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Pro v Con Reviews: Is Food Addictive?:

Obesity and addiction: neurobiological overlaps

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Summary

Drug addiction and obesity appear to share several properties. Both can be defined as disorders in which the saliency of a specific type of reward (food or drug) becomes exaggerated relative to, and at the expense of others rewards. Both drugs and food have powerful reinforcing effects, which are in part mediated by abrupt dopamine increases in the brain reward centres. The abrupt dopamine increases, in vulnerable individuals, can override the brain's homeostatic control mechanisms. These parallels have generated interest in understanding the shared vulnerabilities between addiction and obesity. Predictably, they also engendered a heated debate. Specifically, brain imaging studies are beginning to uncover common features between these two conditions and delineate some of the overlapping brain circuits whose dysfunctions may underlie the observed deficits. The combined results suggest that both obese and drug-addicted individuals suffer from impairments in dopaminergic pathways that regulate neuronal systems associated not only with reward sensitivity and incentive motivation, but also with conditioning, self-control, stress reactivity and interoceptive awareness. In parallel, studies are also delineating differences between them that centre on the key role that peripheral signals involved with homeostatic control exert on food intake. Here, we focus on the shared neurobiological substrates of obesity and addiction.

Keywords

Addiction; dopamine; obesity; prefrontal cortex

Background

Drugs of abuse tap into the neuronal mechanisms that modulate the motivation to consume food, thus, it is not surprising that there is an overlap in the neuronal mechanisms implicated in the loss of control and overconsumption of food intake seen in obesity and in the compulsive intake of drugs seen in addiction. Central to these two pathologies is the disruption of brain dopamine (DA) pathways, which modulate the behavioural responses to environmental stimuli. The dopamine neurons reside in midbrain nuclei (ventral tegmental area or VTA, and substantia nigra pars compacta or SN) that project to striatal (nucleus

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accumbens or NAc and the dorsal striatum), limbic (amygdala and hippocampus) and cortical regions (prefrontal cortex, cingulate gyrus, temporal pole) and modulate the motivation and sustainability of effort necessary to accomplish behaviours needed for survival. To achieve its functions, DA neurons receive projections from brain regions involved with autonomic responses (i.e. hypothalamus, brainstem), memory (hippocampus), emotional reactivity (amygdala), arousal (thalamus) and cognitive control (prefrontal cortex and cingulate) through a vast array of neurotransmitters and peptides. Thus, it is not surprising that neurotransmitters implicated in drug-seeking behaviours are also implicated in food intake and, conversely, that peptides that regulate food intake also influence the reinforcing effects of drugs (Tables 1 and 2). However, in striking contrast to drugs whose actions are triggered by their direct pharmacological effects in the brain reward DA pathway (NAc and ventral pallidum), the regulation of eating behaviours and hence the responses to food, are modulated by multiple peripheral and central mechanisms that directly or indirectly convey information to the brain's DA reward pathway with a particular prominent role of the hypothalamus (Fig. 1).

The peripheral signals include peptides and hormones (e.g. leptin, insulin, cholecystokinin or CCK, tumour necrosis factor-α) but also nutrients (e.g. sugars and lipids), that are transported *via* afferents of the vagus nerve to the nucleus solitary tract and directly through receptors located in the hypothalamus and other autonomic and limbic brain regions. These multiple signalling pathways ensure that food is consumed when needed, even if any one of these redundant mechanisms fails. However, with repeated access to highly palatable food, some individuals (both humans as well as laboratory animals) may eventually override the inhibitory processes that signal satiety and begin to compulsively consume large amounts of food despite nutrition overload and even repulsion at this behaviour in the case of humans. This loss of control and compulsive pattern of food intake is reminiscent of the drug intake patterns seen in addiction and has led to the description of obesity as a form of 'food addiction' (1).

The brain DA reward circuitry, which modulates the responses to the environment, increases the probability that behaviours that activate it (food consumption or drug intake) will be repeated when encountering the same rein-forcer (specific food or drug). Disruption of the DA reward circuit has been implicated in the loss of control seen in both addiction and obesity (2), although the physiological mechanisms that disrupt the function of the DA striatal circuits, including those implicated in reward (ventral striatum) and in habit formation (dorsal striatum), present clear divergences (3). In addition, self-control and compulsive intake (whether of food or drugs) occurs in a dimensional continuum, strongly influenced by the context, which can go from total control to no control at all. The fact that the same individual can exert better control in some circumstances than in others indicates that these are dynamic and flexible processes in the brain. It is when these patterns (loss of control and compulsive intake) become rigid and dictate the behaviour and choices of the individual, despite their adverse consequences, that a pathological state akin to the concept of addiction can be invoked. However, just as most individuals that consume drugs are not addicted, most individuals that eat excessively retain control over their food intake in some instances but not in others. However, the debate over whether obesity reflects 'food addiction' fails to consider the dimensional nature of these two disorders.

Proposals have also been made to model drug addiction as an infectious disease (4,5), which are useful for analyzing its social, epidemiological and economic components (4,6) but lead to the notion that drugs are like infectious agents and that addiction can be solved by eradicating drugs. A corollary is the belief that getting rid of palatable foods would solve 'food addiction'. But this agent-centred conceptual framework flies in the face of our current understanding of drugs (and other behavioural patterns, including disordered eating) as part of a vast and heterogeneous family of 'triggers', with the ability to expose, under the suitable (environmental) circumstances, an underlying (biological) vulnerability.

Finally, this debate is further hindered by the very word 'addiction', which conjures up the stigma linked to a character flaw, thus making it hard to get past its negative connotations. Here, we propose a position that recognizes the fact that these two diseases share neurobiological processes that, when disrupted, can result in compulsive consumption and loss of control in a dimensional continuum, while also involving unique neurobiological processes (Fig. 2). We present key evidence, at various phenomenological levels, of shared neurobiological substrates.

The overwhelming urge to seek and consume a drug is one of the hallmarks of addiction. Multidisciplinary research has linked such powerful craving to adaptations in the brain circuitry in charge of anticipating and assessing reward and learning conditioned associations that drive habits and automatic behaviours (7). In parallel, there are impairments in circuits involved with self-control and decision-making, interoception and mood and stress regulation (8). This functional model of addiction can also be used to understand why *some* obese individuals find it so difficult to properly regulate their caloric intake and maintain energy homeostasis. It is important to mention that we use 'obesity' for the sake of simplicity, for this dimensional analysis also encompasses non-obese individuals suffering from other eating disorders (e.g. binge eating disorder [BED] and anorexia nervosa) (9,10), which are also likely to involve imbalances in reward and self-control circuits.

