REVIEW

Obesity and the Neurocognitive Basis of Food Reward and the Control of Intake[1,2]

Hisham Ziauddeen,[3–5]* Miguel Alonso-Alonso,[6] James O Hill,[7] Michael Kelley,[8] and Naiman A Khan[9]

[3]Department of Psychiatry, University of Cambridge, Cambridge, United Kingdom; [4]Wellcome Trust-MRC, Institute of Metabolic Science, Cambridge, United Kingdom; [5]Cambridgeshire and Peterborough Foundation Trust, Cambridge, United Kingdom; [6]Laboratory of Bariatric and Nutritional Neuroscience, Center for the Study of Nutrition Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA; [7]Anschutz Health and Wellness Center, University of Colorado, Anschutz Medical Campus, Aurora, CO; [8]Scientific and Regulatory Affairs, Wm. Wrigley Jr. Company, Chicago, IL; and [9]Department of Kinesiology and Community Health, University of Illinois, Urbana-Champaign, IL

ABSTRACT

With the rising prevalence of obesity, hedonic eating has become an important theme in obesity research. Hedonic eating is thought to be that driven by the reward of food consumption and not metabolic need, and this has focused attention on the brain reward system and how its dysregulation may cause overeating and obesity. Here, we begin by examining the brain reward system and the evidence for its dysregulation in human obesity. We then consider the issue of how individuals are able to control their hedonic eating in the present obesogenic environment and compare 2 contrasting perspectives on the control of hedonic eating, specifically, enhanced control of intake via higher cognitive control and loss of control over intake as captured by the food addiction model. We conclude by considering what these perspectives offer in terms of directions for future research and for potential interventions to improve control over food intake at the population and the individual levels. *Adv Nutr* 2015;6:474–86.

Introduction

Obesity is a serious global public health concern (1) with 1.46 billion adults and 170 million children categorized as obese (2). In the United States 1 in 3 adults and 1 in 5 children are estimated to be obese (3). Obesity prevention and treatment are important public health priorities in many industrialized nations. Unfortunately, thus far the results from controlled clinical trials in this area are disappointing, and macroenvironmental approaches (e.g., taxing or subsidizing certain foods, modifying access to foods) for improving dietary choices or weight status remain contentious (4).

Important changes in the food environment in recent decades have played a major role in this rising prevalence of obesity (1). A key one is the easy availability of relatively inexpensive, highly palatable, energy-dense foods with little anticipated risk of food scarcity (although not for all individuals). Further, these environments are rich in cues targeted at promoting food intake, for example, advertisements (5). Such cues can induce overeating during periods of hunger by amplifying the salience of food rewards (6), and they retain this motivational power even in the absence of hunger (7). In such environments in which maintaining the homeostatic goals of energy and nutrient balance do not present a challenge, overconsumption is thought to be driven by a more hedonic form of eating (8).

The term hedonic eating refers to intake driven not by metabolic need but by the reward experienced by consuming the food, particularly relevant for highly palatable energy-dense foods (9). We use the term here as a useful shorthand to describe this kind of food intake but acknowledge three caveats. First, food is a primary reward, and there are hedonic aspects to food intake in general. Second, hedonics is only one aspect of reward (see next section) and is important to consider the motivational and learning aspects of reward, which

are more relevant to environmental cues. Third, when we consider intake in excess of homeostatic need (more precisely intake beyond the limits of the homeostatic system's ability to maintain balance over time without storing excess energy), the term hedonic eating seems to capture both this excess and its putative drivers, namely the rewarding aspects of food consumption.

However, despite an overall rightward shift, a normal variability remains in body weight to suggest that individuals vary in their susceptibility to overconsumption. Although this is likely mediated by multiple genetic and environmental factors (10), including the degree of and susceptibility to exposure to these environments, these factors ultimately affect the extent to which the individual is able to control his or her food intake. Over the past 2 decades interest has increased in how alterations in food reward processing in the brain relate to overeating and obesity (6). In this review we focus on the brain reward system and its role in the control of food intake. We begin with an overview of the system, which have been elegantly characterized through animal studies, and then examine the human functional neuroimaging studies of these systems in the context of obesity. After this we consider 2 different perspectives on the control of food intake: the first examines cognitive control of food intake and the second, loss of control over intake in a specific model of dysregulated eating, namely food addiction (FOA)[10]. Finally, we consider what research directions these perspectives suggest for the field and for the development of potential treatment interventions.

Brain Systems Controlling Food Intake and Eating Behavior

The brain's reward and homeostatic systems are often considered separately when examining their roles in food intake and eating behavior. However, these systems are not structurally or functionally separate, so they are described together here.

The homeostatic system responsible for regulation of energy balance is centered in the hypothalamus which integrates neural and nutrient signals with hormonal signals that originate in the small intestine, pancreas, liver, adipose tissue, and brainstem (11). Two neuronal populations are critical in the arcuate nucleus of the hypothalamus: the orexigenic agouti related peptide (AGRP)/neuropeptide Y neurons and the anorexigenic pro-opimelanocortin neurons. The organization of the circuit safeguards consumption as the preferred behavior, and destruction of the AGRP neurons in adult animals results in cessation of eating and death (11–13). Note however that animals can survive early life ablation of these neurons, and even adult animals if kept alive for a period can recover from such lesions (14). In close proximity to the hypothalamus are critical nodes of the

reward circuitry centered on the ventral striatum (VS): the nucleus accumbens (NAcc), ventral pallidum (VP), and the ventral tegmental area (VTA). Both the hypothalamus and VS receive inputs from the prefrontal (PFC) and orbitofrontal cortex (OFC) (15), the amygdala, and the hippocampus. The VS also receives inputs from the anterior cingulate cortex and a large dopaminergic projection from the midbrain (16).

Berridge and Kringelbach (17) describe three components of reward, liking, wanting, and learning, that are linked but yet dissociable in terms of their neural substrates. Liking and wanting, respectively, refer to the hedonic impact of and the motivation for a reward, and we focus on these 2 components here. Learning comprises the associations with and predictions about rewards. The animal literature implicates opioid and cannabinoid systems in hedonic experience and dopamine in the wanting and learning components (18). Distinct hedonic hotspots have been identified in the reward circuitry, sites where stimulation causes the amplification of hedonic liking reactions (19). In the rodent brain, such hotspots were identified in the NAcc, the VP, and the parabrachial nucleus of the pons. In the medial shell of the NAcc is an opioid hotspot, and stimulation here with opioid agonists produces vigorous enhancement of liking reactions to a sweet taste (20, 21). Interestingly, in the rest of the medial shell, opioidergic stimulation amplifies wanting without enhancing liking. An endocannabinoid hotspot that overlaps this opioid hotspot was also identified (22). Another opioid hotspot was identified in the posterior VP (23) which forms a bidirectional circuit with the NAcc hotspot to generate liking reactions (24). The VP hotspot appears to be the most crucial because only its destruction leads to the loss of liking reactions and their conversion to disliking reactions (6). For wanting, the mesolimbic dopamine system is the key neural substrate. Dopaminergic or electrical stimulation in this region enhances wanting and motivational responding with increased food consumption but with no enhancement of liking reactions (25, 26). Sensitization of this system (e.g., by drugs of abuse) leads to enhanced wanting that can occur in the absence of liking, even without declarative awareness (27). Indeed, wanting can occur even when the hedonic experience is aversive; electrical stimulation in the lateral hypothalamus causes increased intake alongside disliking reactions to sucrose in rats (28).

As mentioned before, these systems are not separate. The lateral hypothalamic area (LHA) is thought to integrate homeostatic and reward-related information (29) and through its projections, to modulate the VTA and brainstem nuclei such as the nucleus tractus solitarius, critical in the modulation of gut signals and satiety signaling (11). Another important link is the endocannabinoid system. CB1 receptors in the hypothalamus mediate the activity of the arcuate nucleus of the hypothalamus and LHA neurons that project to the nucleus accumbens (30, 31). Both systems are also modulated by hormonal signals from the circulation. Leptin and insulin modulate the activity of the AGRP and pro-opimelanocortin neurons, serving as adiposity-negative feedback signals. Low

concentrations signal lower peripheral energy stores and promote food consumption, with leptin having a much larger effect (11). The gastric peptide ghrelin serves as a hunger signal at the hypothalamus and brainstem (32, 33), whereas gut peptides such as cholecystokinin, glucagon-like peptide-1, and peptide YY, serve as satiation signals (34, 35). These signals also act on the reward circuitry, either directly or via projections from the hypothalamus and brainstem nuclei such as the nucleus tractus solitarius. Leptin LepRb neurons from the LHA project to the VTA and NAcc (36). These projections seem to inhibit VTA neurons and increase levels of tyrosine hydroxylase and dopamine in the NAcc (37), allowing leptin to modulate the incentive salience of food. Leptin-deficient individuals show intense drives for food, with strong striatal activation (using fMRI) that is unaffected by food consumption. Leptin replacement restores the normal pattern of activation and normalizes eating behavior (38). Glucagon-like peptide-1 concentrations were shown to correlate with increased blood flow in the dorsolateral PFC (dlPFC), suggesting an enhancement of inhibitory control with satiation (39). Experimentally replicating physiologic concentrations of PYY_{3-36} produces activation in the left caudolateral OFC, and this predicts subsequent food consumption (40). Ghrelin was shown to directly potentiate the VTA in animal models (41), and in humans supraphysiologic concentrations of ghrelin increase the neural response to food pictures compared with nonfood pictures in the amygdala, OFC, insula, and striatum (42). Finally, corticotropin-releasing factor and glucorticoids play important roles in both systems, in their development (43) and in mediating stress-related responses (6), but also by affecting peripheral endocannabinoid signaling (44).

