than its role in drug-related reward responding, and the manipulation of food consumption by dopamine release is highly dependent on the site and dose administered. For example, when administered systemically or injected into the nucleus accumbens, low doses of dopamine receptor antagonists can prolong or escalate food consumption (48,49). These effects are potentially due to dopamine's direct influence on eating behavior, modulating activation in the ventromedial hypothalamus and affecting the release of neurochemicals implicated in hunger and satiety (50). These include neuropeptide Y and pro-opiomelanocortin, the release of which are inhibited by dopamine receptor agonists, thereby decreasing food intake (51). However, high doses of dopamine receptor antagonists can also inhibit initiation of feeding and decrease food intake (49). This may be attributed to dopamine's motivational effects, the receptor antagonists interfering with learned appetitive responses required to obtain food reward—i.e., rats will still eat to satiation on a dopamine antagonist if the food is readily available but will not work via lever presses to gain access (42). Conversely, dopamine receptor agonists will increase initiation of behavior and overall responding but typically have an anorectic effect on food consumption (52). However, it should be noted that microinjections of amphetamine into the striatum have also been seen to increase feeding in some instances (53). Thus, there appears to be a dissociation between the role of dopamine in appetitive motivation and consummatory feeding behaviors, though these effects can be site- and dose-dependent (42).

Striatal Dopamine System in Addiction Disorders

A decrease in D2 receptor availability in the striatum is frequently cited in drug addiction literature as a risk factor for stimulant dependence, increasing impulsivity and placing individuals at a greater susceptibility to drugs' rewarding properties (54–56). Diminished dopamine release in the nucleus accumbens in response to methylphenidate has been seen in cocaine-dependent individuals as compared with healthy control subjects, providing evidence of further dopamine dysfunction in drug-dependent individuals (57,58). Conversely, an increase in striatal D2 receptor availability can lead to a decrease in alcohol intake, and individuals with higher endogenous dopamine levels find stimulant drugs less pleasurable than those without (59,60).

This decrease in D2 receptor availability is further linked to a reduction in orbitofrontal cortex (OFC) metabolism in chronic drug users (54,56). This suggests an important feedback loop between the striatum and prefrontal cortex, potentially modulated by dopamine and malfunctioning in stimulant-dependent individuals. Prefrontal cortex involvement in self-control and impulsivity, traits notably diminished in dependent drug users, as well as goal representation, make this dysfunction especially significant. However, it is unknown whether these cortical and subcortical pathologies predate heavy drug use or are a result of the neurotoxic effect of drugs on the brain.

Decreases in striatal D2 receptors are similarly mirrored in morbidly obese individuals, with receptor availability negatively correlated with body mass index (BMI) (51,61). A decrease in dopamine receptor availability in the hypothalamic pathway has also been linked to an increase in food intake and weight gain in genetic ob/ob obese mice (62). However, treatment with a dopamine receptor agonist led to weight loss in these animals, mimicking the anorectic effects these drugs can have in humans (62). Furthermore, prolonged exposure to both highly palatable foods and stimulant drugs can cause an additional downregulation and decrease in striatal dopamine receptor sensitivity (57,63).

Genetic Involvement in Addictive Behaviors

Much of these findings appear to be modified by a genetic profile affecting dopamine pathways, placing individuals at greater susceptibility for reward system dysfunction. Due to its role in dopamine receptor availability, the A1 allele of the Taq1A gene has been a target for drug and alcohol research over the last 20 years (64) and more recently in hyperphagia leading to obesity (64–66). Presence of the A1 allele can cause a 30% to 40% reduction in striatal D2 receptors (67) and has been implicated in corresponding deficits in glucose metabolism in the OFC, frontal and temporal gyri, insula, hippocampus, and dorsal and ventral striatum (68). As such, chronic drug users show a greater preponderance of A1 compared with the general population (64,66) and increased prevalence of the allele has similarly been shown in obese populations (65,69,70).

The mu-opioid receptor gene *OPRM1* has also been implicated in heightened responding to drugs of abuse (71,72). The G allele of *OPRM1* is involved in reward and is thought to be overexpressed in individuals with binge-eating tendencies (70). In one study, obese binge eaters were significantly more likely to have the G allele than not, whereas obese participants without binge behaviors did not have greater expression of the allele (70). Instead, obese participants without binge eating displayed a significantly higher presence of the Taq A1 allele, whereas those with binge tendencies were more likely to be A1 absent (70). Thus, there is evidence

of a dissociation between the dopamine and opioid neurotransmitter systems' involvement in binge-eating behaviors in obese individuals, potentially indicating a difference in reward responsivity. The *OPRM1* G allele seems to increase pleasure derived from food palatability, manifesting as binge-eating tendencies. Conversely, individuals with Taq A1 and subsequent diminished dopamine expression display reward-deficient characteristics leading to chronic overeating.