The evolution of eating behaviours was driven by the need to attain the energy homeostasis required for survival and shaped by complex regulatory mechanisms that involve central (e.g. hypothalamus) and peripheral (e.g. stomach, gastrointestinal tract, fat tissue) structures. Most of the differences between addiction and obesity pathophysiologies arise from dysfunctions at this level of regulation, namely, energy homeostasis. But feeding behaviours are also influenced by another layer of regulation that involves processing of rewards through DA signalling and its ability to condition food-associated stimuli that then will trigger the desire for the associated food. Research is uncovering a high level of communication between these two regulatory processes, such that the line between the homeostatic and the hedonic control of feeding behaviours is becoming increasingly blurred (Tables 1 and 2). A good example is the new genetic, pharmacological and neuroimaging evidence showing direct influences of certain peptide hormones (e.g. peptide YY [PYY], ghrelin and leptin) on DA-modulated regions including those involved in reward (VTA, NAc and ventral pallidum), self-control (prefrontal cortices), interoception (cingulate, insula), emotions (amygdala), habits and routines (dorsal striatum) and learning memory (hippocampus) (11).

Dopamine at the centre of brain networks mediating reactivity to environmental stimuli

Virtually every complex system relies on a highly organized network that mediates effective tradeoffs among efficiency, robustness and evolvability. It has been noted that studying the predictable fragilities of such networks offers some of the best avenues to understand disease pathogenesis (12). In most cases, these networks are arranged in a layered architecture that is often referred to as a 'bow tie' (12), whereby a narrowing funnel of many potential inputs converges onto a relatively small number of processes before fanning out again into a diversity of outputs. Eating behaviours present a great example of this architecture where the hypothalamus subserves the 'knot' of the metabolic bowtie (Fig. 3a) and the DA pathways subserve the 'knot' for reactivity to salient external stimuli (including drugs and food) and internal signals (including hypothalamic signalling and hormones such as leptin and insulin; Fig. 3b). Inasmuch as midbrain DA neurons (both VTA and SN) orchestrate the appropriate behavioural responses to a myriad of external and internal stimuli, they represent a critical 'knot' whose fragilities are bound to underlie dysfunctional responses to a broad array of inputs, including drug and food reward.

The role of dopamine in acute reward to drugs and food

Drugs of abuse act on the reward and ancillary circuits through different mechanisms; however, they all lead to sharp DA increases in the NAc. Interestingly, evidence has been accumulating that comparable dopaminergic responses are linked with food reward and that these mechanisms are likely to play a role in excessive food consumption and obesity. It is well known that certain foods, particularly those rich in sugars and fat, are potently rewarding (13) and can trigger addictive-like behaviours in laboratory animals (14,15). However, the response to foods in humans, is far more complex, and is influenced not just by its palatability but also by its availability (the patterns of restriction plus overeating, referred to as the eating topography (16)), its visual appeal, economics and incentives (i.e., 'super sizing' offers, soda combos), social routines for eating, alternative reinforcement and advertisements (17).

High-calorie foods can promote over-eating (i.e. eating that is uncoupled from energetic needs) and trigger learned associations between the stimulus and the reward (conditioning). In evolutionary terms, this property of palatable foods used to be advantageous in environments where food sources were scarce and/or unreliable because it ensured that food was eaten when available, enabling energy to be stored in the body (as fat) for future use. However, in societies like ours, where food is plentiful and ubiquitous, this adaptation has become a dangerous liability.

Several neurotransmitters, including DA, cannabinoids, opioids, gamma-aminobutyric acid (GABA) and serotonin, as well as hormones and neuropeptides involved in homeostatic regulation of food intake, such as insulin, orexin, leptin, ghrelin, PYY, glucagon-like peptide-1 (GLP-1) have been implicated in the rewarding effects of food and drugs (Tables 1 and 2) (18–21). Of these, DA has been the most thoroughly investigated and is the best characterized. Experiments in rodents have shown that, upon first exposure to a food reward,

the firing of DA neurons in the VTA increases with a resulting increase in DA release in NAc (22). There is also extensive evidence that peripheral signals that modulate food intake exert their actions in part by hypothalamic signalling to VTA but also by their direct effects on the VTA DA meso-accumbens and meso-limbic pathways. Orexigenic peptides/hormones increase the activity of VTA DA cells and increase DA release in NAc (main target of VTA DA neurons) when exposed to food stimuli, whereas anorexigenic ones inhibit DA firing and decrease DA release (23). Moreover, neurons in the VTA and/or NAc express GLP-1 (24,25), ghrelin (26,27), leptin (28,29), insulin (30), orexin (31) and melanocortin receptors (32). Thus, it is not surprising that an increasing number of studies are reporting that these hormone/ peptides can modulate the rewarding effects of drugs of abuse (Table 1), which is also consistent with findings of attenuated responses to drug rewards in animal models of obesity (33,34). In humans, there have been reports of an inverse relationship between body mass index (BMI) and recent illicit drug use (35) and of an association between obesity and a lower risk for substance use disorders (36). Indeed, obese individuals show lower rates of nicotine (37) and marijuana abuse (38) than non-obese individuals. Moreover, juxtaposed interventions that decrease BMI and reduce plasma levels of insulin and leptin enhance the sensitivity to psychostimulant drugs (39). This is consistent with preclinical (40) and clinical (41) studies showing dynamic associations between the changes in neuroendocrine hormones (e.g. insulin, leptin, ghrelin) triggered by food restriction and brain DA signalling and those of recent reports of a relationship between addictive personality and maladaptive eating behaviours following bariatric surgery (42,43). Taken together, these results strongly suggest the possibility that food and drugs may be competing for overlapping reward mechanisms.

Brain imaging studies are beginning to provide important clues about such overlapping functional circuitry. For example, in healthy, normal-weight human subjects, ingestion of palatable food releases DA in the striatum in proportion to the ratings of meal pleasantness (44), while food stimuli activate brain regions that are part of the reward circuitry of the brain (45). It has also been reported more recently, that healthy human volunteers show robust striatal activation upon receipt of a milkshake, and that frequent ice cream consumption blunts the striatal responses (46). Other imaging studies have also shown that, consistent with the findings in laboratory animals, anorexigenic peptides (e.g. insulin, leptin, PYY) decrease the sensitivity of the brain reward system to food reward, whereas orexigenic ones (e.g. ghrelin) increase it (see review (47)).

However, as is the case for drugs and addiction, food-induced increases in striatal DA alone cannot explain the difference between normal food intake and excessive compulsive food consumption since these responses are present in healthy individuals who do not eat excessively. Thus, downstream adaptations are likely to be involved in the loss of control over food intake just as is the case for drug intake.

The transition to compulsive consumption

Dopamine’s role in reinforcement is more complex than just coding for hedonic pleasure. Specifically, stimuli that cause fast and large increases in DA induce conditioned responses and elicit incentive motivation to procure them (48). This is important because, thanks to

conditioning, neutral stimuli that are linked to the reinforcer (whether a natural or a drug reinforcer) acquire the ability by themselves to increase DA in striatum (including NAc) in anticipation of the reward, thus engendering a strong motivation to perform and sustain the behaviours necessary to seek the drug or to seek the food (48). Thus, once conditioning has occurred, DA signals act as a predictor of reward (49), incentivizing the animal to perform the behaviour that will result in consuming the expected reward (drug or food). From preclinical studies, there is also evidence of a gradual shift in DA increases from NAc to dorsal striatum, which occurs for both, food and drugs. Specifically, whereas inherently rewarding novel stimuli engage ventral regions of the striatum (NAc), with repeated exposure, the cues associated with the reward then trigger DA increases in dorsal regions of the striatum (50). This transition is consistent with an initial involvement of the VTA and increasing involvement of SN and its associated dorso-striatalcortical network, with consolidated responses and routines.

