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The drive to eat: comparisons and distinctions between mechanisms of food reward and drug addiction

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The growing rates of obesity have prompted comparisons between the uncontrolled intake of food and drugs; however, an evaluation of the equivalence of food- and drug-related behaviors requires a thorough understanding of the underlying neural circuits driving each behavior. Although it has been attractive to borrow neurobiological concepts from addiction to explore compulsive food seeking, a more integrated model is needed to understand how food and drugs differ in their ability to drive behavior. In this Review, we will examine the commonalities and differences in the systems-level and behavioral responses to food and to drugs of abuse, with the goal of identifying areas of research that would address gaps in our understanding and ultimately identify new treatments for obesity or drug addiction.

Over the past several decades, the developed world has experienced a surge in obesity, with more than 30% of the United States population now considered obese and a much greater proportion considered overweight (http://www.cdc.gov/obesity/data/facts.html). The health consequences of obesity are enormous, leading to more than 200,000 premature deaths each year in the United States alone. Although the obesity epidemic is thought to have several causes, many of these converge to produce excess intake. The inability to control intake is reminiscent of drug addition, and comparisons between the uncontrolled intake of food and drugs have become a predominant[1], and somewhat controversial[2], component of obesity models. In this Review, we will examine the systems-level and behavioral responses to food and drugs of abuse. We will highlight the differences, as well as the commonalities, between the mechanisms driving food intake and drug seeking to identify areas of research that could cover gaps in knowledge of both obesity and addiction.

In our view, obesity should be treated as a behavioral problem in that many people want to use self-control to diet and lose weight but cannot. The distinction between the mechanisms involved in the physiological control of food intake and reward and those involved in the physio-pathological conditions leading to eating disorders and obesity are not yet understood. The distinction between health and disease is not clear in animal models, and is also less clear for sub-threshold eating disorders that do not reach the criteria for diagnosis as a clinical condition. This is the case with obesity (is it abnormal or normal to overeat?) and eating disorders, where no well-accepted animal model exists. Whereas caloric need clearly drives food seeking under conditions of scarcity, overeating when food is ubiquitous is driven by intake of highly palatable foods and continued eating even when metabolic demand has been met. It is this aspect of eating that has been compared most directly to drug addiction; however, to understand whether food- and drug-seeking behaviors are equivalent, it is critical to measure food reward and compulsive eating in models that have face validity for human eating and to define these behaviors more precisely. For example, tests of food intake behavior are often conducted in animals that have been food-restricted, and this may not reflect the neural mechanisms relevant in the overweight condition. In addition, an evaluation of the equivalence in food- and drug-related behaviors requires a thorough understanding of the underlying neural circuits driving each behavior to determine whether surface similarities in behavior are indeed related to common mechanisms. Many components of the neural systems contributing to food intake have been identified. These include identification of the molecules, such as the orexigenic and anorexigenic peptides, that contribute to food seeking under different conditions, as well as the neuroanatomical basis for some aspects of these behaviors (reviewed in refs. 3–5). Although it has been attractive to borrow neurobiological concepts from addiction to explore compulsive food seeking, important pieces of the story are still missing, and a more integrated vision of the underlying neurobiology is needed to understand how food and drugs differ in their ability to drive behavior.

Circuit-level comparisons between food and drug seeking

The decision to eat or not to eat and strategies for obtaining food are core elements of survival and are therefore highly susceptible to selection pressures during evolution. Drug addiction is commonly seen as 'hijacking' these natural reward pathways, and this view has informed much of the basic research that compares neural substrates of food and drug reward. We speculate that drugs of abuse engage only a subset of the circuits evolved for behaviors related to seeking the natural rewards essential for survival. That is, food intake is an evolved behavior that engages many integrated body systems and brain circuits. Drug addiction is also complex, but it starts with

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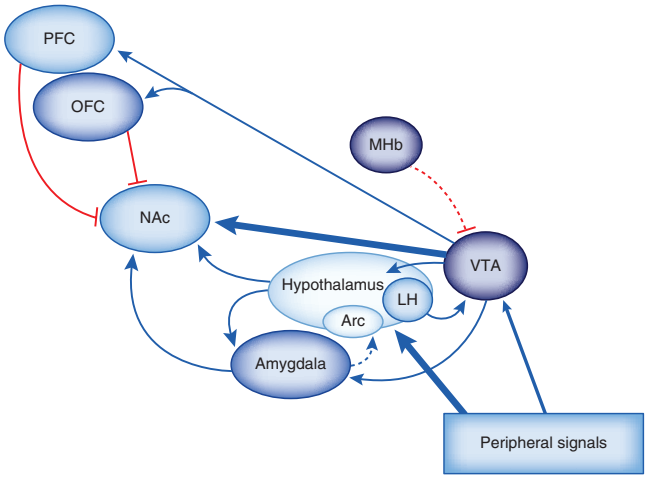

Figure 1 Areas of the brain mediating food intake and drug seeking. Areas that are most critical for food intake are depicted in lighter shades and those areas most critical for drug reward and seeking are depicted in darker shades. Most areas have some influence on both food and drug intake, and the spectrum represents this overlap. The hypothalamus is critical for food intake and is modulated by the darker shaded areas. The VTA and NAc are critical for drug seeking and are modulated by many other brain areas. Inputs from cortex and amygdala provide control over both food- and drug-related behaviors. Arc, arcuate nucleus; LH, lateral hypothalamus; MHb, medial habenula. Red lines, inhibitory connections; dashed lines, indirect projections. Thicker lines indicate stronger connections.

a pharmacological event that triggers downstream pathways that did not evolve to transmit the chemical signal in question.