The aim here was to emphasize the connectedness of the homeostatic and hedonic circuitry. Perhaps the most elegant demonstration of this comes from the animal studies of salt depletion-induced salt appetite. In this state, both the palatability (45) and the neural coding of a normally aversive salty taste in the VP (46) change to resemble the normal response to an appetitive sweet taste. In addition, a cue that previously signaled the aversive salty taste acquires motivational salience and is able to elicit the anticipatory behavior previously elicited by the cue for the sweet taste (47), despite having never been experienced in the salt-depleted state. Alterations in homeostatic state change reward processing and behavior. A final point to emphasize is that the homeostatic system safeguards food intake but is sensitive to satiation. However, liking and wanting are go systems and, although the go signaling may attenuate with satiation, it does not switch to a stop state (6); that is, satiation may decrease liking for the food but does not make it aversive (48, 49)

Studying Reward Systems in Human Obesity

Over the past 2 decades functional neuroimaging has enabled the study of the reward circuit in humans and how perturbations in these systems may occur in or lead to obesity. The techniques used have been fMRI and, to a much lesser extent, positron emission tomography (PET). PET imaging uses radioactive tracers that include ligands for specific receptors to examine regional blood flow and receptor densities in the brain. fMRI relies on the changes in magnetic field that accompany blood flow changes in the brain by using the blood oxygen level dependent response. By using cognitive or sensory tasks (e.g., tasting liquid rewards in the scanner) targeted at specific processes, it is possible to delineate the functional neuroanatomy of the circuits involved in implementing those processes. This has mainly been with fMRI which is noninvasive and has relatively high spatiotemporal resolution but not of a level that allows examination of specific hypothalamic nuclei or neuronal subpopulations within a structure, which is an important limitation in this area (50). The design principles and assumptions of these fMRI experiments are shown in Table 1. The points made are not meant to detract from the findings of neuroimaging experiments but to advocate caution in their interpretation. Functional neuroimaging is an extremely useful tool that has great value in examining the brain mechanisms and in evaluating different models of brain function. What is measured in the scanner may not necessarily reflect what happens in the normal free-living state, for example, patterns of brain activation during peeling an apple were different when subjects did this inside the MRI scanner compared with when they did it outside the scanner (51). However, a more appropriate evaluation of the ecologic validity of fMRI findings is to establish their relations with other measures or with outcomes in the real world, that is, as explanatory or predictive variables.

Two broad approaches have been used in this field. The first has sought to identify a perturbation(s) in reward response that occurs in obese individuals but not in control participants, suggesting that the perturbed process may be relevant to obesity (as a cause, consequence, or correlation). The second approach has sought to characterize the activity of a particular part of the circuit and to examine its predictive value in terms of determining future food intake or weight gain. A third approach that may well become more prominent in the coming years is from neuroeconomics and food-related decision-making field (see next section). Relatively little work has been done in obese populations in this area, but this will no doubt happen shortly.

Presentation of food rewards as pictures (52), tastes (53), or smells (54) produces increased brain activation in the VS, caudate, putamen, and OFC. Not unexpectedly other rewards such as drugs (55), sex (56, 57), music (58), and money (59) produce similar responses. Studies have shown differential activation to food pictures in obese individuals compared with lean control participants in the VS and dorsal striatum, midbrain, OFC, and medial and lateral PFC (52, 60–64). The issue is not with the individual findings but with the lack of consistency among the different studies. With similar (although not identical) experimental paradigms, these studies have shown activations in different regions and in different directions. The same is true for the studies of anticipatory and consummatory food reward, whereby the prediction (from the drug addiction literature) was that of an enhanced anticipatory reward in obesity with

TABLE 1 Design aspects of functional neuroimaging studies of reward processing in obesity[1]

Aspect	Details	Considerations
Design	Case-control obese cases (BMI > 30) vs. healthy weight controls. Some studies have also included bulimia and BED.	Obese cases are likely to represent heterogeneous phenotypes rather than a homogeneous case phenotype. This is particularly relevant in studies with typical sample sizes of 10–30. Cross-sectional designs cannot distinguish between causation, correlation, or consequence.
Reward processes of interest and experimental paradigm	Anticipatory and consummatory reward to cues predicting, and the actual receipt of liquid reward delivery compared with neutral liquid delivery. Brain responses to pictures of rewarding foods compared with pictures of less rewarding foods or neutral images.	There are 2 assumptions here: 1. A brain process that is specifically targeted by the experimental task is clearly defined. 2. The control condition (e.g. neutral liquid) adequately captures any other processes activated by the task, allowing attribution of any differences to the variable of interest. This is not always clear (e.g., differential responses to a picture of a burger compared with picture of a whole raw cabbage) can be due to a high- vs. low-calorie, appetizing vs. bland, or edible vs. not readily edible distinction or likely a combination of the above.
Outcome measure	Differential brain response to the test condition compared with the control condition, and how this differs between the control and obese groups	The outcome measure depends on the above factors and assumptions.

[1] BED, binge eating disorder.

a blunted consummatory response (53, 65–68). Although studies have shown alterations in anticipatory or consummatory reward (not always in the predicted direction), there is little consistent evidence for this specific pattern [see (69) for a review]. Further, for most of these findings, given the cross-sectional nature of studies, it is not possible to determine whether they are causal, correlational, or consequential.

The picture is more encouraging from the smaller group of studies that have used the fMRI signal as a predictive variable. Stice and colleagues (70) demonstrated that the blunting of the striatal response to the receipt of chocolate milkshake predicts weight gain over the subsequent 6 mo. This blunting of response was also related to polymorphisms of the Taq 1A allele (53) and more recently to a multilocus score of different dopamine-related genes (71). Food cue-related activity in the NAcc was shown to relate to subsequent snack food consumption in healthy women, and neither of these was related to hunger or explicit wanting or liking for the snack. However, a relation with BMI was only seen in women with lower self-control scores (72). Burger and Stice (73) presented women with repeated exposures to cues predicting imminent milkshake receipt. Subjects with the greatest increase in VP responsivity to food reward cues and greatest decrease in caudate response to the milkshake had significantly larger increases in BMI over the subsequent 2 y. Indeed the decreased caudate response to milkshake was shown to negatively correlate with BMI (74). In adolescents greater striatal activation to food advertisements was shown to correlate with weight gain over the subsequent year (75). Collectively, these studies indicate the potential value of fMRI as a tool to study vulnerabilities to weight gain. They also urge caution in drawing direct links between altered brain responses and obesity, given that even here there seem to be other mediators such as impulsivity and self-control.

In summary, we have encouraging findings of reward dysfunction in obesity, but the lack of consistency does not allow us to make firm conclusions about its nature at present. Although some of these inconsistencies may relate to experimental differences, a much more important factor is likely to be the inherent heterogeneity of the obese phenotype in these studies. More precise phenotypes are needed in which specific mechanisms can be examined and also for newer methods that can be used in experimental settings less restrictive and more ecologically valid than the MRI scanner.

The Control of Hedonic Food Intake: Cognitive Control

Cognitive control is the ability to orchestrate thought and action in accordance with internal goals (76). Despite liking and wanting being go systems embedded in environments where highly rewarding foods are widely available, individuals are able to control their hedonic intake (to varying degrees) in line with ethical motivations, religious beliefs, and health and fitness goals. Critical here is the ability to self-regulate consumption (i.e., resist immediate food rewards) to achieve/maintain long-term goals (77).

A widely held view of food-related decision making is that we are rational, reflective, and goal-directed decision makers. According to neuroeconomic models this involves first assigning goal values to all options under consideration and then selecting the one with the highest goal value (78). This is implemented by a set of the critical nodes in the PFC:

the OFC integrates internal state information with the sensory and reward aspects of foods, the dlPFC codes longer-term attributes such as health and the expected taste reward from the foods, and the ventromedial PFC computes the goal values from these inputs (79, 80) and sends this output to effector circuits (such as the motor cortex) that implement the decision. The dlPFC is also a key area for executive functions, for example, inhibitory control, working memory, cognitive flexibility, and planning (81–83). Inhibitory control is closely related to the personality trait of impulsivity, defined as behavior characterized by poor planning, premature actions, that may be risky or inappropriate to the context, without due consideration of the (often undesirable) consequences (84). As Dalley et al. (84) have astutely pointed out, this encompasses multiple components: acting without due consideration of the available evidence (reflection impulsivity), failing to inhibit actions (impulsive action), accepting smaller immediate rewards over larger delayed rewards (impulsive choice/delay discounting), and behavior that puts the individual at risk of harm. Although there are different perspectives on how these functions and their elements are conceptualized (85), in considering cognitive control of food intake, we can think of the interplay between executive control and impulsivity as a core aspect of self-regulation, with executive control keeping longer-term goals and consequences in mind and reining in the tendency to impulsive choice and actions.