Reward Deficiency Theory

It can be argued that there is heightened anticipation to reward in individuals at risk for drug abuse or obesity, perhaps stemming from a constitutional decrease in basal dopamine levels, resulting in a hypothetical reward deficiency state. This may place the individual at increased risk for self-medication, whether conscious or subconscious, with drugs of abuse or highly palatable foods. However, the effects of prolonged dopamine receptor stimulation from long-term sugar/fat or drug consumption can result in downregulation of these receptors, leading to a further reduction in sensitivity to dopamine and potentially blunting the response to reward receipt (63,73). This suggests that obese individuals may exhibit tolerance to the rewarding properties of food, as similarly occurs in chronic drug users. The individual then requires greater exposure to rewarding stimuli, whether drugs or food, to achieve the same level of pleasure previously experienced, which can result in an escalation of consumption (22). This may then become cyclical, with greater amounts needed to counteract the increase in tolerance and to obtain the pleasure originally derived from eating or drug use (Figure 1). This idea of tolerance to food should be pursued empirically, in addition to the anecdotal evidence already reported, and potentially related to D2 receptor downregulation present in obese individuals.

Heightened Anticipatory Cue Sensitivity

Exposure to cues of highly palatable foods can also cause changes in brain activity of overweight individuals and those at genetic risk for obesity. Using a variety of positron emission tomography and functional magnetic resonance imaging paradigms, obese individuals exhibit a greater increase in fronto-striatal circuitry activation during anticipation of high-caloric foods as compared with lean control subjects (10,74,75). Areas activated include the OFC, ventral and dorsal striatum, cingulate, and amygdala, as well as areas involved in the gustatory circuit (76), such as the anterior insula, frontal operculum, and somatosensory regions representing the mouth and tongue. Elevated responsivity to food cues may enhance vulnerability to the rewarding properties of food, and blood oxygen level-dependent (BOLD) activation levels positively correlated with BMI in several studies (10,74). Given the decrease in striatal D2 receptor availability in obese individuals, it is possible that these increases in activation in response to food cues may be associated with a decrease in D2 receptor levels, the individuals being more susceptible to anticipated reward (10,61). Positron emission tomography studies investigating dopamine receptor binding and food cue anticipation would be a valuable contribution to the literature to help elucidate this interaction.

These patterns of activation are mirrored in studies investigating the neural responses to drug cues in substance-dependent individuals. Specifically, greater BOLD activity is seen in the ventral and dorsal striatum, insula, cingulate gyrus, OFC, and prefrontal regions, with activation levels correlating with self-report ratings of craving (77,78).

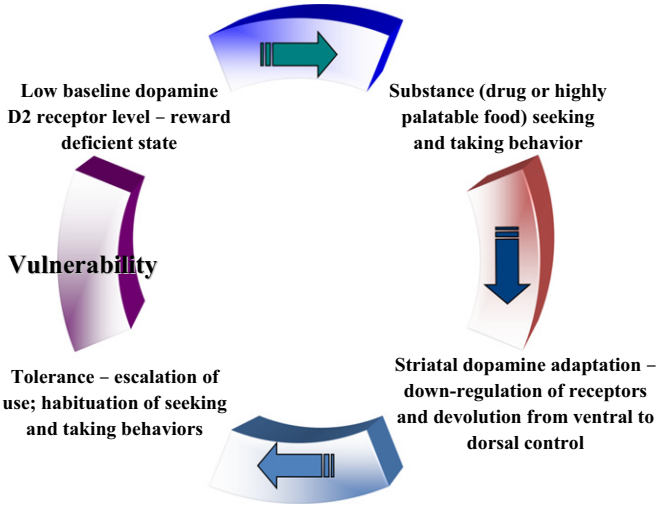

Figure 1. Reward deficiency circuit demonstrating the initial vulnerability to food or drug dependence from a baseline decreased dopamine D2 receptor availability, contributing to a reward deficient state. This may cause an individual to self-medicate with rewarding stimuli, which may, in turn, cause an exacerbation of the reward-deficient symptoms via a further downregulation of dopamine receptor sensitivity. The overconsumption of highly palatable foods or drugs of abuse can also lead to tolerance, thereby requiring higher doses of these substances and further impacting the striatal dopamine system. Empirical investigations into this notion of tolerance for high-fat/high-sugar food items should be pursued. Additionally, a longitudinal study confirming the decrease in D2 receptor binding potential following severe weight gain, as seen with long-term stimulant abuse, would be extremely valuable to the field.

Additional evidence suggests there may be a dissociation between responses during anticipation and consumption of food in obese individuals. Stice *et al.* (10,69) have shown an overactivation in the OFC, striatum, insula, and opercular regions in overweight adolescents during anticipation of food reward. However, during food receipt, there was an inverse correlation between BMI and dorsal striatal activation, such that higher BMI related to a decrease in BOLD response (10,69). Decreased activity was also associated with weight gain at 6-month follow-up (79). This is in contrast to normal-weight adolescents with greater familial risk for obesity who show increased caudate and opercular activation in response to food receipt (80). This suggests that young individuals at risk for obesity may initially be hyperresponsive to food, but that over time, due to a downregulation of striatal dopamine receptors from chronic overstimulation, the individual is left in a reward-deficient state. They may then self-medicate through consumption of increasingly larger portions of high-fat/high-sugar foods.