Mesolimbic dopamine system. The initial site of action for addictive drugs is predominantly mesolimbic dopamine circuits[6] (see **Fig. 1**). In contrast, the role of mesolimbic circuits in food intake is more nuanced. Mesolimbic circuits influence many behaviors, including reward prediction[7], hedonia[8], reinforcement[9], motivation[10] and incentive salience[11]. In contrast to its effect on behaviors related to drug addiction, nucleus accumbens (NAc) dopamine depletion alone does not alter feeding[12]. Pharmacological blockade of D1 and D2 dopamine receptors in the NAc affects motor behavior and has small effects on feeding patterns, but it does not reduce the amount of food consumed[13]. Animals lacking dopamine throughout the brain and body do not eat[14,15]; however, it is difficult to distinguish effects on movement from those on intake and reinforcement *per se*. In fact, if food is placed into the mouth of animals lacking dopamine they will show normal sucrose preference, suggesting that animals can have hedonic responses for food in the absence of dopamine[16].

Hypothalamus. Although activity in the mesolimbic dopamine system is important for the rewarding and reinforcing properties of drugs of abuse and drives some aspects of food seeking as well, a major difference between food seeking and intake of addictive drugs is that hypothalamic nuclei receive and integrate signals, such as leptin and ghrelin, from peripheral tissues and coordinate peripheral metabolic need and food seeking[17] (see **Fig. 1**). Whereas activation of ventral tegmental area (VTA)-to-NAc dopamine signaling is necessary for drug self-administration, direct stimulation of neuropeptide Y (NPY)/agouti-related peptide (AgRP) neurons in the hypothalamus is sufficient to drive food intake, even in the absence of dopamine system activation[18]. Moreover, vagal feedback from the stomach and intestine has an important influence on brainstem activity and ultimately on food intake and metabolism[19]. The identification and study of these key signals has contributed greatly to our understanding of food intake and has resulted in models of feeding that incorporate both neural and whole body physiology. In contrast, neural models of drug intake often do not consider how the brain and body interact (although there are some exceptions, such as effects of corticosterone on addiction[20]). This is an area that deserves more attention in studies of drug addiction. Indeed, human studies, particularly studies of smokers, suggest that interoceptive cues are essential for ongoing drug taking behavior[21,22]. Similarly, we know that peripheral metabolic signals can influence dopamine system function and behavioral responses to both food and drugs of abuse[23,24].

Notably, hypothalamic nuclei, and particularly the lateral hypothalamus, also affect the rewarding properties of abused drugs[25]. This leads to the idea that the mesolimbic circuit mediates drug reinforcement, which is modulated by some hypothalamic systems, whereas the hypothalamus mediates food seeking and consumption, which is modulated by the dopaminergic system.

Hypothalamic-peripheral communication. In general, a distinction between drugs and food is most apparent when sensory and gustatory feedback is considered. In particular, gut-derived signals are critical determinants of both behavioral and metabolic responses to food[26]. This includes direct hormonal signals such as cholecystokinin (CCK) and ghrelin, as well as other physical and hormonal effects conveyed by the vagal nerves to the brainstem. Post-ingestive effects of food intake are also important regulators of food-related behaviors, and food is reinforcing when directly infused into the stomach[27], suggesting that the digestive system is a key component in modulating food intake.

Consistent with the central role of hypothalamic circuits in driving food intake, the termination of food seeking can also be induced by activation of a specific circuit: activation of pro-opiomelanocortin (POMC)-expressing neurons in the arcuate nucleus and the subsequent release of melanocortin peptides are thought to mediate satiety[18]. With drugs of abuse, recent work has identified the habenula as a brain area involved in aversion to nicotine[28,29] (see **Fig. 1**). This aversive component of drug response may be responsible for the well-known phenomenon of animals maintaining stable blood levels of drug in self-administration models[30]. Of note, tastants can also become aversive and lead to decreased reward sensitivity when given before drug self-administration[31]. Finally, drug satiety may also occur via aversive feedback from peripheral homeostatic systems regulating heart rate and blood pressure or from gut systems indicating gastrointestinal distress[32]. This highlights the need for further study of brain-periphery interactions in the regulation of drug intake. It should be noted that under conditions of extended drug access, animals will escalate their drug intake and this self-regulation is disrupted[33]. This will be discussed further below.

It is likely that the persistent strong aversion to foods that cause nausea or gastric pain evolved as protection against consumption of toxic agents. One pathway thought to be involved in disgust is the projection from the POMC neurons in the arcuate nucleus to the parabrachial nucleus[34]. A great deal of work has also implicated the amygdala and brain stem in conditioned taste aversion (the avoidance of a stimulus paired with a noxious tastant)[35]. Human imaging studies have suggested that disgust is also likely mediated by the brainstem as well as by the insular cortex[36], providing converging evidence that brainstem nuclei encode information about avoidance of noxious foods. The consequence of the existence of dedicated pathways mediating disgust is that the connection between the periphery,

in particular the digestive system, and the brain centers mediating food seeking provide a hardwired brake on food reward. This connection has been harnessed in the use of disulfiram (Antabuse) to provide protection against consumption of alcohol, the one addictive drug that is caloric. The consensus among clinicians is that the effects of disulfiram are due to the nausea and other aversive symptoms it causes if alcohol is consumed[37]. Although the dysphoric effect of disulfiram may be akin to the disruption of habitual responding to drug-paired cues after pairing with a noxious tastant, it may also be related to the peripheral connections from the digestive system that are particularly important for alcohol. In contrast, since most drugs of abuse are not ingested, this pathway has no effect on other drug seeking or taking.