Inhibitory control and trait impulsivity are the most studied areas in the human literature. By using questionnaire measures of trait impulsivity or laboratory measures such as the stop-signal reaction task, it has been shown that obese adults and children have higher impulsivity (86 87), and this relates to greater intake, weight gain, and poorer response to weight reduction treatments (88–90). Obese individuals show steeper delay discounting, even with monetary rewards (91). A recent systematic review of executive function studies in obese adults found overall an executive impairment, but the variability in the measures used did not permit the determination of a consistent pattern (92). A systematic review of studies in children and adolescents is more compelling. Once again, there is the issue of the variability of measures used, but inhibitory control in particular emerges as a strong factor. Two points are particularly striking. First, impairments in executive function are seen in obese children from a young age. Second, poorer executive function is related to BMI later in childhood and adolescence. Better inhibitory control (particularly from a young age) seems to protect individuals from future weight gain. Studies of self-regulation and the ability to delay gratification in young children have shown that better performance on these measures is predictive of lower subsequent weight gain in adolescence and adulthood (93–95). Further, the degree to which an individual is able to develop this capacity can determine their ability to lose weight and more critically maintain weight loss. Obese individuals show lower levels of dlPFC activation in response to food (96, 97) and higher levels of disinhibited eating (98). However,

formerly obese individuals who successfully maintain their weight loss show greater dlPFC activation in response to food (99, 100), lower levels of disinhibited eating, and greater dietary restraint (101–104), suggesting that these mechanisms can be successfully learned.

Do these cognitive impairments cause obesity or vice versa? This is unlikely to be straightforward, given the multiple mechanisms involved in the development of obesity. However, these may be interacting mechanisms (i.e., poorer inhibitory control causes overeating) which worsens the cognitive impairment (105). The determinants of these mechanisms likely extend into the prenatal period. Feeding rat mothers a diet rich in fatty, sugary, and salty snacks during pregnancy and lactation enhances the preference for junk food and increases the propensity for obesity in the offspring (106). Extensive animal work shows the deleterious effect of overeating, particularly of high-fat and -carbohydrate foods, on brain structure and function [for a review see (107)]. Of particular note is the finding that rats fed a Western diet exhibited cognitive impairments even before developing substantial excess body weight gain (108). Less direct evidence comes from the human studies that show an association between obesity and decreased brain volume (109, 110) and the association between obesity and later life cognitive decline and dementias (111).

Although there is strong focus on goal-directed decision making in food choice and intake, given that we make several food-related decisions everyday [as many as 200–250 by some estimates (112)], it is extremely unlikely that every single decision is a considered goal-directed one. In fact, it is likely that many of these decisions are more habitual, driven by internal (e.g., hunger, stress) and external (e.g., advertisements, foods) cues without much deliberation (80, 113). This is certainly a more rapid and efficient way to make these decisions but a less flexible one [although it is possible that cognitive control mechanisms can be triggered unconsciously (114, 115)]. We emphasize this point because these cognitive control mechanisms may, to some extent, be enduring personality traits and cognitive styles that endow individuals with varying degrees of control over their habitual choices and intake, thus determining their weight trajectories perhaps even from early childhood. However, they can also be successfully learned as demonstrated by formerly obese individuals who maintain their weight loss.

Loss of Control over Hedonic Food Intake: FOA
At perhaps the other extreme from using strong cognitive control for weight loss and maintenance is the idea of FOA, inherent in which is loss of control over intake. Two ideas in the literature are key as to what FOA is (70, 116). The first is that certain foods, specifically highly palatable foods rich in fat and sugar, are addictive and like drugs of abuse activate brain reward systems and induce patterns of overeating that resemble drug addiction. The second is that certain individuals (with obesity) show a pattern of food-related behavior characterized by loss of control over intake and compulsive consumption despite adverse

consequences, which strongly resembles the behavioral syndrome of drug addiction. We shall consider both of these in turn but emphasize that they are not mutually exclusive.

Can certain foods be potentially addictive? Rats allowed intermittent access to high-sugar and high-fat foods develop escalating, binge-like eating (117, 118). Enforced abstinence from sugar and administration of the opioid antagonist naloxone results in a withdrawal syndrome with a behavioral (enhanced anxiety, teeth chattering, forepaw tremor, and head shakes) (119) and neural profile (low levels of dopamine and high levels of acetylcholine in NAcc) similar to that seen in drug withdrawal (119, 120). This is not seen in animal models of intermittent access to fat (118). Importantly, these animals do not become obese (121) because their daily intake remains unchanged, but a larger proportion of it occurs during the intermittent access period (117, 118). However, when fat and sugar are combined in cafeteria diets with foods such as bacon and cheesecake, animals increase their intake and gain weight (122–124). Their eating becomes compulsive, and they continue to seek food despite aversive consequences such as electric foot shock (122–124).

What neural mechanisms underlie these changes? In animals binging on high sugar and fat, even those who are sham fed (food is consumed orally but is removed immediately via a gastric cannula), the enhanced dopamine release in the NAcc that occurs with food exposure fails to habituate with loss of novelty (125–127). Animals on cafeteria diets show reductions in presynaptic dopamine and, although palatable foods still produce a dopamine response, the response to standard chow is blunted (128). In the sugar-binging and the cafeteria diet animals, striatal dopamine D2 receptor values fall (119, 122). In the latter animals, brain self-stimulation thresholds (the minimum intensity of electrical stimulation in the lateral hypothalamus that will maintain self-administration of the stimulation by the animal) increase and remain elevated 2 weeks after cessation of the diet. This indicates early and persistent alteration of reward thresholds (122), suggestive of the development of a reward deficiency state similar to drug addiction (129). The overall picture shows strong similarities to animal models of drug addiction. An important conceptual issue to consider is that, although these changes occur in areas implicated in drug addiction, in drug addiction they are thought to represent a hijacking of the food reward circuitry by drugs of abuse, so it is not surprising to see similar areas here. However, Carelli et al. (130, 131) have shown that distinct populations within the accumbens respond to food and drug rewards, but we do not have sufficient spatial resolution to detect these subpopulations with human neuroimaging.

The animal literature presents compelling proof of concept for the FOA model with the combination of high fat and sugar producing the most striking phenotype. This is important but unfortunately does not help us identify a putative agent which becomes an important issue as we move on to consider the human literature on FOA which is mainly based on the behavioral syndrome of FOA (132). This is modeled on the criteria for substance dependence from the Diagnostic and Statistical Manual of Mental Disorders,

Fourth Edition (DSM-IV) (136), which were translated into equivalents for food, but this translation is not entirely satisfactory (Table 2).

Three conceptual issues are important to consider [for a review see (116)]. The first issue is that DSM-IV substance dependence criteria (136) are defined as behavioral criteria for an addictive agent, and it is difficult to apply them without such an agent. The FOA literature considers hyperpalatable and/or highly processed foods to be key (137–139), although these are not an explicit part of the criteria. To refine this model and to develop interventions that are based on it, a more precise definition of the addictive agent(s) will be necessary to be able to say what composition of a common food, such as cheesecake, would make it hyperpalatable and addictive. The second issue is that, although these clinical criteria are behavioral, they have been validated by a large body of neuroscientific research that has examined their neural underpinnings, and this broader understanding is part of the clinical syndrome; that is, both the syndrome and the term addiction imply a specific set of underlying neural mechanisms. Behaviors that look like addiction would suggest, but do not on their own confirm, the possibility of an addiction syndrome (i.e., anatine morphology alone does not confirm anatine identity). We emphasize this because FOA does derive some legitimacy from comparisons with this broader understanding of drug addiction. The third issue is that drug addiction results from the combination of an addictive agent, an individual with vulnerabilities to drug addiction, and time. Only 15% of individuals who use drugs develop dependence (140). This is especially critical when the substance (food) is universally consumed (although not necessarily in the aforementioned hyperpalatable forms), but some individuals may develop a FOA. This is not easily examined in a body of work that, given the infancy of the field, is almost entirely cross-sectional in design. It is acknowledged that FOA is not a general mechanism to explain overeating and obesity, but one that may be relevant to specific subgroups with obesity (although theoretically an individual could be addicted to food and not, or not yet, be obese), the strongest candidate being binge eating disorder (BED) (141). However, the case has been made that such potentially addictive foods present a risk to the population at large (142).