Structural Abnormalities in Food and Drug Dependence

In addition to the acute effects of drugs and high-fat/high-sugar foods on the striatal dopamine system, there are long-term changes that occur in brain structure and function of drug- and food-dependent individuals. As stated previously, decreases in D2 receptor binding are associated with OFC hypometabolism in substance-dependent and obese individuals (54,56,81), with BMI negatively correlating with OFC metabolism (82). Moreover,

several studies have reported decreases in frontal cortical gray matter volume in obese individuals, again correlating with BMI, and similar structural deficits are reflected in chronic drug users (83–85).

These abnormalities are often associated with cognitive deficits, with drug users showing impairments in executive functions such as cognitive control, flexibility, decision making, and working memory (86–88). Similar decreases in orbitofrontal volume and activation in obese individuals would suggest analogous impairments in cognition in this population. As such, executive function difficulties have been seen in overweight and obese individuals (82,89,90), and a decrease in OFC volume correlated with disinhibited eating in obese adolescents (91). However, the scope of disability does not appear to be as severe as in drug-dependent individuals. This suggests there is an important distinction in the neurotoxic effects of drugs of abuse on the brain as compared with high-fat/high-sugar foods.

Action-to-Habit Devolution

The OFC/prefrontal cortex is critical for self-control, inhibition, and goal representation, and reduced activity in this region is associated with higher levels of impulsivity and compulsivity. Impulsive traits are strongly linked to drug abuse, and compulsive tendencies can lead to an increased susceptibility for addiction (25,92–94). Indeed, we have put forth the action-to-habit theory of addiction, with an increase in impulsively driven, hedonically motivated actions that, through a process of signaling transfer, devolve from ventral to dorsal striatal control, becoming compulsive, habit-driven responses (94,95). As drug taking is devalued, drug-seeking behavior becomes compulsive and habituated, triggered by salient cues like environment- or drug-related paraphernalia. Overconsumption of palatable foods could initiate a similar devolution from goal-directed to habitual behavior, the consumption of high-fat/high-sugar foods becoming less pleasurable and instead transferring to a compulsive response triggered by cues such as advertisements, mood, and setting (96).

The critical question remains as to whether these structural and functional changes are predisposing risk factors for addiction or are a consequence of prolonged substance abuse. A recent study investigating stimulant-dependent individuals and their biological siblings suggests that these structural differences may predate heavy drug use, with decreases in gray and white matter seen in both groups (83). Furthermore, a decrease in prefrontal white matter connectivity was significantly related to impairments on an assessment of motor control and impulsivity, on which both groups were equally impaired (83). This indicates that cortical abnormalities and accompanying deficits in cognitive control may predispose an individual for drug dependence. However, additional structural changes present in the stimulant users suggest there is an exacerbation of these abnormalities from chronic use.

Extrapolating this finding to obese individuals, there may be underlying abnormalities in fronto-striatal circuitry and executive function that serve as risk factors for weight gain. However, while the neurotoxic effects of drugs on the central nervous system have long been established, it is less well known whether a high-fat/high-sugar diet and subsequent health problems, such as hypertension, diabetes, and cardiovascular ailments, have similar effects on the brain. It would appear, though, that the acute effects of highly palatable foods on the dopamine-modulated fronto-striatal pathways, similar to drugs of abuse, may exacerbate underlying structural and functional abnormalities in overweight or at-risk individuals, possibly leading to increases in impulsivity and compulsive tendencies. A similar endophenotype study of overweight and normal-weight sibling pairs would be an ideal way to investigate this phenomenon in pathological eating behaviors.

Distinctions between Food and Drug Consumption

Despite the many parallels outlined in this review, there are still numerous distinctions between drug addiction and hyperphagia leading to obesity, the most notable being the necessity of food consumption for energy, growth, and survival. As such, there are a multitude of anatomical regions and hormone and neurotransmitter systems that modulate food intake beyond reward and pleasurable responding. The mechanisms implicated in obesity in different individuals could stem from alterations in any one of these systems, causing dysfunction of hunger and satiety signals. Additionally, there is sufficient evidence that the reward responses elicited by highly palatable foods' action on opioid and dopamine systems are not as potent as those of addictive drugs, which more directly influence these neurochemical pathways (6,97). Furthermore, differences in the magnitude of aberrant cognitive processes associated with addictive disorders and obesity are cited above, as well as important distinctions in the physiological symptoms of withdrawal associated with each type of substance. However, these caveats do not diminish the compulsive nature or lack of control associated with binge eating or the neurochemical changes that can occur following chronic sugar and fat consumption, mimicking drug effects. Therefore, in some individuals who struggle with weight and eating behaviors, it is possible that an addiction model would best fit their symptoms and behaviors, and potential treatment options, such as those involving opioid receptor antagonists, could be targeted to them as such.

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