Sensory perceptions of food are also key elements of intake, food memory and the drive to eat[38]. The sight and smell of food drive anticipatory behavior and motivation to eat. Again, it seems that drugs have co-opted circuits that evolved to connect our behavior to our environment. These sensory components of anticipatory behavior and consumption are also critical in addiction and relapse to drug intake[39]. Cues associated with drug use become secondary, or conditioned, reinforcers[39]. As these cues have gained incentive value, they appear to engage neural circuits similar to those that are normally triggered by sensory stimuli that predict food reward. An example of this is conditioned potentiation of feeding, in which a cue associated with eating can later increase food intake in a sated state[40]. This effect depends on amygdala-prefrontal-striatal circuits that also influence drug-associated conditioned reinforcers[40]. (Cue-driven drug taking will be discussed in more detail below.)

Although we have emphasized the behavioral control of food intake here to draw analogies with drug addiction, it is clear that metabolic adaptations also have substantial effects on body weight. It is notable that most manipulations that affect food intake in one direction also influence metabolism in a complementary fashion. For example, leptin decreases food intake while also increasing metabolic rate (decreased efficiency), leading to reduced weight[41]. There is no clear equivalent to this dual mode of action in drug addiction, where drug taking or seeking is the relevant measurement. This integration with other physiological systems can make the study of obesity more challenging because motivation to eat is only one component of overall weight control.

Cerebral cortex. Studies of drug addiction have incorporated frontal regions of the brain that have not been incorporated fully into animal models of intake. The prefrontal cortex (PFC) can influence drug reinstatement via interactions with mesolimbic and amygdala systems[42]. These models are generally consistent with the view that the PFC influences inhibitory control and that alterations in limbic cortico-striatal circuitry may be both a vulnerability factor for, and a consequence of, addiction[43,44]; however, rodent studies have shown little effect of PFC lesion on food intake[45]. It is notable that PFC lesions can also leave addictive behaviors such as self-administration intact[46] while impairing drug reinstatement[47]. The negative data showing little effect of cortical lesions on food intake are in contrast to a key study exploring the role of prefrontal μ-opioid receptors in food intake and locomotor behavior[48]. Infusion of a μ-opioid agonist in the PFC increases intake of sweet food. In addition, recent studies have identified molecular changes in the cortex in response to high-fat diets, suggesting that neuronal plasticity in cortex may contribute to diet-induced behavioral changes[49]. Molecular and cellular changes in prefrontal cortex have also been identified in response to diets such as highly palatable food[50,51]. These studies suggest that the PFC likely has a complex role in modulation of feeding behavior, and it is reasonable to assume that some sets of neurons may drive intake while others may inhibit the behavior. In addition, future work could focus on the orbitofrontal cortex (OFC) in impulsive or perseverant behaviors related to food intake, as cocaine, sucrose and food can all maintain responding in tasks dependent on the OFC.

Imaging studies in human subjects have also implicated frontal cortical regions in responses to food and control over intake[2]. For example, the orbitofrontal cortex responds to the odors and flavor of a palatable drink when it is being consumed[52]. In agreement with these data, patients with frontotemporal dementia demonstrate increased drive to eat, suggesting that loss of cortical control can disinhibit circuits promoting food intake[53]. This is consistent with the rodent studies described above showing that association of a cue or context with eating during a highly motivated (food-restricted) state will lead the animal to eat more in a sated state in response to the same cue or context[40].

Table 1 Effects of neuropeptides on food intake and cocaine reward

	Opioids	MCH	MC4	NPY	Galanin	Orexin	Leptin	NT	CART	Ghrelin
Food	+	+	–	+	+	+	–	–	–	+
Cocaine	+	+	+	+	–	+	–?	–	+	+

Results taken from refs. 1,48,54–59,63,82–93. MCH, melanin-concentrating hormone; MC4, melanocortin 4 receptor agonists; NT, neurotensin; CART, cocaine- and amphetamine-regulated transcript.

Neuropeptides involved in food and drug seeking

The neuropeptide systems regulating food intake and satiety can also modulate behavioral responses to drugs of abuse. The mechanisms that these neuropeptides subserve in food- and drug-related behaviors are distinct, however. Although there are some neuropeptides that modulate feeding and drug reward in the same direction, there is another group of neuropeptides that regulate food and drug intake in opposite directions. For example, the neuropeptides galanin[54] and NPY[55] both increase food intake, but NPY signaling increases cocaine reward[56], whereas galanin signaling decreases cocaine reward[57] (**Table 1**). Although there is a consensus that neuropeptides that increase VTA dopamine neuron firing augment responses to drugs and food[1], there are clearly additional, more complex, interactions that can over-rule this relationship. For example, melanocortin 4 activation augments cocaine reward[58], likely through increased dopamine signaling in the NAc, but decreases food intake through actions in the paraventricular nucleus of the hypothalamus[59]. Similar mechanisms are also involved in the ability of nicotine acting through nicotinic acetylcholine receptors (nAChRs) to potentiate conditioned reinforcement for sucrose through nAChRs in the VTA[60] and to decrease food intake through activation of nAChRs on POMC neurons in the hypothalamus[61].

The conditions under which drug reward or drug seeking and food intake are evaluated may contribute to some of these similarities and differences. There may be differences in the effects of neuropeptides on intake of highly palatable food and standard chow, or under satiated conditions and in obese animals[62]. Similarly, there may be differences in the effects of neuropeptides on drug seeking between animals that are drug naive or drug dependent or are tested in different behavioral models, such as conditioned place preference and self-administration[57,63]. This emphasizes the challenge and importance of studying food and drug intake using parallel, or equivalent, behavioral conditions.