The extensive glutamatergic afferents to DA neurons from regions involved in the processing of sensory (insula or primary gustatory cortex), homeostatic (hypothalamus), reward (NAc and ventral pallidum), emotional (amygdala and hippocampus) and multimodal (orbitofrontal cortex [OFC] for salience attribution) information, modulate their activity in response to rewards and to conditioned cues (51). Similarly, glutamatergic projections to the hypothalamus are involved in the neuroplastic changes that follow fasting and that facilitate feeding (52). For the reward network, projections from the amygdala and the OFC to DA neurons and to NAc are involved in conditioned responses to food (53) and drugs (54,55). Indeed, imaging studies showed that when non-obese male subjects were asked to inhibit their craving for food while being exposed to food cues, they exhibited decreased metabolic activity in amygdala and OFC (as well as in hippocampus), insula and striatum, and that the decreases in OFC were associated with reductions in food craving (56). A similar inhibition of the metabolic activity in the OFC (and also in NAc) has been observed in cocaine abusers when they were asked to inhibit their drug craving upon exposure to cocaine cues (57).

It should be mentioned in this context that, when compared to food cues, drug cues are more powerful triggers of reinforcer-seeking behaviour following a period of abstinence, at least in the case of animals that have not been food deprived (58). Also, once extinguished, drug-reinforced behaviours are far more susceptible to stress-induced reinstatement than food-reinforced behaviours (58). However, the difference appears to be one of degree rather than principle. Indeed, stress is not only associated with increased consumption of palatable foods and weight gain, but acute stress also uncovers a strong correlation between BMI and a potentiated activation in response to milkshake consumption in the OFC (59), a brain region that contributes to the encoding of salience and motivation. The dependence of the responses to food cues on the nutrition status (60,61) highlights the role of the homeostatic network in the control of the reward network, which in turn is also influenced by neuronal pathways that process stress.

The impact of dysfunction in self-control

The emergence of cue-conditioned cravings would not be as deleterious if they were not coupled with growing deficits in the brain’s ability to inhibit maladaptive behaviours.

Indeed, the capacity to inhibit prepotent responses and exert self-control is bound to contribute to an individual's ability to avoid engaging in excessive behaviours, such as taking drugs or eating past the point of satiety, and thus increasing his/her vulnerability to addiction (or obesity) (62,63).

Positron emission tomography (PET) studies have uncovered significant reductions in dopamine 2 receptor (D2R) availability in the striatum of addicted subjects that persist for months after protracted detoxification (reviewed in (64)). Similarly, preclinical studies in rodent and non-human primates have shown that repeated drug exposures are associated with reductions in striatal D2R levels and in D2R signalling (65–67). In the striatum, D2Rs mediate signalling in the striatal indirect pathway that modulates frontal cortical regions; and their down-regulation enhances sensitization to the effects of drugs in animal models (68), whereas their up-regulation interferes with drug consumption (69,70). Moreover, inhibition of striatal D2R or activation of D1R-expressing striatal neurons (which mediate signalling in the striatal direct pathway) enhance the sensitivity to the rewarding effects of drugs (71–73). However, the extent to which there are similar opposite regulatory processes for the direct and indirect pathways in food-eating behaviours remains to explored.

In humans addicted to drugs, the reduction in striatal D2R is associated with decreased activity of prefrontal regions, OFC, anterior cingulate gyrus (ACC) and dorsolateral prefrontal cortex (DLPFC) (67,74,75). Insofar as OFC, ACC and DLPFC are involved with salience attribution, inhibitory control/emotion regulation and decision-making, respectively, it has been postulated that their improper regulation by D2R-mediated DA signalling in addicted subjects could underlie the enhanced motivational value of drugs in their behaviour and the loss of control over drug intake (62). In addition, because impairments in OFC and ACC are associated with compulsive behaviours and impulsivity, DA's impaired modulation of these regions is likely to contribute to the compulsive and impulsive drug intake seen in addiction (76). A reverse scenario would depend on a pre-existing vulnerability for drug use in prefrontal regions, possibly exacerbated by further decreases in striatal D2R triggered by repeated drug use. Indeed, a study performed in subjects who, despite having a high risk for alcoholism (positive family history of alcoholism) were not alcoholics, revealed a higher than normal striatal D2R availability that was associated with normal metabolism in OFC, ACC and DLPFC (77). This suggests that, in these subjects at risk for alcoholism, the normal prefrontal function was linked to enhanced striatal D2R signalling, which in turn may have protected them from alcohol abuse. Interestingly, a recent study of siblings discordant for their addiction to stimulant drugs (78) showed brain differences in the morphology of the OFC, which were significantly smaller in the addicted sibling than in controls, whereas in the non-addicted siblings, the OFC did not differ from that of controls (79).

Evidence of dysregulated D2R striatal signalling has also been detected among obese individuals. Both preclinical and clinical studies have provided evidence of decreases in striatal D2R, which, through the NAc, are linked with reward and through the dorsal striatum with the establishment of habits and routines in obesity (80–82). So far, the one study that failed to detect a statistically significant reduction in striatal D2R between obese individuals and non-obese controls (83), may have been hampered by its low statistical

power (n = 5/group). It is important to emphasize that, while these studies cannot address the question of whether the emerging association between low D2R and high BMI points to causality, decreased striatal D2R availability has been linked to compulsive food intake in obese rodents (84) and with decreased metabolic activity in OFC and ACC in obese humans (63). Given that dysfunction in OFC and ACC results in compulsivity (see review (85)), this might be part of the mechanism by which low-striatal D2R signalling facilitates hyperphagia (86,87). In addition, since decreased striatal D2R-related signalling is also likely to reduce the sensitivity to other natural rewards, this deficit in obese individuals may also contribute to compensatory overeating (88). It is pertinent to mention that the relative imbalance between brain reward and inhibitory circuits differs between patients suffering from Prader–Willi syndrome (characterized by hyperphagia and hyperghrelinemia) and simply obese patients (87), which, highlights the complex dimensionality of these disorders and their diversity.

The hypothesis of compensatory overeating is consistent with preclinical evidence showing that decreased DA activity in VTA results in a dramatic increase in the consumption of high-fat foods (89). Similarly, compared with normal-weight individuals, obese individuals who were presented with pictures of high-calorie food (stimuli to which they are conditioned) showed increased neural activation in regions that are part of reward and motivation circuits (NAc, dorsal striatum, OFC, ACC, amygdala, hippocampus and insula) (90). By contrast, in normal-weight controls, the activation of the ACC and OFC (regions involved in salience attribution that project into the NAc) during presentation of high-calorie food was found to be negatively correlated with their BMI (91). This suggests a dynamic interaction between the amount of food eaten (reflected in part in the BMI) and the reactivity of reward regions to high-calorie food (reflected in the activation of OFC and ACC) in normal-weight individuals but which was not observed in obese individuals.