The human model of FOA was operationalized in the now widely used Yale Food Addiction Scale (YFAS) for adults (139) and more recently for children (143). However, the scale has certain limitations [Table 2; for a review see (116)]. Without a clear addictive agent it is difficult to identify features of its consumption that discriminate use from abuse/addiction. The scale applies severity thresholds and an overall distress/impairment criterion to determine whether an individual is addicted. There is also a danger of circularity. The YFAS is designed to capture eating behaviors that may be addiction-like, so certain aspects of its validity hinge on the degree to which FOA is a valid model of disordered eating. The potential circularity is as follows: FOA exists because certain people are defined as food addicts on the YFAS; the YFAS is valid because it can identify FOA.

TABLE 2 Comparison of the DSM-IV substance use criteria and the YFAS[1]

DSM-IV criteria for substance dependence	YFAS equivalent	Comment
Persistent desire for and unsuccessful attempts to cut drug use.	Persistent desire for food and unsuccessful attempts to cut down the amount of food eaten.	Without a clear agent or substance this criterion requires the application of severity and impairment thresholds to be meaningful. The YFAS asks about certain foods and gives examples of energy-dense and fast foods and does indeed apply severity and impairment thresholds.
Larger amounts of drug are taken than intended.	Larger amounts of food are eaten than intended.	As above.
Substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem caused or exacerbated by the drug.	Overeating is maintained despite knowledge of adverse physical and psychological consequences caused by excessive food consumption.	As above.
Great deal of time spent on getting, using, or recovering from using the substance.	Great deal of time is spent eating.	As above. Less useful to distinguish use from abuse or addiction for foods, given their easy availability in most developed societies.
Important social, occupational, or recreational activities are given up or reduced because of substance abuse.	Activities are given up because of overeating or recovering from overeating.	
Tolerance: increasing amounts of drug are required to reach intoxication.	Tolerance: increased amounts of food are required to get the same pleasure or relief from negative emotions.	Tolerance and withdrawal have not been demonstrated for any foods. The proposed equivalents are not convincing, particularly given that in substance dependence these relate to physiologic adaptations that occur with sustained substance use.
Withdrawal symptoms on drug discontinuation, including dysphoria and autonomic symptoms (such as shakes and sweats).	Withdrawal symptoms such as anxiety, agitation, or other physical symptoms.	Importantly, tolerance and withdrawal are not seen with all substances and may not be relevant to foods at all. However, despite being poorly characterized by the YFAS, these criteria are strongly endorsed by participants in studies that use this measure (133–135).

[1] DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; YFAS, Yale Food Addiction Scale.

The YFAS is nevertheless a popular research tool, and numerous studies have used it to examine the prevalence of FOA in different populations. We focus here on the studies that have sought to validate the model and to examine its mechanisms. Much of this work focused on an association with BED (133, 141), which is classified as an eating disorder in the DSM. BED is characterized by recurrent episodes (binges) of uncontrolled, often rapid consumption of large amounts of food, usually in isolation, even in the absence of hunger. Eating persists despite physical discomfort, and binges are associated with marked distress, guilt, and disgust. Binges can be triggered by negative mood states that are not necessarily ameliorated by the binge (144). Here, we have a behavioral syndrome, more convincingly like that of drug addiction, including loss of control of eating, escalating consumption, and possibly consuming to ameliorate dysphoric and negative effects (145). It appears that the face validity of the FOA construct is strongest when it is applied to certain (although not all) individuals with BED (133, 141). An important caveat is that, although BED is associated with obesity, a substantial number of people who show binge eating behavior are not obese, and most obese people do not have BED (146). Three studies found high values of comorbidity between BED and FOA as defined by the YFAS as follows: 72% (141), 56.8% (133), and 41.5% (134). The considerable overlap between FOA and BED and also other eating disorders such as anorexia and bulimia nervosa (147–149) raises the following important question: is FOA a unique nosological entity?

Determining the underlying mechanisms may help answer this question. Davis and colleagues (150) found that participants who met YFAS criteria for FOA showed a distinct composite genetic index of dopamine signaling, suggesting that these individuals may have some degree of up-regulation in the dopamine system, a finding complemented by the demonstration that the genetic profile's effect on YFAS scores was mediated by craving, bingeing, and emotion. The evidence most cited in support of the model however comes from the field of neuroimaging, from PET and fMRI studies of obese individuals. The first and most influential finding was the demonstration of lower values of striatal D2 receptors in obese individuals than in control participants, a pattern similar to that seen in drug-dependent individuals (151). This study compared severely obese individuals (BMI > 40 kg/m^2) with controls (BMI < 30 kg/m^2) and there was a considerable overlap between the groups. Since then,

this finding has been replicated twice with different approaches (152, 153), although at least 3 studies have failed to replicate it (154–156). The 1 study that specifically looked at individuals with BED did not find any difference in D2 receptor binding in this group compared with non-BED obese individuals (157). With the use of PET, Guo et al. (158) showed that increasing BMI is related to increased D2 receptor binding in the dorsal striatum and decreased binding in the ventromedial striatum. As already described in the functional neuroimaging section, no single mechanism has been consistently implicated in obesity, let alone an addictive one. To date only 1 study has specifically examined people phenotyped with the YFAS and found that individuals with higher FOA scores showed greater responses to anticipation of food in the anterior cingulate cortex, OFC, and amygdala (159). However, these findings were not entirely as predicted, and some of these effects were driven by a decreased response to the control taste rather than an increased response to the food. More importantly, 46 of 48 subjects did not qualify for a YFAS diagnosis of FOA, so the scores were treated as a continuous variable and the sample was divided into high and low scorers in the analyses. Interpretation of these findings therefore depends on the validity of the scale and the extent to which the scores do represent a real continuous variable, and any conclusions must necessarily be tentative.

In summary, the animal evidence for the FOA model is supportive. The human evidence is still preliminary, and this may relate to the relative infancy of the field (69, 160, 161). Nevertheless, it is a compelling idea and perhaps most importantly offers an explanation for individuals who struggle to control their food intake and casts their difficulties in a more sympathetic light to others (162). Some investigators have suggested recently that instead of FOA, it may be more useful to think of an eating addiction (163) more akin to behavioral addictions, although some of the conceptual concerns raised in this section may apply here too.

Toward Future Research and Treatment Strategies

The FOA perspective. Preclinical studies may be the most rigorous way to determine what the addictive agent/food might be. Synthesizing the data from the growing number of YFAS studies may help determine which criteria are most informative and discriminatory. It may well transpire that a precise addictive agent may not be critical and that substance addiction is not the most appropriate human model for FOA. Longer-term prospective studies would help define the natural history of FOA and refine the phenotype. One valuable approach may be to study individuals who score highly on the YFAS as an extreme phenotype of FOA. Such work in extreme phenotypes could be performed in parallel in animal models and may offer critical insights into the syndrome and its underlying mechanisms.

What about potential interventions? If it could be established that certain foods are addictive, this could reasonably demand a policy response that would look at the important issues of availability of and access to such foods, particularly in vulnerable groups such as children (142, 164). The issue is not that we lack evidence from other lines of health research to justify such policies, but that there are multiple challenges, including political will, industry agreement, issues of individual choice, and restricting access to particular groups and individuals. However, a confirmed FOA may change the picture because it invokes a specific model of state responsibility as for other substances (142). At the individual level, if FOA can be validated as a clinical disorder, it could suggest different treatment approaches for these individuals. These may include controlled consumption of or abstinence from specific foods, psychological treatments such as individual cognitive behavior therapy or 12-step programs to help individuals gain control over their eating. It is important to note that cognitive behavior therapy approaches for binge eating do not advocate avoidance or abstinence as addiction treatments do, but instead they focus on decreasing dietary restraint and enhancing the individual's sense of control over food (165).

The cognitive control perspective. Although a lot of research into the mechanisms of cognitive control have been done, large-scale intervention trials in overeating and obesity are few, though some of the preliminary evidence is compelling (166). Given the link between impulsivity and inhibitory control and obesity, this would be a good treatment target. Another potentially valuable strategy is to capitalize on the shared neurocognitive links between physical activity and eating behaviors. Habitual physical activity and healthy diet appear to share an interactive and reinforcing relation (167, 168), and physically active individuals were observed to exercise higher cognitive restraint of appetite (169). In addition, physical activity may potentially build cognitive resources or inhibitory control to down-regulate or reduce sensitivity to impulsive drives that underlie overeating (168). Aerobic fitness has been shown to correlate with cognitive control and its neural substrates in both children and adults (170). This hypothesis needs direct investigation to demonstrate this important additional benefit of physical activity. Finally, there is the possibility of modulating food reward via strategies based on cognitive enhancement, which include a growing list of nonpharmacologic options, such as foods/nutrients, physical activity, sleep, and computerized training (171). A key area of further research in this field is the identification of treatment targets and the development of interventions that can be evaluated, and this is an aspect of the field that is still at an early stage.

A particular appeal of successful cognitive control approaches is their potential to be developed as preventative public health interventions. The data on the role of early life inhibitory control in determining BMI strongly support the ongoing interest in intervening in childhood. The development of a validated treatment approach that could be included in school curricula as a group level intervention/training to improve inhibitory control, for example, could have an important population-level effect over time, not

only on weight but possibly on other health-related behaviors such as substance use.