Behavioral comparisons between food and drug seeking

In many ways, we have a greater understanding of the detailed neural and behavioral basis of drug intake and seeking than we do of food

intake and seeking. Addiction studies often involve detailed analysis of self-administration and reinstatement (relapse) that can model the human condition closely; however, it is notable that most behavioral studies done with drugs of abuse, such as operant studies, have been performed in hungry animals. Nonetheless, there is much less consensus on behavioral models that best capture the factors underlying obesity. That is, behavioral models of food seeking, such as responding on a progressive ratio schedule, may not be face-valid models of human food seeking.

Interestingly, whereas drugs are often thought to be very highly reinforcing, rodents are more likely to work for sweet rewards such as sucrose or saccharin, even when not food deprived, than to work for cocaine[64]. This may reflect a greater susceptibility to seeking of highly palatable foods than drugs of abuse at baseline as a result of differential stimulation of reward circuits by sweet tastants. Although extended access increases the reinforcing efficacy of cocaine much more than it increases that of sweet tastants, rodents are still more likely to work for sucrose or saccharin after chronic exposure to cocaine[64]. Although the neurobiological reasons for these differences are not known, one possibility is that the evolutionary advantage of obtaining sweet and highly caloric foods has resulted in several neuronal mechanisms driving seeking of these food rewards, whereas only a subset of these mechanisms are recruited by cocaine. This is speculative, however, and must be investigated in more detail through human imaging studies as well as animal models.

Repeated administration of sugar in a binge-like model does increase the locomotor response to an acute administration of amphetamine; however, one behavioral difference between intermittent sugar administration and intermittent administration of drugs of abuse is that there does not appear to be significant locomotor sensitization in response to sugar administration itself[65]. Similarly, some studies have shown escalation of drug intake, but not sucrose intake, in an extended access paradigm[33], although others have shown escalation of intake of a vanilla-flavored solution and, in other cases, saccharin or sucrose[66]. This suggests that drugs of abuse may be more likely to provoke neuronal plasticity that leads to increased responding over time.

Recent work has applied reinstatement models from drug addiction to studies of food intake[67]. This is a welcome development that is likely to help extend eating behavior research beyond models of free-feeding of chow, and into more specific behaviors with better face validity for human patterns of eating. At the same time, it is not clear if this relapse model captures the neural circuits that are engaged when people attempt to control their food intake. Part of the challenge that is inherent in studies of feeding, unlike studies of drugs, is the inability to withhold all food from the animals. The inability to provide a state of abstinence is a technical challenge, and it also reflects the complexities of dieting in human populations. Much recent research has focused on high-fat or sugar foods as the 'substance', but clearly people can gain weight on a variety of diets, given the current high rates of obesity.

Despite these caveats and the differences in initial escalation of food and drug intake, increased responding for both drug and a sweet tastant has been observed after increasing withdrawal time (incubation of craving)[68]. The incubation effect appears to be weaker for sucrose than for cocaine, however, and the increase in responding for sucrose peaks earlier in withdrawal than for cocaine[68]. In addition, after rodents have learned to self-administer cocaine or sucrose and the response has been extinguished, some studies suggest that stress (unpredictable footshock) can induce reinstatement of responding for cocaine but not for sucrose[69], although other studies have shown that stress can lead to food seeking[70]. This is relevant to the observation in human subjects that acute stress can precipitate binge eating[71]. Indeed, in rodent models, stress generally results in anorexia and decreased food seeking[72–74].

Some of these behavioral disparities may reflect differences in responses to substances that are ingested orally rather than administered through other routes. For example, rodents will approach and bite a lever that is presented with food and will slurp levers noncontingently presented with water, but these responses are not observed for cocaine, perhaps because no physical response is necessary to 'ingest' intravenously delivered drug[66].

Another area of difference between food intake and habitual responding for cues related to food is that, although animals and humans can become habitual in their food seeking (they will work for cues that predict food availability even if the food has been paired with an agent that causes gastric distress, such as lithium chloride), consumption of a food will decrease even though the animals have worked for its delivery[75]. In addition, the transition from goal-directed to habitual responding occurs more quickly for cues paired with drugs, including alcohol, than for food[76]. Indeed, goal-directed drug-seeking behavior has been argued to become habitual after prolonged self-administration[42,77]. Rodents show habitual drug-seeking responding that appears insensitive to devaluation. Although this study did not use lithium chloride to devalue cocaine, devaluation of the chained drug seeking–taking link by extinction did not disrupt habitual responding for cues after prolonged access to cocaine[78]. Recent work with food intake has shown that intake of high-fat diets can lead to "compulsive" intake despite negative consequences[79], which is another way to test for habitual behavior.

Overall, cues associated with availability of abused drugs result in more reinforcer-seeking behavior than food-paired cues after abstinence. Similarly, drug-associated behaviors appear to be more susceptible to stress-induced reinstatement than food-associated behaviors[66]. Of course, conditioned stimuli associated with drugs are both limited and discrete, and they become tightly associated with the interoceptive effects of the drugs that are powerful unconditioned stimuli. In contrast, cues associated with food are multimodal and less salient in terms of their interoceptive effects. Thus, food appears to be a more potent driver of behavior at baseline, whereas drugs of abuse seem to be more able to potentiate the control of behavior by conditioned environmental stimuli. Taken together, it has been suggested that cues that predict cocaine availability promote drug seeking more persistently than cues that predict availability of palatable tastants such as sucrose; thus, palatable foods may begin as relatively strong reinforcers compared to drugs of abuse, but the important factor in the development of addictive behavior may be that cocaine and other drugs can create associations that last longer than associations between stimuli paired with natural reinforcers such as food[66].