Surprisingly, obese individuals exhibited less activation of reward circuits from actual food consumption (*consummatory* food reward) than lean individuals, whereas they showed greater activation of somatosensory cortical regions that process palatability when they anticipated consumption (91). The latter observation corresponded to regions where a previous study had revealed enhanced activity in obese subjects tested without any stimulation (92). An enhanced activity in brain regions that process palatability could make obese subjects favour food over other natural reinforcers, whereas decreased activation of dopaminergic targets by the actual food consumption might lead to overconsumption as a means to compensate for weak D2R-mediated signalling (93). This blunted response to food consumption in the reward circuitry of obese individuals is reminiscent of the reduced DA increases triggered by drug consumption in addicted individuals when compared to non-addicted subjects (94). As seen in addiction, it is also possible that some eating disorders may actually result from hypersensitivity to conditioned food cues. Indeed, in non-obese individuals with BED, we documented higher than normal release of DA in dorsal striatum (caudate) when exposed to food cues and this increase predicted the severity of the binge eating behaviours (95).

The prefrontal cortex (PFC) plays a crucial role in executive function, including self-control. These processes are modulated by D1R and D2R (presumably also D4R) and thus, the

decreased activity in PFC, both in addiction and in obesity, is likely to contribute to poor self-control, impulsivity and high compulsivity. The lower-than-normal availability of D2R in the striatum of obese individuals, which has been associated with reduced activity in PFC and ACC (63) is therefore likely to contribute to their deficient control over food intake. Indeed, the negative correlation between BMI and striatal D2R reported in obese (81) and in overweight (96) individuals, as well as the correlation between BMI and decreased blood flow in prefrontal regions in healthy individuals (97,98) and decreased prefrontal metabolism in obese subjects (63) support this. A better understanding of the mechanisms that lead to impaired PFC function in obesity (or addiction) could facilitate the development of strategies to ameliorate, or perhaps even reverse, specific impairments in crucial cognitive domains. For example, delay discounting, which is the tendency to devalue a reward as a function of the temporal delay of its delivery, is one of the most extensively investigated cognitive operations in relation to disorders associated with impulsivity and compulsivity. Delay discounting has been most exhaustively investigated in drug abusers who exhibit an exaggerated preference of small-but-immediate over large-but-delayed rewards (99). However, studies performed with obese individuals have begun to uncover evidence of a preference for high, immediate rewards, despite an increased chance of suffering higher future losses (100,101). A recent functional magnetic resonance imaging (fMRI) study of executive function in obese women, for example, identified regional differences in brain activation during delayed discounting tasks that were predictive of future weight gain (102). Yet, another study found a positive correlation between BMI and *hyperbolic* discounting, whereby future *negative* payoffs are discounted less than future positive payoffs (103). Interestingly, delay discounting seems to depend on the function of the ventral striatum (104) and of the PFC, including OFC (105) and its connections to the NAc (106), and is sensitive to DA manipulations (107).

Overlapping dysfunction in the motivation circuits

Dopaminergic signalling also modulates motivation. Behavioural traits such as vigor, persistence and investing a continued effort towards achieving a goal, are all subject to modulation by DA acting through several target regions, including NAc, ACC, OFC, DLPFC, amygdala, dorsal striatum and ventral pallidum (108). Dysregulated DA signalling is associated with enhanced motivation to procure drugs, a hallmark of addiction, which is why drug-addicted individuals often engage in extreme behaviours to obtain drugs, even when they entail known severe and adverse consequences and may require sustained and complex behaviours to obtain them (109). Because drug taking becomes the main motivational drive in drug addiction (110), addicted subjects are aroused and motivated by the process of obtaining the drug but tend to become withdrawn and apathetic when exposed to non–drug-related activities. This shift has been studied by comparing the brain activation patterns occurring upon exposure to conditioned cues with those occurring in the absence of such cues. In contrast to the decreases in prefrontal activity reported in detoxified cocaine abusers when not stimulated with drug or drug cues (see review (64)), these prefrontal regions become activated when cocaine abusers are exposed to craving-inducing stimuli (either drugs or cues) (111–113). Moreover, when the responses to i.v. methylphenidate are compared between cocaine-addicted and non-addicted individuals, the former responded

with increased metabolism in ventral ACC and medial OFC (an effect associated with craving), while the latter showed decreased metabolism in these regions (114). This suggests that the activation of these prefrontal regions with drug exposure may be specific to addiction and associated with the enhanced desire for the drug. In addition, a study that prompted cocaine-addicted subjects to purposefully inhibit craving when exposed to drug cues showed that those subjects who were successful at inhibiting craving displayed decreased metabolism in medial OFC (which processes the motivational value of a reinforcer) and NAc (which predicts reward) (57). These findings further corroborate the involvement of OFC, ACC and striatum in the enhanced motivation to procure the drug seen in addiction.

The OFC is also involved in attributing salience value to food (115,116), helping to assess its expected pleasantness and palatability as a function of its context. PET studies with FDG to measure brain glucose metabolism in normal-weight individuals reported that exposure to food cues increased metabolic activity in OFC, which was associated with the desire for the food (117). The enhanced OFC activation by the food stimulation is likely to reflect downstream dopaminergic effects and participate in DA's involvement in the drive for food consumption. The OFC plays a role in learning stimulus-reinforcement associations and conditioning (118,119), supports conditioned-cue-elicited feeding (120) and probably contributes to overeating irrespective of hunger signals (121). Indeed, damage to the OFC can result in hyperphagia (122,123).

Clearly, some of the individual differences in executive function can constitute a prodromal risk for later obesity in some individuals, as revealed by a recent latent class analysis of 997 fourth graders in a school-based obesity prevention program (124). Interestingly, albeit predictably, a cross-sectional investigation of children's ability to self-regulate, solve problems and engage in goal-directed health behaviours reveals executive function proficiency to be negatively correlated not only with substance use but also with the consumption of high-calorie snack foods, and with sedentary behaviours (125).

In spite of some inconsistencies among studies, brain imaging data also support the notion that structural and functional changes in brain regions implicated in executive function (including inhibitory control) may be associated with high BMI in otherwise healthy individuals. For example, an MRI study done in elderly women, using voxel-based morphometry, found a negative correlation between BMI and grey matter volumes (including frontal regions), which, in the OFC, was associated with impaired executive function (126). Using PET to measure brain glucose metabolism in healthy controls, we reported a negative correlation between BMI and metabolic activity in DLPFC, OFC and ACC. In this study, the metabolic activity in prefrontal regions predicted the subjects' performance in tests of executive function (98). Similarly, a nuclear magnetic resonance spectroscopic study in healthy middle age and elderly controls showed that BMI was negatively associated with the levels of N-acetyl-aspartate (a marker of neuronal integrity) in frontal cortex and ACC (98,127).