Conclusions

In this concluding paragraph we return to the food environment and particularly to food-related cues, which remain a relative constant whether we consider the addictive potential of certain foods or the ability to exercise cognitive control over intake. Such cues are ubiquitous, on television, street signs, and in the media. They can motivate consumption even in the absence of hunger and bias choices toward them (172). Advertising fosters associations between these cues and activities such as sport and socializing, and the relation between branding and advertising and food intake has been demonstrated (75, 173, 174). Although we may think of ourselves as rational arbitrators of food-related decisions, much of our food decisions are probably habitual, established by experience and driven by environmental cues (80, 113), which are not in short supply. The challenge for the individual is to control his or her intake in the face of an onslaught of such cues, and this would be particularly difficult for individuals with particular neurocognitive vulnerabilities such as poor inhibitory control. However, changing the food environment will be a major challenge that will require a collaborative effort by scientists, health care workers, industry, and lawmakers. Certainly, one appeal of the FOA idea is that, if this were to be conclusively demonstrated, it would provide an important and different impetus to this effort.

References

1. Swinburn BA, Sacks G, Hall KD, McPherson K, Finegood DT, Moodie ML, Gortmaker SL. The global obesity pandemic: shaped by global drivers and local environments. Lancet 2011;378:804–14.
2. Finucane MM, Stevens GA, Cowan MJ, Danaei G, Lin JK, Paciorek CJ, Singh GM, Gutierrez HR, Lu Y, Bahalim AN. National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants. Lancet 2011;377:557–67.
3. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011–2012. JAMA 2014;311:806–14.
4. Faith MS, Fontaine KR, Baskin ML, Allison DB. Toward the reduction of population obesity: macrolevel environmental approaches to the problems of food, eating, and obesity. Psychol Bull 2007;133:205–26.
5. Jones SC, Mannino N, Green J. "Like me, want me, buy me, eat me": relationship-building marketing communications in children's magazines. Public Health Nutr 2010;13:2111–8.
6. Berridge KC, Ho C-Y, Richard JM, Difeliceantonio AG. The tempted brain eats: pleasure and desire circuits in obesity and eating disorders. Brain Res 2010;1350:43–64.
7. Weingarten HP. Conditioned cues elicit feeding in sated rats: a role for learning in meal initiation. Science 1983;220:431–3.
8. Zheng H, Berthoud H-R. Neural systems controlling the drive to eat: mind versus metabolism. Physiology (Bethesda) 2008;23:75–83.
9. Lowe MR, Butryn MI. Hedonic hunger: a new dimension of appetite? Physiol Behav 2007;91:432–9.
10. Hill JO, Wyatt HR, Melanson EL. Genetic and environmental contributions to obesity. Med Clin North Am 2000;84:333–46.
11. Morton GJ, Meek TH, Schwartz MW. Neurobiology of food intake in health and disease. Nat Rev Neurosci 2014;15:367–78.
12. Coll AP, Farooqi IS, O'Rahilly S. The hormonal control of food intake. Cell 2007;129:251–62.
13. Lenard NR, Berthoud H-R. Central and peripheral regulation of food intake and physical activity: pathways and genes. Obesity (Silver Spring) 2008;16: Suppl 3:S11–22.
14. Wu Q, Boyle MP, Palmiter RD. Loss of GABAergic signaling by AgRP neurons to the parabrachial nucleus leads to starvation. Cell 2009;137:1225–34.
15. Berthoud H-R. Multiple neural systems controlling food intake and body weight. Neurosci Biobehav Rev 2002;26:393–428.
16. Haber SN, Knutson B. The reward circuit: linking primate anatomy and human imaging. Neuropsychopharmacology 2010;35:4–26.
17. Berridge KC, Kringelbach ML. Affective neuroscience of pleasure: reward in humans and animals. Psychopharmacology (Berl) 2008;199:457–80.
18. Berridge KC, Robinson TE, Aldridge JW. Dissecting components of reward: 'liking', "wanting," and learning. Curr Opin Pharmacol 2009;9:65–73.
19. Berridge KC. 'Liking' and "wanting" food rewards: brain substrates and roles in eating disorders. Physiol Behav 2009;97:537–50.
20. Peciña S, Berridge KC. Hedonic hot spot in nucleus accumbens shell: where do mu-opioids cause increased hedonic impact of sweetness? J Neurosci 2005;25:11777–86.
21. Peciña S. Opioid reward 'liking' and "wanting" in the nucleus accumbens. Physiol Behav 2008;94:675–80.
22. Mahler SV, Smith KS, Berridge KC. Endocannabinoid hedonic hotspot for sensory pleasure: anandamide in nucleus accumbens shell enhances "liking" of a sweet reward. Neuropsychopharmacology 2007;32:2267–78.
23. Smith KS, Berridge KC. The ventral pallidum and hedonic reward: neurochemical maps of sucrose "liking" and food intake. J Neurosci 2005;25:8637–49.
24. Smith KS, Berridge KC. Opioid limbic circuit for reward: interaction between hedonic hotspots of nucleus accumbens and ventral pallidum. J Neurosci 2007;27:1594–605.
25. Wyvell CL, Berridge KC. Intra-accumbens amphetamine increases the conditioned incentive salience of sucrose reward: enhancement of reward "wanting" without enhanced "liking" or response reinforcement. J Neurosci 2000;20:8122–30.
26. Peciña S, Cagniard B, Berridge KC, Aldridge JW, Zhuang X. Hyperdopaminergic mutant mice have higher "wanting" but not "liking" for sweet rewards. J Neurosci 2003;23:9395–402.
27. Robinson TE, Berridge KC. Review. The incentive sensitization theory of addiction: some current issues. Philos Trans R Soc Lond B Biol Sci 2008;363:3137–46.
28. Berridge KC, Valenstein ES. What psychological process mediates feeding evoked by electrical stimulation of the lateral hypothalamus? Behav Neurosci 1991;105:3–14.
29. Kelley AE, Baldo BA, Pratt WE, Will MJ. Corticostriatal-hypothalamic circuitry and food motivation: integration of energy, action and reward. Physiol Behav 2005;86:773–95.
30. Zahm DS. An integrative neuroanatomical perspective on some subcortical substrates of adaptive responding with emphasis on the nucleus accumbens. Neurosci Biobehav Rev 2000;24:85–105.
31. Di Marzo V, Ligresti A, Cristino L. The endocannabinoid system as a link between homoeostatic and hedonic pathways involved in energy balance regulation. Int J Obes (Lond) 2009;33: Suppl 2:S18–24.
32. Cummings DE, Purnell JQ, Frayo RS, Schmidova K, Wisse BE, Weigle DS. A preprandial rise in plasma ghrelin levels suggests a role in meal initiation in humans. Diabetes 2001;50:1714–9.

33. Cummings DE. Ghrelin and the short-and long-term regulation of appetite and body weight. Physiol Behav 2006;89:71–84.

34. Anini Y, Hansotia T, Brubaker PL. Muscarinic receptors control postprandial release of glucagon-like peptide-1: in vivo and in vitro studies in rats. Endocrinology 2002;143:2420–6.

35. Williams KW, Elmquist JK. From neuroanatomy to behavior: central integration of peripheral signals regulating feeding behavior. Nat Neurosci 2012;15:1350–5.

36. Leinninger GM, Jo Y-H, Leshan RL, Louis GW, Yang H, Barrera JG, Wilson H, Opland DM, Faouzi MA, Gong Y, et al. Leptin acts via leptin receptor-expressing lateral hypothalamic neurons to modulate the mesolimbic dopamine system and suppress feeding. Cell Metab 2009;10:89–98.

37. Opland DM, Leinninger GM. Modulation of the mesolimbic dopamine system by leptin. Brain Res 2010;1350:65–70.

38. Farooqi IS, Bullmore E, Keogh J, Gillard J, O'Rahilly S, Fletcher PC. Leptin regulates striatal regions and human eating behavior (case report). Science 2007;317:1355.

39. Pannacciulli N, Le DSNT, Salbe AD, Chen K, Reiman EM, Tataranni PA, Krakoff J. Postprandial glucagon-like peptide-1 (GLP-1) response is positively associated with changes in neuronal activity of brain areas implicated in satiety and food intake regulation in humans. Neuroimage 2007;35:511–7.

40. Batterham RL, Ffytche DH, Rosenthal JM, Zelaya FO, Barker GJ, Withers DJ, Frost GS, Ghatei MA, Bloom SR. PYY modulation of cortical and hypothalamic brain areas predicts feeding behaviour in humans. Nature 2007;450:106–9.

41. Skibicka KP, Hansson C, Alvarez-Crespo M, Friberg PA, Dickson SL. Ghrelin directly targets the ventral tegmental area to increase food motivation. Neuroscience 2011;180:129–37.