Conclusions and goals for future work

Comparisons of drug addiction and compulsive food intake leading to obesity must take into account the fundamental difference between modeling a 'disease state' (that is, addiction) and modeling a complex physiological response that may lead to later somatic disease. The goal of experiments on feeding is to identify circuits that evolved to respond to food scarcity and to determine what happens with those circuits under conditions of food abundance. In contrast, the goal of experiments on addiction is to model a human disorder that uses particular circuits evolved for a different purpose and, ultimately, to treat that disorder. Thus, abstinence is not a goal for control of food intake, but abstinence is an important goal of research on drug addiction.

The evolutionary pressures that lead to behaviors essential for survival have shaped feeding circuits to favor ongoing food intake over decreased food intake as a result of satiation. Similarly, the circuits evolved to protect against ingestion of toxic substances and promote disgust can dominate over the hedonic pathways that drive drug seeking. That said, it is important when considering distinctions between food and drug reward to distinguish apparent differences, which may stem from the limitations of existing knowledge, from true differences; that is, to explore potential commonalities. Of course, the acute toxic effects of drugs of abuse are distinct from the long-term consequences of overconsumption of palatable foods that lead to obesity.

There are both advantages and limitations of existing animal models of food intake, food reward and obesity. In many respects, animal models of food intake are representative of key biological and physiological processes regulating hunger and satiety. Further, the molecular and neural pathways underlying food intake appear to be conserved across species[80]; however, there are unique evolutionary contexts across species with different environmental pressures that result in differences between rodent models and the human condition.

One level of control that warrants further research, and may be different for behaviors related to food and drug intake, is the involvement of cortical activity. For example, the ability of discrete regions of the PFC to regulate self-control over subcortical motivational and hypothalamic circuits is not well-integrated into current animal models of food intake or binge eating. This is a major limitation considering data suggesting that top-down cortical control is critical for human food intake and regulation. In addition, there are excellent models for how whole-body systems and brain circuits contribute to food intake, but much less is known about how effects of drugs of abuse on peripheral systems contribute to addiction. Finally, there have been several behavioral studies that have used the same conditions to study the effects of food reinforcers and addictive drugs, but many comparisons have been made across studies that use different parameters and conditions to draw conclusions about similarities or differences in food- or drug-related responses. Side-by-side comparisons will be necessary to conclude that food reinforcement involves circuits and molecular substrates equivalent to those involved in drug addiction and results in behaviors that resemble drug addiction. Many drug self-administration studies have already used food or sucrose intake as a control condition. Reanalysis of these existing 'control' experiments may provide more information about the similarities and differences between food- and drug-related reinforcement and reinstatement, although additional naive or sham conditions may be needed to determine adaptations specific to food.

In conclusion, food 'addiction' does not have to be the same as drug addiction to be a major health problem. Moreover, many obese individuals may not show signs of addiction[81], as there are likely many behavioral paths to gaining weight. Identifying the parallels as well as the points of divergence between physiological and behavioral regulation of excessive food and drug intake will provide greater possibilities for interventions to combat both obesity and drug addiction.