Brain imaging studies comparing obese and lean individuals have also reported lower grey matter density in frontal regions (frontal operculum and middle frontal gyrus) and in post-

central gyrus and putamen (128). Another study found no differences in grey matter volumes between obese and lean subjects; however, it did record a positive correlation between white matter volume in basal brain structures and waist to hip ratios, a trend that was partially reversed by dieting (129). Interestingly, cortical areas, like the DPFC and OFC that are involved in inhibitory control, have also been found to become activated in successful dieters in response to meal consumption (130), suggesting a potential target for behavioural retraining in the treatment of obesity (and also in addiction).

The involvement of interoceptive circuitry

Neuroimaging studies have revealed that the middle insula plays a critical role in cravings for food, cocaine and cigarettes (131–133). The importance of the insula has been highlighted by a study that reported that smokers with damage to this region (but not smokers who had suffered extra-insular lesions) were able to stop smoking easily and without experiencing either cravings or relapse (134). The insula, particularly its more anterior regions, is reciprocally connected to several limbic regions (e.g. ventromedial prefrontal cortex, amygdala, and ventral striatum) and appears to have an interoceptive function, integrating the autonomic and visceral information with emotion and motivation, thus providing conscious awareness of these urges (135). Indeed, brain lesion studies suggest that the ventromedial PFC and insula are necessary components of the distributed circuits that support emotional decision-making (136). Consistent with this hypothesis, many imaging studies show differential activation of the insula during craving (135). Accordingly, the reactivity of this brain region has been suggested to serve as a biomarker to help predict relapse (137).

The insula is also a primary gustatory area, which participates in many aspects of eating behaviours, such as taste. In addition, the rostral insula (connected to primary taste cortex) provides information to the OFC that influences its multimodal representation of the pleasantness or reward value of incoming food (138). Because of the insula's involvement in the interoceptive sense of the body, in emotional awareness (139) and in motivation and emotion (138), a contribution of insular impairment in obesity should not be surprising. And indeed, gastric distension results in activation of the posterior insula, consistent with its role in the awareness of body states (in this case of fullness) (140). Moreover, in lean, but not in obese subjects, gastric distension resulted in activation of the amygdala and deactivation of the anterior insula (141). The lack of amygdalar response in obese subjects could reflect a blunted interoceptive awareness of bodily states linked with satiety (full stomach). Even though the modulation of insular activity by DA has been poorly investigated, it is recognized that DA is involved in the responses to tasting of palatable foods that are mediated through the insula (142). Human imaging studies have shown that tasting palatable foods activated the insula and midbrain areas (143,144). DA signalling may also be necessary for sensing the calorie content of food. For example, when normal-weight women tasted a sweetener with calories (sucrose), both the insula and dopaminergic midbrain areas became activated, whereas tasting a calorie-free sweetener (sucralose) only activated the insula (144). Obese subjects exhibit greater insular activation than normal controls when tasting a liquid meal that consists of sugar and fat (143). In contrast, when tasting sucrose, subjects who have recovered from anorexia nervosa show less insular activation and no

association with feelings of pleasantness as observed in controls (145). Furthermore, a recent fMRI study that compared brain responses to repeated presentations of appetizing and bland food pictures in morbidly obese vs. non-obese individuals (146) found functional changes in the responsiveness and interconnectivity among key regions of the reward circuit that might help explain the oversensitivity to food cues in obese individuals. The observed changes suggest excessive input from the amygdala and insula; these, in turn could trigger exaggerated stimulus-response learning and incentive motivation to food cues in the dorsal caudate nucleus, which could become overwhelming in light of weak inhibitory control by fronto-cortical regions.

The circuitry of aversion and stress reactivity

As mentioned before, training (conditioning) on a cue that predicts reward leads to dopaminergic cells firing in response to reward prediction, and not to the reward itself. On the other hand, and consistent with this logic, it has been observed that dopaminergic cells will fire *less than normal* if the expected reward fails to materialize (147). Cumulative evidence (148–151) points to the habenula as one of the regions that controls the decreases in firing of dopaminergic cells in VTA that may follow the failure to receive an expected reward (152). Thus, an enhanced sensitivity of the habenula, as a result of chronic drug exposures, could underlie a greater reactivity to drug cues when not followed by consumption of the drug or when the drug effects do not fulfil the expected reward outcome. Indeed, activation of the habenula, in animal models of cocaine addiction, has been associated with relapse to drug taking upon cue exposure (153,154). In the case of nicotine, a5 nicotinic receptors in the habenula appear to modulate the aversive responses to large doses of nicotine (155), and a5 and a2 receptors to modulate nicotine withdrawal (156). Because of the habenula's opposite response to that of DA neurons with reward exposure (deactivation vs. activation) and its activation with exposure to aversive stimuli, we refer here to the signalling from the habenula as conveying an 'antireward' input.

The habenula appears to play a similar role with regards to food reward. A highly palatable food diet can induce obesity in rats, with the weight increases correlating with increases in m-opioid peptide binding in the basolateral and basomedial amygdala. Interestingly, the medial habenula showed significantly higher m-opioid peptide binding (by approximately 40%) after exposure to the palatable food in the rats that gained weight (those that consumed more food) but not in those that did not (157). This suggests that the habenula may be involved in over-eating when palatable food is available. Moreover, neurons in the rostromedial tegmental nucleus, which receive a major input from the lateral habenula, project to VTA DA neurons and are activated after food deprivation (158). These findings are consistent with a role for the habenula (both medial and lateral) in mediating responses to aversive stimuli or to states of deprivation such as during dieting or drug withdrawal.

The involvement of the habenula as an antireward hub within emotional networks is consistent with prior theoretical models of addiction that postulated that sensitized stress reactivity and negative mood (mediated through enhanced sensitivity of the amygdala and increased signalling although the corticotrophin-releasing factor) drives drug intake in addiction (159). Similar antireward responses (including increased stress reactivity, negative

mood and discomfort) may also contribute to excessive food consumption in obesity and to the high propensity to relapse when dieting after exposure to a stressful or frustrating event.

In closing

The ability to resist the urge to use a drug or eat past the point of satiety requires the proper functioning of neuronal circuits involved in top-down control to oppose the conditioned responses that trigger the desire to ingest the food/ drug. Whether or not certain types of obesity should be defined as behavioural addictions (160), there are several identifiable circuits in the brain (2), whose dysfunctions uncover real and clinically meaningful parallels between the two disorders. The picture that is emerging is that obesity, similar to drug addiction (226), appears to result from imbalanced processing in a range of regions implicated in reward/saliency, motivation/drive, emotion/stress reactivity, memory/ conditioning, executive function/self-control and interoception, in addition to possible imbalances in the homeostatic regulation of food intake.