42. Malik S, McGlone F, Bedrossian D, Dagher A. Ghrelin modulates brain activity in areas that control appetitive behavior. Cell Metab 2008;7:400–9.

43. Crespi EJ, Unkefer MK. Hormones and behavior. Horm Behav 2014; 66:74–85.

44. Bowles NP, Karatsoreos IN, Li X, Vemuri VK, Wood J-A, Li Z, Tamashiro KLK, Schwartz GJ, Makriyannis AM, Kunos G, et al. A peripheral endocannabinoid mechanism contributes to glucocorticoid-mediated metabolic syndrome. Proc Natl Acad Sci USA 2015;112: 285–90.

45. Berridge KC, Flynn FW, Schulkin J, Grill H. Sodium depletion enhances salt palatability in rats. Behav Neurosci 1984;98:652–60.

46. Tindell AJ, Smith KS, Peciña S, Berridge KC, Aldridge JW. Ventral pallidum firing codes hedonic reward: when a bad taste turns good. J Neurophysiol 2006;96:2399–409.

47. Robinson MJF, Berridge KC. Instant transformation of learned repulsion into motivational "wanting". Curr Biol 2013;23:282–9.

48. Small DM, Zatorre RJ, Dagher A, Evans AC, Jones-Gotman M. Changes in brain activity related to eating chocolate: from pleasure to aversion. Brain 2001;124:1720–33.

49. Berridge KC. Modulation of taste affect by hunger, caloric satiety, and sensory-specific satiety in the rat. Appetite 1991;16:103–20.

50. Carnell S, Gibson C, Benson L, Ochner CN, Geliebter A. Neuroimaging and obesity: current knowledge and future directions. Obes Rev 2012;13:43–56.

51. Okamoto M, Dan H, Shimizu K, Takeo K, Amita T, Oda I, Konishi I, Sakamoto K, Isobe S, Suzuki T. Multimodal assessment of cortical activation during apple peeling by NIRS and fMRI. Neuroimage 2004; 21:1275–88.

52. Stoeckel LE, Weller RE, Cook EW III, Twieg DB, Knowlton RC, Cox JE. Widespread reward-system activation in obese women in response to pictures of high-calorie foods. Neuroimage 2008;41:636–47.

53. Stice E, Spoor S, Bohon C, Small DM. Relation between obesity and blunted striatal response to food is moderated by TaqIA A1 allele. Science 2008;322:449–52.

54. O'Doherty J, Rolls ET, Francis S, Bowtell R, McGlone F, Kobal G, Renner B, Ahne G. Sensory-specific satiety-related olfactory activation of the human orbitofrontal cortex. Neuroreport 2000;11: 893–7.

55. Koob GF, Volkow ND. Neurocircuitry of addiction. Neuropsychopharmacology 2010;35:217–38.

56. Georgiadis JR, Kortekaas R, Kuipers R, Nieuwenburg A, Pruim J, Reinders AATS, Holstege G. Regional cerebral blood flow changes associated with clitorally induced orgasm in healthy women. Eur J Neurosci 2006;24:3305–16.

57. Holstege G, Georgiadis JR, Paans AMJ, Meiners LC, van der Graaf FHCE, Reinders AATS. Brain activation during human male ejaculation. J Neurosci 2003;23:9185–93.

58. Salimpoor VN, van den Bosch I, Kovacevic N, McIntosh AR, Dagher A, Zatorre RJ. Interactions between the nucleus accumbens and auditory cortices predict music reward value. Science 2013;340:216–9.

59. Pessiglione M, Schmidt L, Draganski B, Kalisch R, Lau H, Dolan RJ, Frith CD. How the brain translates money into force: a neuroimaging study of subliminal motivation. Science 2007;316:904–6.

60. Rothemund Y, Preuschhof C, Bohner G, Bauknecht H-C, Klingebiel R, Flor H, Klapp BF. Differential activation of the dorsal striatum by high-calorie visual food stimuli in obese individuals. Neuroimage 2007;37:410–21.

61. Killgore WDS, Yurgelun-Todd DA. Body mass predicts orbitofrontal activity during visual presentations of high-calorie foods. Neuroreport 2005;16:859–63.

62. Killgore WD, Young AD, Femia LA, Bogorodzki P, Rogowska J, Yurgelun-Todd DA. Cortical and limbic activation during viewing of high- versus low-calorie foods. Neuroimage 2003;19:1381–94.

63. Schienle A, Schäfer A, Hermann A, Vaitl D. Binge-eating disorder: reward sensitivity and brain activation to images of food. Biol Psychiatry 2009;65:654–61.

64. Brooks SJ, O'Daly OG, Uher R, Friederich H-C, Giampietro V, Brammer M, Williams SCR, Schioth HB, Treasure J, Campbell IC. Differential neural responses to food images in women with bulimia versus anorexia nervosa. PLoS One 2011;6:e22259.

65. Stice E, Spoor S, Ng J, Zald DH. Relation of obesity to consummatory and anticipatory food reward. Physiol Behav 2009;97:551–60.

66. Bohon C, Stice E. Reward abnormalities among women with full and subthreshold bulimia nervosa: a functional magnetic resonance imaging study. Int J Eat Disord 2011;44:585–95.

67. Stice E, Spoor S, Bohon C, Veldhuizen MG, Small DM. Relation of reward from food intake and anticipated food intake to obesity: a functional magnetic resonance imaging study. J Abnorm Psychol 2008;117:924–35.

68. Ng J, Stice E, Yokum S, Bohon C. An fMRI study of obesity, food reward, and perceived caloric density. Does a low-fat label make food less appealing? Appetite 2011;57:65–72.

69. Ziauddeen H, Farooqi IS, Fletcher PC. Obesity and the brain: how convincing is the addiction model? Nat Rev Neurosci 2012;13:279–86.

70. Stice E, Yokum S, Blum K, Bohon C. Weight gain is associated with reduced striatal response to palatable food. J Neurosci 2010;30: 13105–9.

71. Stice E, Yokum S, Burger K, Epstein L, Smolen A. Multilocus genetic composite reflecting dopamine signaling capacity predicts reward circuitry responsivity. J Neurosci 2012;32:10093–100.

72. Lawrence NS, Hinton EC, Parkinson JA, Lawrence AD. Nucleus accumbens response to food cues predicts subsequent snack consumption in women and increased body mass index in those with reduced self-control. Neuroimage 2012;63:415–22.

73. Burger KS, Stice E. Greater striatopallidal adaptive coding during cue-reward learning and food reward habituation predict future weight gain. Neuroimage 2014;99:122–8.

74. Babbs RK, Sun X, Felsted J, Chouinard-Decorte F, Veldhuizen MG, Small DM. Decreased caudate response to milkshake is associated with higher body mass index and greater impulsivity. Physiol Behav 2013;121:103–11.

75. Yokum S, Gearhardt AN, Harris JL, Brownell KD, Stice E. Individual differences in striatum activity to food commercials predict weight gain in adolescents. Obesity (Silver Spring) 2014;22:2544–51.

76. Miller EK, Cohen JD. An integrative theory of prefrontal cortex function. Annu Rev Neurosci 2001;24:167–202.

77. Heatherton TF, Wagner DD. Cognitive neuroscience of self-regulation failure. Trends Cogn Sci 2011;15:132–9.

78. Rangel A, Camerer C, Montague PR. A framework for studying the neurobiology of value-based decision making. Nat Rev Neurosci 2008;9:545–56.

79. Hare TA, Malmaud J, Rangel A. Focusing attention on the health aspects of foods changes value signals in vmPFC and improves dietary choice. J Neurosci 2011;31:11077–87.

80. Rangel A. Regulation of dietary choice by the decision-making circuitry. Nat Neurosci 2013;16:1717–24.

81. Alonso-Alonso M. Brain imaging, the prefrontal cortex, and obesity: where do we stand? Obes Weight Manag 2010;6:126–30.

82. Ersche KD, Jones PS, Williams GB, Turton AJ, Robbins TW, Bullmore ET. Abnormal brain structure implicated in stimulant drug addiction. Science 2012;335:601–4.

83. Aron AR, Behrens TE, Smith S, Frank MJ, Poldrack RA. Triangulating a cognitive control network using diffusion-weighted magnetic resonance imaging (MRI) and functional MRI. J Neurosci 2007;27:3743–52.

84. Dalley JW, Everitt BJ, Robbins TW. Impulsivity, compulsivity, and top-down cognitive control. Neuron 2011;69:680–94.

85. Diamond A. Executive functions. Annu Rev Psychol 2013;64:135–68.

86. Nederkoorn C, Smulders FTY, Havermans RC, Roefs A, Jansen A. Impulsivity in obese women. Appetite 2006;47:253–6.

87. Nederkoorn C, Braet C, Van Eijs Y, Tanghe A, Jansen A. Why obese children cannot resist food: the role of impulsivity. Eat Behav 2006;7:315–22.

88. Nederkoorn C, Jansen E, Mulkens S, Jansen A. Impulsivity predicts treatment outcome in obese children. Behav Res Ther 2007;45:1071–5.