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1. Kenny, P.J. Common cellular and molecular mechanisms in obesity and drug addiction. *Nat. Rev. Neurosci.* **12**, 638–651 (2011).
2. Ziauddeen, H., Farooqi, I.S. & Fletcher, P.C. Obesity and the brain: how convincing is the addiction model? *Nat. Rev. Neurosci.* **13**, 279–286 10.1038/nrn3212 (2012).
3. Baldo, B.A. & Kelley, A.E. Discrete neurochemical coding of distinguishable motivational processes: insights from nucleus accumbens control of feeding. *Psychopharmacology (Berl.)* **191**, 439–459 (2007).
4. Horvath, T.L. & Diano, S. The floating blueprint of hypothalamic feeding circuits. *Nat. Rev. Neurosci.* **5**, 662–667 (2004).
5. van den Pol, A.N. Weighing the role of hypothalamic feeding neurotransmitters. *Neuron* **40**, 1059–1061 (2003).
6. Koob, G.F. Drugs of abuse: anatomy, pharmacology and function of reward pathways. *Trends Pharmacol. Sci.* **13**, 177–184 (1992).
7. Schultz, W. Behavioral dopamine signals. *Trends Neurosci.* **30**, 203–210 (2007).
8. Wise, R.A., Spindler, J. & Legault, L. Major attenuation of food reward with performance-sparing doses of pimozide in the rat. *Can. J. Psychol.* **32**, 77–85 (1978).
9. Wise, R.A. Role of brain dopamine in food reward and reinforcement. *Phil. Trans. R. Soc. Lond. B* **361**, 1149–1158 (2006).
10. Wise, R.A. Dopamine, learning and motivation. *Nat. Rev. Neurosci.* **5**, 483–494 (2004).
11. Berridge, K.C. The debate over dopamine's role in reward: the case for incentive salience. *Psychopharmacology (Berl.)* **191**, 391–431 (2007).
12. Salamone, J.D., Mahan, K. & Rogers, S. Ventrolateral striatal dopamine depletions impair feeding and food handling in rats. *Pharmacol. Biochem. Behav.* **44**, 605–610 (1993).
13. Baldo, B.A., Sadeghian, K., Basso, A.M. & Kelley, A.E. Effects of selective dopamine D1 or D2 receptor blockade within nucleus accumbens subregions on ingestive behavior and associated motor activity. *Behav. Brain Res.* **137**, 165–177 (2002).
14. Palmiter, R.D. Is dopamine a physiologically relevant mediator of feeding behavior? *Trends Neurosci.* **30**, 375–381 (2007).
15. Zhou, Q.Y. & Palmiter, R.D. Dopamine-deficient mice are severely hypoactive, adipsic, and aphagic. *Cell* **83**, 1197–1209 (1995).
16. Cannon, C.M. & Palmiter, R.D. Reward without dopamine. *J. Neurosci.* **23**, 10827–10831 (2003).
17. Kelley, A.E., Baldo, B.A., Pratt, W.E. & Will, M.J. Corticostriatal-hypothalamic circuitry and food motivation: integration of energy, action and reward. *Physiol. Behav.* **86**, 773–795 (2005).
18. Aponte, Y., Atasoy, D. & Sternson, S.M. AGRP neurons are sufficient to orchestrate feeding behavior rapidly and without training. *Nat. Neurosci.* **14**, 351–355 (2011).
19. Schwartz, G.J. The role of gastrointestinal vagal afferents in the control of food intake: current prospects. *Nutrition* **16**, 866–873 (2000).
20. Goeders, N.E. Stress and cocaine addiction. *J. Pharmacol. Exp. Ther.* **301**, 785–789 (2002).
21. Dar, R. & Frenk, H. Do smokers self-administer pure nicotine? A review of the evidence. *Psychopharmacology (Berl.)* **173**, 18–26 (2004).
22. Gray, M.A. & Critchley, H.D. Interoceptive basis to craving. *Neuron* **54**, 183–186 (2007).
23. Hommel, J.D. *et al.* Leptin receptor signaling in midbrain dopamine neurons regulates feeding. *Neuron* **51**, 801–810 (2006).
24. Fulton, S. *et al.* Leptin regulation of the mesoaccumbens dopamine pathway. *Neuron* **51**, 811–822 (2006).
25. DiLeone, R.J., Georgescu, D. & Nestler, E.J. Lateral hypothalamic neuropeptides in reward and drug addiction. *Life Sci.* **73**, 759–768 (2003).
26. Havel, P.J. Peripheral signals conveying metabolic information to the brain: short-term and long-term regulation of food intake and energy homeostasis. *Exp. Biol. Med. (Maywood)* **226**, 963–977 (2001).
27. Ren, X. *et al.* Nutrient selection in the absence of taste receptor signaling. *J. Neurosci.* **30**, 8012–8023 (2010).
28. Fowler, C.D., Lu, Q., Johnson, P.M., Marks, M.J. & Kenny, P.J. Habenular alpha5 nicotinic receptor subunit signalling controls nicotine intake. *Nature* **471**, 597–601 (2011).
29. Frahm, S. *et al.* Aversion to nicotine is regulated by the balanced activity of beta4 and alpha5 nicotinic receptor subunits in the medial habenula. *Neuron* **70**, 522–535 (2011).
30. Koob, G.F. Animal models of drug addiction. in *Psychopharmacology: The Fourth Generation of Progress* (eds. Bloom, F.E. & Kupfer, D.J.) 759–772 (Lippincott Williams & Wilkins, 1995).
31. Wheeler, R.A. *et al.* Cocaine cues drive opposing context-dependent shifts in reward processing and emotional state. *Biol. Psychiatry* **69**, 1067–1074 (2011).
32. Wise, R.A. & Kiyatkin, E.A. Differentiating the rapid actions of cocaine. *Nat. Rev. Neurosci.* **12**, 479–484 (2011).
33. Ahmed, S.H. & Koob, G.F. Transition from moderate to excessive drug intake: change in hedonic set point. *Science* **282**, 298–300 (1998).
34. Wu, Q., Boyle, M.P. & Palmiter, R.D. Loss of GABAergic signaling by AgRP neurons to the parabrachial nucleus leads to starvation. *Cell* **137**, 1225–1234 (2009).
35. Yamamoto, T. Brain regions responsible for the expression of conditioned taste aversion in rats. *Chem. Senses* **32**, 105–109 (2007).