The data accumulated so far suggests that it is the discrepancy between the expectation for the drug/food effects (conditioned responses) and the blunted reward experience that sustains drug taking/food overconsumption behaviour in an attempt to attain the expected reward. Also, whether tested during early or protracted periods of abstinence/ dieting, addicted/obese subjects show lower D2R in striatum (including NAc), which are associated with decreases in baseline activity in frontal brain regions implicated in salience attribution (OFC) and inhibitory control (ACC and DLPFC), whose disruption results in compulsivity and impulsivity. Finally, evidence has also surfaced about the role of interoceptive and aversive circuitry in the systemic imbalances that result in the compulsive intake of either drugs or food. As a consequence of sequential disruptions in these circuits, individuals may experience (i) an enhanced motivational value of the drug/food (secondary to learned associations through conditioning and habits) at the expense of other reinforcers (secondary to decreased sensitivity of the reward circuit), (ii) an impaired ability to inhibit the intentional (goal-directed) actions triggered by the strong desire to take the drug/food (secondary to impaired executive function) that result in compulsive drug/food taking and (iii) enhanced stress and ‘antireward reactivity’ that results in impulsive drug taking to escape the aversive state.

The many mechanistic and behavioural parallels identified between addiction and obesity suggest the value of multipronged parallel therapeutic approaches for both of these disorders. Such approaches should attempt to decrease the reinforcing properties of drug/ food, re-establish/enhance the rewarding properties of alternative reinforcers, inhibit conditioned learned associations, enhance motivation for non-drug/food-related activities, decrease stress reactivity, improve mood and strengthen general-purpose self-control.

Abbreviations

D2R	dopamine 2 receptor
DA	dopamine

NAc nucleus accumbens

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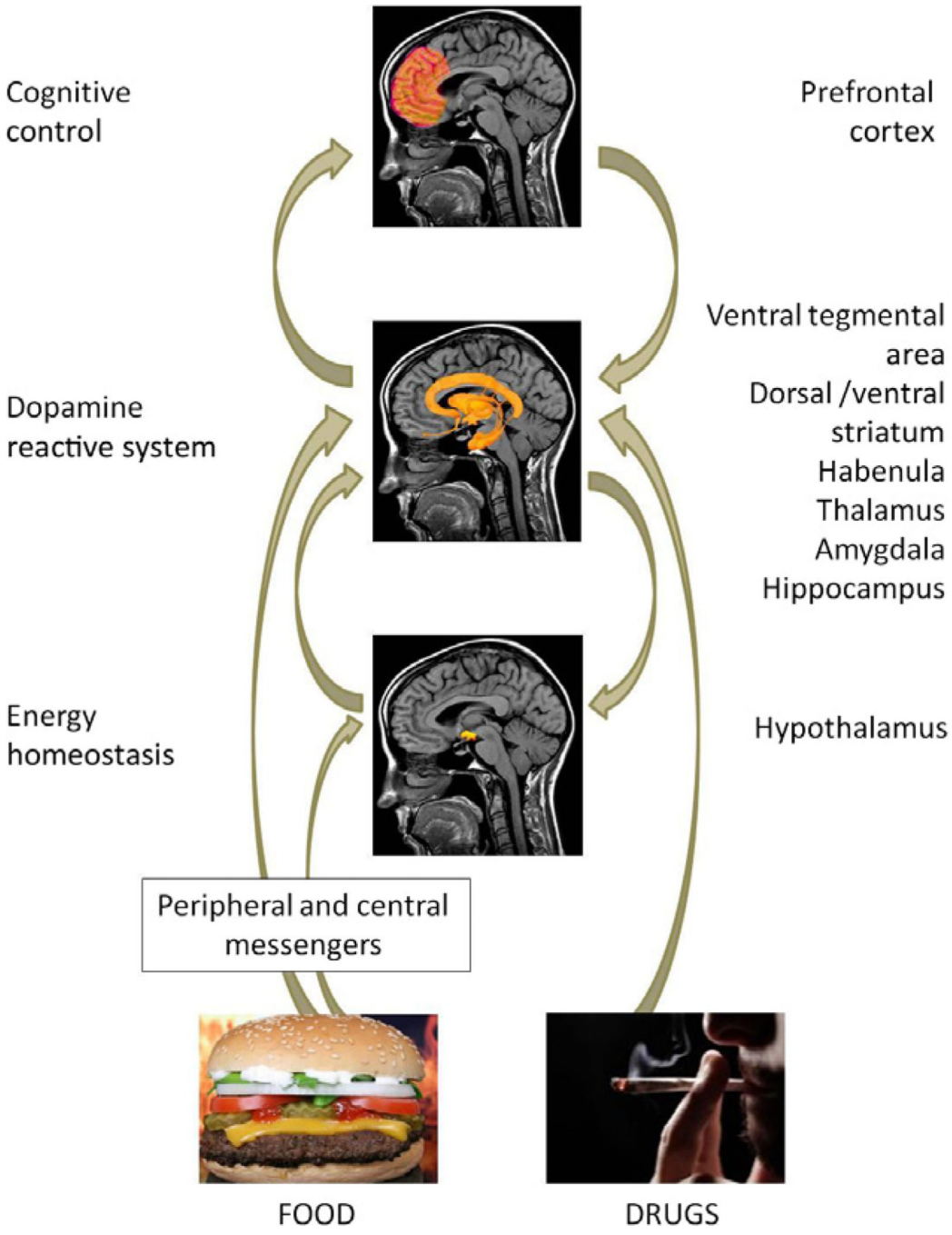

Figure 1.

Schematic representation of the highly interconnected system that affects the intake of food and drugs. It includes food-responsive peptides and hormones, energy homeostatic structures in the hypothalamus, the core of the dopamine reactive system in the ventral tegmental area and the striatum, and various cortical areas in charge of processing affect, motor and cognitive information. In contrast to drugs whose effects are exerted directly at the level of the brain reward dopamine pathway, food affects first multiple peripheral and central mechanisms that directly and indirectly convey information to the brain's DA reward

pathway. The hypothalamus plays a particularly prominent role in this regard although it is also strongly implicated in drug reward (225).