89. Nederkoorn C, Guerrieri R, Havermans RC, Roefs A, Jansen A. The interactive effect of hunger and impulsivity on food intake and purchase in a virtual supermarket. Int J Obes (Lond) 2009;33:905–12.

90. Guerrieri R, Nederkoorn C, Stankiewicz K, Alberts H, Geschwind N, Martijn C, Jansen A. The influence of trait and induced state impulsivity on food intake in normal-weight healthy women. Appetite 2007;49:66–73.

91. Weller RE, Cook EWI, Avsar KB, Cox JE. Obese women show greater delay discounting than healthy-weight women. Appetite 2008;51:563–9.

92. Fitzpatrick S, Gilbert S, Serpell L. Systematic review: are overweight and obese individuals impaired on behavioural tasks of executive functioning? Neuropsychol Rev 2013;23:138–56.

93. Mischel W, Shoda Y, Peake PK. The nature of adolescent competencies predicted by preschool delay of gratification. J Pers Soc Psychol 1988;54:687–96.

94. Schlam TR, Wilson NL, Shoda Y, Mischel W, Ayduk O. Preschoolers' delay of gratification predicts their body mass 30 years later. J Pediatr 2013;162:90–3.

95. Seeyave DM, Coleman S, Appugliese D, Corwyn RF, Bradley RH, Davidson NS, Kaciroti N, Lumeng JC. Ability to delay gratification at age 4 years and risk of overweight at age 11 years. Arch Pediatr Adolesc Med 2009;163:303–8.

96. Le DSNT, Pannacciulli N, Chen K, Del Parigi A, Salbe AD, Reiman EM, Krakoff D. Less activation of the left dorsolateral prefrontal cortex in response to a meal: a feature of obesity. Am J Clin Nutr 2006;84:725–31.

97. Gautier JF, Del Parigi A, Chen K, Salbe AD, Bandy D, Pratley RE, Ravussin E, Reiman EM, Tataranni PA. Effect of satiation on brain activity in obese and lean women. Obes Res 2001;9:676–84.

98. Lindroos AK, Lissner L, Mathiassen ME, Karlsson J, Sullivan M, Bengtsson C, Sjostrom L. Dietary intake in relation to restrained eating, disinhibition, and hunger in obese and nonobese Swedish women. Obes Res 1997;5:175–82.

99. DelParigi A, Chen K, Salbe AD, Hill JO, Wing RR, Reiman EM, Tataranni PA. Successful dieters have increased neural activity in cortical areas involved in the control of behavior. Int J Obes (Lond) 2007;31:440–8.

100. Le DSN, Pannacciulli N, Chen K, Salbe AD, Del Parigi A, Hill JO, Wing RR, Reiman EM, Krakoff J. Less activation in the left dorsolateral prefrontal cortex in the reanalysis of the response to a meal in obese than in lean women and its association with successful weight loss. Am J Clin Nutr 2007;86:573–9. Erratum in: Am J Clin Nutr 2008;87:463.

101. Bryant EJ, King NA, Blundell JE. Disinhibition: its effects on appetite and weight regulation. Obes Rev 2008;9:409–19.

102. Bryant EJ, Caudwell P, Hopkins ME, King NA, Blundell JE. Psychomarkers of weight loss. The roles of TFEQ disinhibition and restraint in exercise-induced weight management. Appetite 2012;58:234–41.

103. Linde JA, Rothman AJ, Baldwin AS, Jeffery RW. The impact of self-efficacy on behavior change and weight change among overweight participants in a weight loss trial. Health Psychol 2006;25:282–91.

104. Wing RR, Papandonatos G, Fava JL, Gorin AA, Phelan S, McCaffery J, Tate DF. Maintaining large weight losses: the role of behavioral and psychological factors. J Consult Clin Psychol 2008;76:1015–21.

105. Davidson TL, Martin AA. Obesity: cognitive impairment and the failure to "eat right." Curr Biol 2014;24:R685–7.

106. Bayol SA, Farrington SJ, Stickland NC. A maternal 'junk food' diet in pregnancy and lactation promotes an exacerbated taste for 'junk food' and a greater propensity for obesity in rat offspring. Br J Nutr 2007;98:843–51.

107. Shefer G, Marcus Y, Stern N. Neuroscience and biobehavioral reviews. Neurosci Biobehav Rev 2013;37:2489–503.

108. Davidson TL, Kanoski SE, Chan K, Clegg DJ, Benoit SC, Jarrard LE. Hippocampal lesions impair retention of discriminative responding based on energy state cues. Behav Neurosci 2010;124:97–105.

109. Taki Y, Kinomura S, Sato K, Inoue K, Goto R, Okada K, Uchida S, Kawashima R, Fukuda H. Relationship between body mass index and gray matter volume in 1,428 healthy individuals. Obesity (Silver Spring) 2008;16:119–24.

110. Walther K, Birdsill AC, Glisky EL, Ryan L. Structural brain differences and cognitive functioning related to body mass index in older females. Hum Brain Mapp 2010;31:1052–64.

111. García-Ptacek S, Faxén-Irving G, Cermáková P, Eriksdotter M, Religa D. Body mass index in dementia. Eur J Clin Nutr 2014;68:1204–9.

112. Wansink B, Sobal J. Mindless eating. Environ Behav 2007;39:106–23.

113. Marteau TM, Hollands GJ, Fletcher PC. Changing human behavior to prevent disease: the importance of targeting automatic processes. Science 2012;337:1492–5.

114. Aarts H, Dijksterhuis A. Habits as knowledge structures: automaticity in goal-directed behavior. J Pers Soc Psychol 2000;78:53–63.

115. van Gaal S, Ridderinkhof KR, Fahrenfort JJ, Scholte HS, Lamme VAF. Frontal cortex mediates unconsciously triggered inhibitory control. J Neurosci 2008;28:8053–62.

116. Ziauddeen H, Fletcher PC. Is food addiction a valid and useful concept? Obes Rev 2013;14:19–28.

117. Avena NM, Rada P, Hoebel BG. Evidence for sugar addiction: behavioral and neurochemical effects of intermittent, excessive sugar intake. Neurosci Biobehav Rev 2008;32:20–39.

118. Bocarsly ME, Berner LA, Hoebel BG, Avena NM. Rats that binge eat fat-rich food do not show somatic signs or anxiety associated with opiate-like withdrawal: implications for nutrient-specific food addiction behaviors. Physiol Behav 2011;104:865–72.

119. Colantuoni C, Schwenker J, McCarthy J, Rada P, Ladenheim B, Cadet JL, Schwartz GJ, Moran TH, Hoebel BG. Excessive sugar intake alters binding to dopamine and mu-opioid receptors in the brain. Neuroreport 2001;12:3549–52.

120. Avena NM, Long KA, Hoebel BG. Sugar-dependent rats show enhanced responding for sugar after abstinence: evidence of a sugar deprivation effect. Physiol Behav 2005;84:359–62.

121. Avena NM, Rada P, Hoebel BG. Sugar and fat bingeing have notable differences in addictive-like behavior. J Nutr 2009;139:623–8.

122. Johnson PM, Kenny PJ. Dopamine D2 receptors in addiction-like reward dysfunction and compulsive eating in obese rats. Nat Neurosci 2010;13:635–41.

123. Oswald KD, Murdaugh DL, King VL, Boggiano MM. Motivation for palatable food despite consequences in an animal model of binge eating. Int J Eat Disord 2011;44:203–11.

124. Krasnova IN, Marchant NJ, Ladenheim B, McCoy MT, Panlilio LV, Bossert JM, Shaham Y, Cadet JL. Incubation of methamphetamine and palatable food craving after punishment-induced abstinence. Neuropsychopharmacology 2014;39:2008–16.

125. Avena NM, Rada P, Moise N, Hoebel BG. Sucrose sham feeding on a binge schedule releases accumbens dopamine repeatedly and eliminates the acetylcholine satiety response. Neuroscience 2006;139:813–20.

126. Rada P, Avena NM, Hoebel BG. Daily bingeing on sugar repeatedly releases dopamine in the accumbens shell. Neuroscience 2005;134:737–44.

127. Liang NC, Hajnal A, Norgren R. Sham feeding corn oil increases accumbens dopamine in the rat. Am J Physiol Regul Integr Comp Physiol 2006;291:R1236–9.

128. Geiger BM, Haburcak M, Avena NM, Moyer MC, Hoebel BG, Pothos EN. Deficits of mesolimbic dopamine neurotransmission in rat dietary obesity. Neuroscience 2009;159:1193–9.

129. Ahmed SH, Kenny PJ, Koob GF, Markou A. Neurobiological evidence for hedonic allostasis associated with escalating cocaine use. Nat Neurosci 2002;5:625–6.

130. Carelli RM, Ijames SG, Crumling AJ. Evidence that separate neural circuits in the nucleus accumbens encode cocaine versus "natural" (water and food) reward. J Neurosci 2000;20:4255–66.