36. Stark, R. *et al.* Erotic and disgust-inducing pictures–differences in the hemodynamic responses of the brain. *Biol. Psychol.* **70**, 19–29 (2005).
37. Wright, C. & Moore, R.D. Disulfiram treatment of alcoholism. *Am. J. Med.* **88**, 647–655 (1990).
38. Sorensen, L.B., Moller, P., Flint, A., Martens, M. & Raben, A. Effect of sensory perception of foods on appetite and food intake: a review of studies on humans. *Int. J. Obes. Relat. Metab. Disord.* **27**, 1152–1166 (2003).
39. Stewart, J., de Wit, H. & Eikelboom, R. Role of unconditioned and conditioned drug effects in the self-administration of opiates and stimulants. *Psychol. Rev.* **91**, 251–268 (1984).
40. Seymour, B. Carry on eating: neural pathways mediating conditioned potentiation of feeding. *J. Neurosci.* **26**, 1061–1062 discussion 1062 (2006).
41. Singh, A. *et al.* Leptin-mediated changes in hepatic mitochondrial metabolism, structure, and protein levels. *Proc. Natl. Acad. Sci. USA* **106**, 13100–13105 (2009).
42. Everitt, B.J. & Robbins, T.W. Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. *Nat. Neurosci.* **8**, 1481–1489 (2005).
43. Dalley, J.W., Everitt, B.J. & Robbins, T.W. Impulsivity, compulsivity, and top-down cognitive control. *Neuron* **69**, 680–694 (2011).
44. Jentsch, J.D. & Taylor, J.R. Impulsivity resulting from frontostriatal dysfunction in drug abuse: implications for the control of behavior by reward-related stimuli. *Psychopharmacology (Berl.)* **146**, 373–390 (1999).
45. Davidson, T.L. *et al.* Contributions of the hippocampus and medial prefrontal cortex to energy and body weight regulation. *Hippocampus* **19**, 235–252 (2009).
46. Grakalic, I., Panlilio, L.V., Quiroz, C. & Schindler, C.W. Effects of orbitofrontal cortex lesions on cocaine self-administration. *Neuroscience* **165**, 313–324 (2010).
47. Kalivas, P.W., Volkow, N. & Seamans, J. Unmanageable motivation in addiction: a pathology in prefrontal-accumbens glutamate transmission. *Neuron* **45**, 647–650 (2005).
48. Mena, J.D., Sadeghian, K. & Baldo, B.A. Induction of hyperphagia and carbohydrate intake by mu-opioid receptor stimulation in circumscribed regions of frontal cortex. *J. Neurosci* **31**, 3249–3260 (2011).
49. Vucetic, Z., Kimmel, J. & Reyes, T.M. Chronic high-fat diet drives postnatal epigenetic regulation of mu-opioid receptor in the brain. *Neuropsychopharmacology* **36**, 1199–1206 (2011).
50. Guegan, T. *et al.* Operant behavior to obtain palatable food modifies ERK activity in the brain reward circuit. *Eur. Neuropsychopharmacol.* 10.1016/j.euroneuro.2012.04.009 (2012).
51. Guegan, T. *et al.* Operant behavior to obtain palatable food modifies neuronal plasticity in the brain reward circuit. *Eur. Neuropsychopharmacol.* 10.1016/j.euroneuro.2012.04.004 (2012).
52. Small, D.M., Veldhuizen, M.G., Felsted, J., Mak, Y.E. & McGlone, F. Separable substrates for anticipatory and consummatory food chemosensation. *Neuron* **57**, 786–797 (2008).
53. Piguet, O. Eating disturbance in behavioural-variant frontotemporal dementia. *J. Mol. Neurosci.* **45**, 589–593 (2011).
54. Kyrkouli, S.E., Stanley, B.G., Seirafi, R.D. & Leibowitz, S.F. Stimulation of feeding by galanin: anatomical localization and behavioral specificity of this peptide's effects in the brain. *Peptides* **11**, 995–1001 (1990).
55. Stanley, B.G. & Leibowitz, S.F. Neuropeptide Y injected in the paraventricular hypothalamus: a powerful stimulant of feeding behavior. *Proc. Natl. Acad. Sci. USA* **82**, 3940–3943 (1985).
56. Maric, T., Cantor, A., Cuccioletta, H., Tobin, S. & Shalev, U. Neuropeptide Y augments cocaine self-administration and cocaine-induced hyperlocomotion in rats. *Peptides* **30**, 721–726 (2009).
57. Narasimhaiah, R., Kamens, H.M. & Picciotto, M.R. Effects of galanin on cocaine-mediated conditioned place preference and ERK signaling in mice. *Psychopharmacology (Berl.)* **204**, 95–102 (2009).
58. Hsu, R. *et al.* Blockade of melanocortin transmission inhibits cocaine reward. *Eur. J. Neurosci.* **21**, 2233–2242 (2005).
59. Benoit, S.C. *et al.* A novel selective melanocortin-4 receptor agonist reduces food intake in rats and mice without producing aversive consequences. *J. Neurosci.* **20**, 3442–3448 (2000).
60. Löf, E., Olausson, P., Stomberg, R., Taylor, J.R. & Soderpalm, B. Nicotinic acetylcholine receptors are required for the conditioned reinforcing properties of sucrose-associated cues. *Psychopharmacology (Berl.)* **212**, 321–328 (2010).
61. Mineur, Y.S. *et al.* Nicotine decreases food intake through activation of POMC neurons. *Science* **332**, 1330–1332 (2011).
62. Zhang, M., Gosnell, B.A. & Kelley, A.E. Intake of high-fat food is selectively enhanced by mu opioid receptor stimulation within the nucleus accumbens. *J. Pharmacol. Exp. Ther.* **285**, 908–914 (1998).
63. Brabant, C., Kuschpel, A.S. & Picciotto, M.R. Locomotion and self-administration induced by cocaine in 129/OlaHsd mice lacking galanin. *Behav. Neurosci.* **124**, 828–838 (2010).
64. Lenoir, M., Serre, F., Cantin, L. & Ahmed, S.H. Intense sweetness surpasses cocaine reward. *PLoS ONE* **2**, e698 (2007).