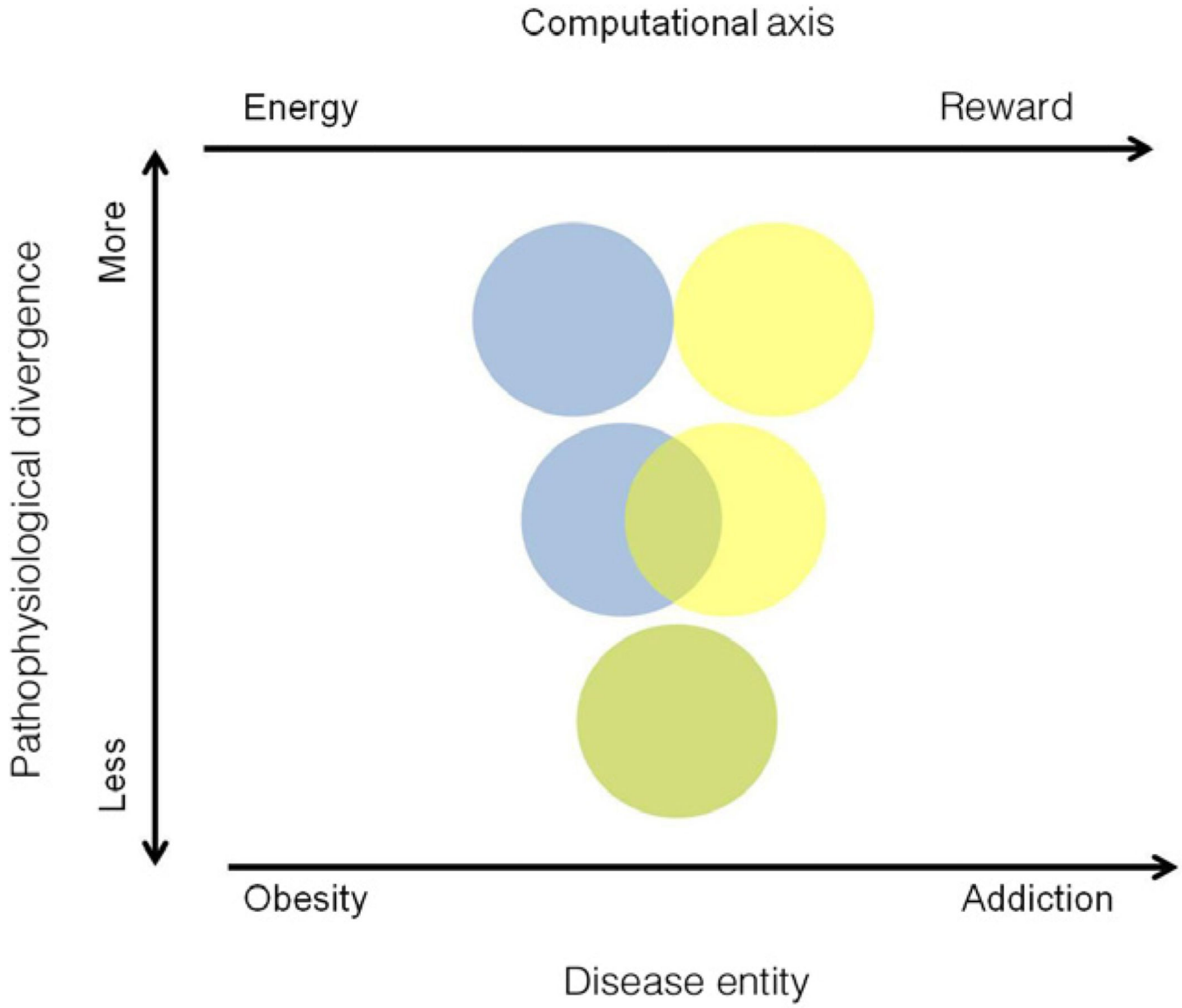

Figure 2.

Obesity and addiction are complex bio-behavioural disorders that exist along various aetiological, pathological and physiological dimensions, all of which are likely to display some similarities as well as differences.

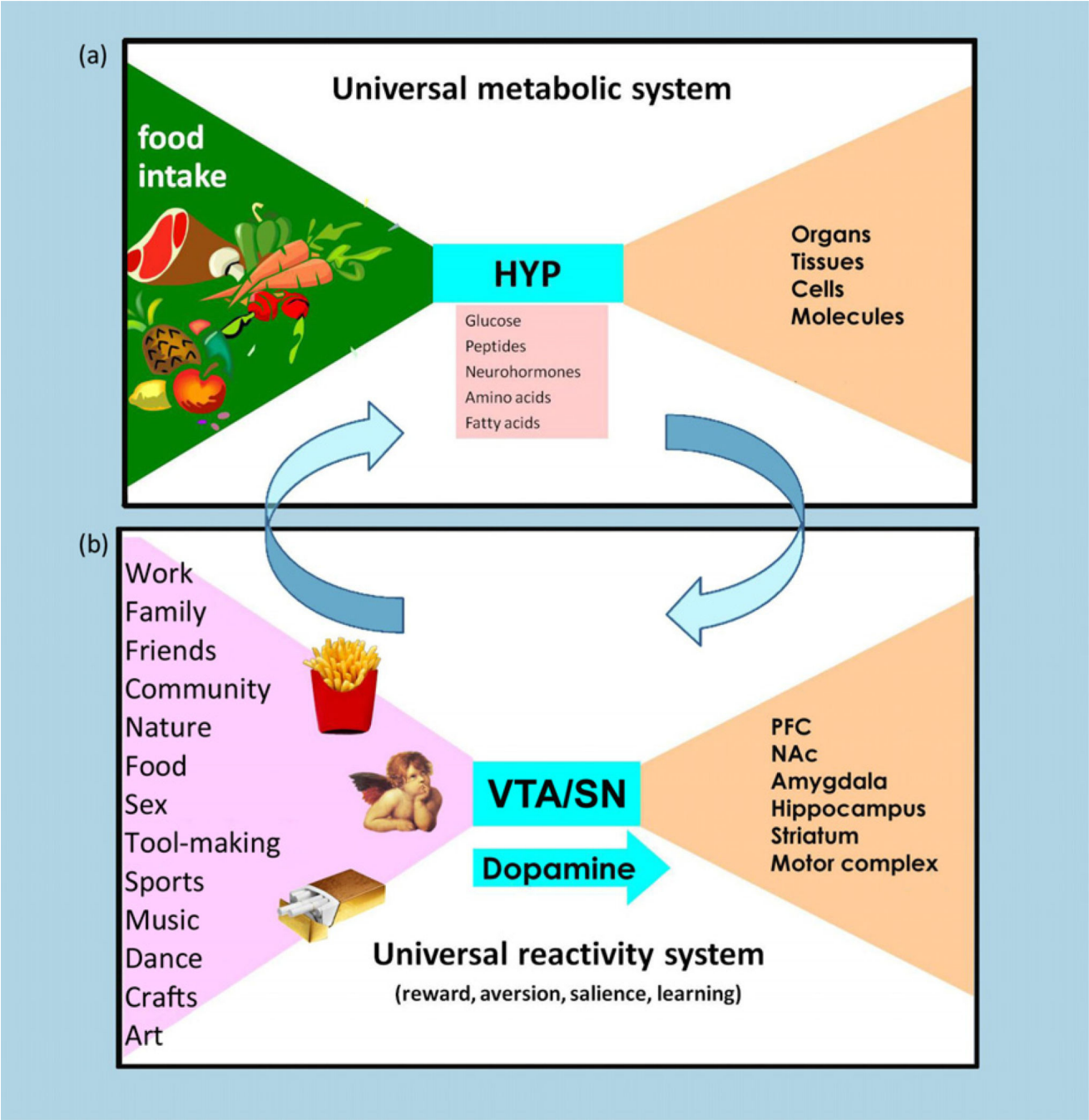

Figure 3.

The nested bow tie architectures of complex systems allow for the input of a wide range of elements, be they nutrients (a) or rewarding stimuli (b), and produce a large variety of products/macromolecules (a) or goal-directed behaviours (b) using a relatively few intermediate common currencies. In this case, the common currencies that form the ‘knot’ of the bow tie are the various orexigenic/anorexigenic signals (a) and dopamine (b) (12) (slightly modified with permission from an original presentation by Dr. John Doyle).