131. Carelli RM, Wondolowski J. Selective encoding of cocaine versus natural rewards by nucleus accumbens neurons is not related to chronic drug exposure. J Neurosci 2003;23:11214–23.

132. Gearhardt AN, Corbin WR, Brownell KD. Food addiction: an examination of the diagnostic criteria for dependence. J Addict Med 2009;3:1–7.

133. Gearhardt AN, White MA, Masheb RM, Morgan PT, Crosby RD, Grilo CM. An examination of the food addiction construct in obese patients with binge eating disorder. Int J Eat Disord 2012;45:657–63.

134. Gearhardt AN, White MA, Masheb RM, Grilo CM. An examination of food addiction in a racially diverse sample of obese patients with binge eating disorder in primary care settings. Compr Psychiatry 2013;54:500–5.

135. Eichen DM, Lent MR, Goldbacher E, Foster GD. Exploration of "food addiction" in overweight and obese treatment-seeking adults. Appetite 2013;67:22–4.

136. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 4th ed, text revision (DSM-IV-TR). Arlington (VA): American Psychiatric Association; 2000.

137. Ifland JR, Preuss HG, Marcus MT, Rourke KM, Taylor WC, Burau K, Jacobs WS, Kadish W, Manso G. Refined food addiction: a classic substance use disorder. Med Hypotheses 2009;72:518–26.

138. Avena NM, Gold MS. Variety and hyperpalatability: are they promoting addictive overeating? Am J Clin Nutr 2011;94:367–8.

139. Gearhardt AN, Corbin WR, Brownell KD. Preliminary validation of the Yale Food Addiction Scale. Appetite 2009;52:430–6.

140. Anthony JC, Warner LA, Kessler RC. Comparative epidemiology of dependence on tobacco, alcohol, controlled substances, and inhalants: basic findings from the National Comorbidity Survey. Exp Clin Psychopharmacol 1994;2:244–68.

141. Davis C, Curtis C, Levitan RD, Carter JC, Kaplan AS, Kennedy JL. Evidence that "food addiction" is a valid phenotype of obesity. Appetite 2011;57:711–7.

142. Gearhardt ANA, Grilo CMC, DiLeone RJR, Brownell KDK, Potenza MNM. Can food be addictive? Public health and policy implications. Addiction 2011;106:1208–12.

143. Gearhardt AN, Roberto CA, Seamans MJ, Corbin WR, Brownell KD. Preliminary validation of the Yale Food Addiction Scale for children. Eat Behav 2013;14:508–12.

144. Stein RI, Kenardy J, Wiseman CV, Dounchis JZ, Arnow BA, Wilfley DE. What's driving the binge in binge eating disorder?: a prospective examination of precursors and consequences. Int J Eat Disord 2007;40:195–203.

145. Cassin SE, von Ranson KM. Is binge eating experienced as an addiction? Appetite 2007;49:687–90.

146. Striegel-Moore RH, Franko DL. Epidemiology of binge eating disorder. Int J Eat Disord 2003;34: Suppl 1:S19–29.

147. Meule A, von Rezori V, Blechert J. Food addiction and bulimia nervosa. Eur Eat Disord Rev 2014;22:331–7.

148. Gearhardt AN, Boswell RG, White MA. The association of "food addiction" with disordered eating and body mass index. Eat Behav 2014;15:427–33.

149. Granero R, Hilker I, Agüera Z, Jiménez-Murcia S, Sauchelli S, Islam MA, Fagundo AB, Sanchez I, Riesco N, Dieguez C, et al. Food addiction in a Spanish sample of eating disorders: DSM-5 diagnostic subtype differentiation and validation data. Eur Eat Disord Rev 2014;22:389–96.

150. Davis C, Loxton NJ. Addictive behaviors and addiction-prone personality traits: associations with a dopamine multilocus genetic profile. Addict Behav 2013;38:2306–12.

151. Wang G-J, Volkow ND, Logan J, Pappas NR, Wong CT, Zhu W, Netusil N, Fowler JS. Brain dopamine and obesity. Lancet 2001;357:354–7.

152. de Weijer BA, van de Giessen E, van Amelsvoort TA, Boot E, Braak B, Janssen IM, van de Laar A, Fliers E, Serlie MJ, Booij J. Lower striatal dopamine D2/3 receptor availability in obese compared with non-obese subjects. EJNMMI Res 2011;1:37.

153. van de Giessen E, Celik F, Schweitzer DH, van den Brink W, Booij J. Dopamine D2/3 receptor availability and amphetamine-induced dopamine release in obesity. J Psychopharmacol 2014;28:866–73.

154. Eisenstein SA, Antenor-Dorsey JA, Gredysa DM, Koller JM, Bihun EC, Ranck SA, Arbeláez AM, Klein S, Perlmutter JS, Moerlein SM, et al. A comparison of D2 receptor specific binding in obese and normal-weight individuals using PET with (N-[(11)C]methyl)benperidol. Synapse 2013;67:748–56.

155. Dunn JP, Kessler RM, Feurer ID, Volkow ND, Patterson BW, Ansari MS, Li R, Marks-Shulman P, Abumrad NN. Relationship of dopamine type 2 receptor binding potential with fasting neuroendocrine hormones and insulin sensitivity in human obesity. Diabetes Care 2012;35:1105–11.

156. Haltia LT, Rinne JO, Merisaari H, Maguire RP, Savontaus E, Helin S, Nagren K, Kaasinen V. Effects of intravenous glucose on dopaminergic function in the human brain in vivo. Synapse 2007;61:748–56.

157. Wang G-J, Geliebter A, Volkow ND, Telang FW, Logan J, Jayne MC, Galanti K, Selig PA, Han H, Zhu W, et al. Enhanced striatal dopamine release during food stimulation in binge eating disorder. Obesity (Silver Spring) 2011;19:1601–8.

158. Guo J, Simmons WK, Herscovitch P, Martin A, Hall KD. Striatal dopamine D2-like receptor correlation patterns with human obesity and opportunistic eating behavior. Mol Psychiatry 2014;19:1078–84.

159. Gearhardt AN, Yokum S, Orr PT, Stice E, Corbin WR, Brownell KD. Neural correlates of food addiction. Arch Gen Psychiatry 2011;68:808–16.

160. Ziauddeen H, Farooqi IS, Fletcher PC. Food addiction: is there a baby in the bathwater? Nat Rev Neurosci 2012;13:1–1.

161. Avena NM, Gearhardt AN, Gold MS, Wang G-J, Potenza MN. Tossing the baby out with the bathwater after a brief rinse? The potential downside of dismissing food addiction based on limited data. Nat Rev Neurosci 2012;13:514.

162. Latner JD, Puhl RM, Murakami JM, O'Brien KS. Food addiction as a causal model of obesity. Effects on stigma, blame, and perceived psychopathology. Appetite 2014;77:77–82.

163. Hebebrand J, Albayrak Ö, Adan R, Antel J, Dieguez C, de Jong J, Leng G, Menzies J, Mercer JG, Murphy M, et al. "Eating addiction", rather than "food addiction", better captures addictive-like eating behavior. Neurosci Biobehav Rev 2014;47:295–306.

164. Gearhardt A, Roberts M, Ashe M. If sugar is addictive...what does it mean for the law? J Law Med Ethics 2013;41 Suppl 1:46–9.

165. Wilson GT. Eating disorders, obesity and addiction. Eur Eat Disord Rev 2010;18:341–51.

166. Verbeken S, Braet C, Goossens L, van der Oord S. Executive function training with game elements for obese children: a novel treatment to enhance self-regulatory abilities for weight-control. Behav Res Ther 2013;51:290–9.

167. Johnson MF, Nichols JF, Sallis JF, Calfas KJ, Hovell MF. Interrelationships between physical activity and other health behaviors among university women and men. Prev Med 1998;27:536–44.

168. Joseph RJ, Alonso-Alonso M, Bond DS, Pascual-Leone A, Blackburn GL. The neurocognitive connection between physical activity and eating behaviour. Obes Rev 2011;12:800–12.

169. Martins C, Morgan L, Truby H. A review of the effects of exercise on appetite regulation: an obesity perspective. Int J Obes (Lond) 2008;32:1337–47.

170. Hillman CH, Erickson KI, Kramer AF. Be smart, exercise your heart: exercise effects on brain and cognition. Nat Rev Neurosci 2008;9:58–65.

171. Dresler M, Sandberg A, Ohla K, Bublitz C, Trenado C, Mroczko-Wasowicz A, Kuehn S, Repantis D. Non-pharmacological cognitive enhancement. Neuropharmacology 2013;64:529–43.

172. Johnson AW. Eating beyond metabolic need: how environmental cues influence feeding behavior. Trends Neurosci 2013;36:101–9.

173. Burger KS, Stice E. Neural responsivity during soft drink intake, anticipation, and advertisement exposure in habitually consuming youth. Obesity (Silver Spring) 2014;22:441–50.

174. Boyland EJ, Halford JCG. Television advertising and branding. Effects on eating behaviour and food preferences in children. Appetite 2013;62:236–41.