65. Avena, N.M. & Hoebel, B.G. A diet promoting sugar dependency causes behavioral cross-sensitization to a low dose of amphetamine. *Neuroscience* **122**, 17–20 (2003).
66. Kearns, D.N., Gomez-Serrano, M.A. & Tunstall, B.J. A review of preclinical research demonstrating that drug and non-drug reinforcers differentially affect behavior. *Curr. Drug Abuse Rev.* **4**, 261–269 (2011).
67. Pickens, C.L. *et al.* Effect of fenfluramine on reinstatement of food seeking in female and male rats: implications for the predictive validity of the reinstatement model. *Psychopharmacology (Berl.)* **221**, 341–353 (2012).
68. Lu, L., Grimm, J.W., Hope, B.T. & Shaham, Y. Incubation of cocaine craving after withdrawal: a review of preclinical data. *Neuropharmacology* **47** (suppl. 1) 214–226 (2004).
69. Ahmed, S.H. & Koob, G.F. Cocaine- but not food-seeking behavior is reinstated by stress after extinction. *Psychopharmacology (Berl.)* **132**, 289–295 (1997).
70. Nair, S.G., Gray, S.M. & Ghitza, U.E. Role of food type in yohimbine- and pellet-priming-induced reinstatement of food seeking. *Physiol. Behav.* **88**, 559–566 (2006).
71. Troop, N.A. & Treasure, J.L. Psychosocial factors in the onset of eating disorders: responses to life-events and difficulties. *Br. J. Med. Psychol.* **70**, 373–385 (1997).
72. Blanchard, D.C. *et al.* Visible burrow system as a model of chronic social stress: behavioral and neuroendocrine correlates. *Psychoneuroendocrinology* **20**, 117–134 (1995).
73. Dulawa, S.C. & Hen, R. Recent advances in animal models of chronic antidepressant effects: the novelty-induced hypophagia test. *Neurosci. Biobehav. Rev.* **29**, 771–783 (2005).
74. Smagin, G.N., Howell, L.A., Redmann, S. Jr., Ryan, D.H. & Harris, R.B. Prevention of stress-induced weight loss by third ventricle CRF receptor antagonist. *Am. J. Physiol.* **276**, R1461–R1468 (1999).
75. Torregrossa, M.M., Quinn, J.J. & Taylor, J.R. Impulsivity, compulsivity, and habit: the role of orbitofrontal cortex revisited. *Biol. Psychiatry* **63**, 253–255 (2008).
76. Pierce, R.C. & Vanderschuren, L.J. Kicking the habit: the neural basis of ingrained behaviors in cocaine addiction. *Neurosci. Biobehav. Rev.* **35**, 212–219 (2010).
77. Belin, D. & Everitt, B.J. Cocaine seeking habits depend upon dopamine-dependent serial connectivity linking the ventral with the dorsal striatum. *Neuron* **57**, 432–441 (2008).
78. Zapata, A., Minney, V.L. & Shippenberg, T.S. Shift from goal-directed to habitual cocaine seeking after prolonged experience in rats. *J. Neurosci.* **30**, 15457–15463 (2010).
79. Johnson, P.M. & Kenny, P.J. Dopamine D2 receptors in addiction-like reward dysfunction and compulsive eating in obese rats. *Nat. Neurosci.* **13**, 635–641 (2010).
80. Forlano, P.M. & Cone, R.D. Conserved neurochemical pathways involved in hypothalamic control of energy homeostasis. *J. Comp. Neurol.* **505**, 235–248 (2007).
81. Gearhardt, A.N., Corbin, W.R. & Brownell, K.D. Food addiction: an examination of the diagnostic criteria for dependence. *J. Addict. Med.* **3**, 1–7 (2009).
82. DiLeone, R.J., Georgescu, D. & Nestler, E.J. Lateral hypothalamic neuropeptides in reward and drug addiction. *Life Sci.* **73**, 759–768 (2003).
83. Shalev, U., Yap, J. & Shaham, Y. Leptin attenuates acute food deprivation-induced relapse to heroin seeking. *J. Neurosci.* **21**, RC129 (2001).
84. Smith, R.J., Tahsili-Fahadan, P. & Aston-Jones, G. Orexin/hypocretin is necessary for context-driven cocaine-seeking. *Neuropharmacology* **58**, 179–184 (2010).
85. Shiraishi, T., Oomura, Y., Sasaki, K. & Wayner, M.J. Effects of leptin and orexin-A on food intake and feeding related hypothalamic neurons. *Physiol. Behav.* **71**, 251–261 (2000).
86. Edwards, C.M. *et al.* The effect of the orexins on food intake: comparison with neuropeptide Y, melanin-concentrating hormone and galanin. *J. Endocrinol.* **160**, R7–R12 (1999).
87. Chung, S. *et al.* The melanin-concentrating hormone system modulates cocaine reward. *Proc. Natl. Acad. Sci. USA* **106**, 6772–6777 (2009).
88. Boules, M. *et al.* The neurotensin receptor agonist NT69L suppresses sucrose-reinforced operant behavior in the rat. *Brain Res.* **1127**, 90–98 (2007).
89. Richelson, E., Boules, M. & Fredrickson, P. Neurotensin agonists: possible drugs for treatment of psychostimulant abuse. *Life Sci.* **73**, 679–690 (2003).
90. Hunter, R.G. & Kuhar, M.J. CART peptides as targets for CNS drug development. *Curr. Drug Targets CNS Neurol. Disord.* **2**, 201–205 (2003).
91. Jerlhag, E., Egecioglu, E., Dickson, S.L. & Engel, J.A. Ghrelin receptor antagonism attenuates cocaine- and amphetamine-induced locomotor stimulation, accumbal dopamine release, and conditioned place preference. *Psychopharmacology (Berl.)* **211**, 415–422 (2010).
92. Abizaid, A. *et al.* Reduced locomotor responses to cocaine in ghrelin-deficient mice. *Neuroscience* **192**, 500–506 (2011).
93. Abizaid, A. *et al.* Ghrelin modulates the activity and synaptic input organization of midbrain dopamine neurons while promoting appetite. *J. Clin. Invest.* **116**, 3229–3239 (2006).