Table 1

Peptides that regulate food intake can also influence the reinforcing effects of drugs of abuse

Endocrine hormones	Origin	Non-hypothalamic mechanism	Drugs/reward connection
Orexigenic			
Ghrelin	Stomach	Amygdala, OFC, anterior insula, striatum (161). Through the GHS-receptor 1a, ghrelin also affects memory, learning and neuroprotection (162).	Central ghrelin is required for alcohol reward (163)
Orexin	Lateral hypothalamus	Facilitates glutamate-dependent long-term potentiation in VTA DA neurons (164)	Role in cocaine cue-induced reinstatement (165) and in morphine-conditioned place preference (166)
Melanocortin	Hypothalamus	MC4R is co-expressed with the dopamine 1 receptor (D1R) in the ventral striatum (167).	Melanocortin receptor type 2 variants were associated with a protective effect from heroin addiction in Hispanics (168)
Neuropeptide Y (NPY)	Hypothalamus	NPY receptors (Y1, Y2, Y4 and Y5) have been found in various limbic structures, which is consistent with its involvement in obesity and in the regulation of emotional states (169,170).	Plays a role in alcohol drinking, withdrawal and dependence NPY modulates alcohol dependence (163,171).
Anorexigenic			
Leptin	Fat	Hypothalamic projections to VTA. Also in insular cortex (172), NAc (173), lateral septal nucleus, medial pre-optic area and rostral linear nucleus (38,174).	Alcohol (175) Leptin appears to play a critical role in mesoaccumbens DA signalling, contributing to also integrating non-feeding motivated behaviours (176). Chronic ICV leptin infusion in *ad libitum* fed rats reversibly potentiates the rewarding effects of d-AMP (177).
Insulin	Pancreas	Hypothalamic projections to VTA. Cognitive regulation in the hippocampus (178).	Stimulants increased insulin levels in a PCP-induced model of schizophrenia (179)
Glucagon-like peptide-1 (GLP-1) (180)	Small intestine Oral taste buds	Some anorexic effects appear to be exerted at the level of the mesolimbic reward system (181)	Exendin, a GLP-1 receptor agonist modulates behavioural activation by amphetamine (182)
Cholecystokinin (CCK)	Small intestine (duodenal and ileal cells).	CCK receptor distribution appears to overlap significantly with that of the opioid (183) and dopamine (184) systems in the limbic system.	DA – CCK interactions in the Nucleus accumbens contribute to psychostimulant reward-related behaviours (185,186) (184). Adult OLETF rats (CCK-1 KO) show altered D2R signalling (NAc shell) similar to drug-induced sensitization, suggesting a link with their avidity for sucrose and abnormal craving response (187).
Peptide YY (PYY)	Endocrine cells of the ileum and colon	Caudolateral OFC, ACC and ventral striatum. High plasma PYY mimics the fed state: changes in neural activity within the caudolateral OFC predict feeding behaviour independently of meal-related sensory experiences. Under low PYY, hypothalamic activation predicts food intake. After a meal PPY switches food intake regulation from homeostatic to hedonic (188),	(None found)

Endocrine hormones	Origin	Non-hypothalamic mechanism	Drugs/reward connection
Galanin (GAL)	CNS	Antinociceptive effects of galanin in the nucleus accumbens (189) amygdala (190). Potent modulator of serotonin neurotransmission in the brain (191).	Alcohol, nicotine (192). GAL increases the consumption of fat or alcohol which, stimulates the expression of GAL, leading to overconsumption (193).
Cocaine- and amphetamine-regulated transcript (CART) (194)	Widely expressed in the central nervous system	NAc shell. accumbal projections to lateral hypothalamus (195)	Modulation of opioid-mesolimbic-dopamine circuitry and or responses to cocaine and amphetamine (196)
Corticotropin-releasing hormone (CRH)	Paraventricular nucleus (PVN)	Amygdalar expression of CRH in the rat is modulated by acute stress (197) and cannabis dependence (198).	CRF receptors and stress-induced relapse to cocaine (199) and alcohol (200).
Oxytocin	Paraventricular nucleus (PVN)	Oxytocin may modulate amygdalar development and volume (201)	Oxytocin modulates methamphetamine induced CPP: down (during extinction) or up (during reinstatement) (202) .

Table 2

Neurotransmitters implicated in drug-seeking behaviours that have also been found to influence food intake

Neurotransmitter	Origin	Mechanism	Drugs and food
Dopamine	VTA, SN, hypothalamus	Enhances incentive salience, conditioning	All drugs Increased prevalence of DRD2 *Taq*1A A1 allele in obese patients with other drug dependencies compared to non-abusing obese patients (203)
Opioids	Throughout the brain	Hedonic responses, pain modulation. Interacts with ghrelin and NPY1 to modulate food reward (204)	All drugs most prominent heroin and opiate analgesics Endogenous opioids facilitate intake of sweet and fat tastants (205). In a targeted study of food addiction, the functional A118G polymorphism of the muopioid receptor gene was associated with binge eating disorders (206)
Cannabinoids	Throughout the brain	Reward and homeostatic regulation, short-term and long-term synaptic plasticity throughout the brain (207)	All drugs most prominent marihuana Endocannabinoids interact with peripheral signals, like leptin, insulin, ghrelin and satiety hormones affecting energy balance and adiposity (208)
Serotonin	Raphe nuclei	Control of behavioural, perceptual (e.g. olfaction) and regulatory systems, including mood, hunger, body temp. Sexual behaviour, muscle control and sensory perception. Hypothalamic control of food intake (209)	Ecstasy, hallucinogens (LSD, mescaline, psilocybin) 5-HT drugs reduce food intake in rodents in a manner consistent with an enhancement of satiety (210).
Histamine	Tuberomamillary nucleus (TMN) of the posterior hypothalamus	Regulation of the sleep-wake cycle, appetite, endocrine homeostasis, body temperature, pain perception, learning, memory and emotion (211).	Alcohol and nicotine (212,213) (214). Sustained histaminergic blockade in rats is associated with decreased body weight (215).
Cholinergic (216)	Nicotine receptors in VTA and hypothalamus	Regulates activity in DA neurons and in MCH neurons. Nicotine administration into the lateral hypothalamus significantly decreases food intake (217)	Nicotine. Hyperphagia: a major deterrent to smoking cessation (218)
Glutamate	Throughout the brain	Perception of pain, responses to the environment and memory. Injection of glutamate into the lateral hypothalamus elicits an intense feeding in satiated rats (219)	All drugs most prominent PCP and ketamine Selective stimulation of AMPAR in the LH is sufficient to elicit feeding (220).
GABA	Throughout the brain	Modulates striatal signalling from D1R and D2R expressing neurons and modulates reactivity of DA neurons in midbrain	Alcohol, opiates, inhalants, benzodiazepines (171). When released from leptin-inhibited neurons, GABA can promote weight gain (221).
Norepinephrine	Locus coeruleus	NE (like NPY and AGRP) reported to modulate the circuitry of consummatory ingestive responses via its actions in both hypothalamic and hindbrain sites (222).	Memory to drugs (223) Memories to food properties (224)