FOOD INTAKE, METABOLISM AND THE BRAIN

The dopamine motive system: implications for drug and food addiction

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Abstract | Behaviours such as eating, copulating, defending oneself or taking addictive drugs begin with a motivation to initiate the behaviour. Both this motivational drive and the behaviours that follow are influenced by past and present experience with the reinforcing stimuli (such as drugs or energy-rich foods) that increase the likelihood and/or strength of the behavioural response (such as drug taking or overeating). At a cellular and circuit level, motivational drive is dependent on the concentration of extrasynaptic dopamine present in specific brain areas such as the striatum. Cues that predict a reinforcing stimulus also modulate extrasynaptic dopamine concentrations, energizing motivation. Repeated administration of the reinforcer (drugs, energy-rich foods) generates conditioned associations between the reinforcer and the predicting cues, which is accompanied by downregulated dopaminergic response to other incentives and downregulated capacity for top-down self-regulation, facilitating the emergence of impulsive and compulsive responses to food or drug cues. Thus, dopamine contributes to addiction and obesity through its differentiated roles in reinforcement, motivation and self-regulation, referred to here as the 'dopamine motive system', which, if compromised, can result in increased, habitual and inflexible responding. Thus, interventions to rebalance the dopamine motive system might have therapeutic potential for obesity and addiction.

Obesity
Body weight that is above what is considered a healthy weight for a given height, normally ascertained through the screening tool referred to as the body mass index (BMI). Obesity (BMI > 30) is associated with increased risk of illness, disability and death.

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Despite the adverse health effects and stigma of obesity, most obese persons are unable to regulate their food intake and relapse towards their elevated body weight after repeated dieting attempts. This cycle of overconsumption, dieting and relapse is reminiscent of the cycle of drug intoxication, abstinence and relapse observed in addiction. Increasingly, research has revealed an overlap between the neurobiological substrates that drive drug seeking and food seeking[1,2] that implicates neuroadaptations in the dopamine (DA) system. Although traditionally, this system has been referred to as the 'DA reward system', we refer to it instead as the 'DA motive system' to better differentiate its dual roles in motivation and reinforcement. Short-term fluctuations in DA concentrations mediate the sensitivity of the animal to reinforcing and reinforcement-predictive stimuli. Neuroadaptations in the 'motive system' mediate enhanced motivation towards reinforcer predictors (cues) as well as shifts in the executive system from long-term to short-term considerations favouring immediate gratification (reviewed in REF. 3). Here, we suggest three mechanisms by which the DA motive system guides the animal to food or to addictive drugs: tonic activation of the system provides the motivational level of arousal that encourages preferential responding to reinforcer-predictive stimuli; phasic activation of the system strengthens associations between active predictors and reinforcers; and repeated phasic activation of the system causes widespread downregulation of DA receptors. Whereas this model specifies only stimuli that are detectable by the animal at the time of action, in each case the resulting behaviour has the appearance of being controlled by its eventual consequences.

The DA motive system is under considerable influence by factors that regulate appetite (BOX 1), and some of these metabolic signals also modulate the reinforcing effects of drugs (BOX 2). Here, we review the latest findings at the intersection between the fields of addiction and obesity with the underlying hypothesis that both drug addiction and (at least) some forms of obesity are partly the result of imbalances between two main functions of the DA motive system: one that mediates the approach to (movement towards) reinforcers[4–6] and another that instils sensitivity to environmental reinforcement predictors[7]. Additionally, the mesocortical DA pathway participates in top-down self-regulation

Box 1 | **Homeostatic signals and the DA motive system**

Peripheral and central homeostatic signals influence the dopamine (DA) motive system directly by stimulating or inhibiting ventral tegmental area (VTA) DA neurons through cognate receptors or indirectly through intermediate relay neurons (Supplementary information S1 (Table)). Peripheral signals that inhibit VTA DA neurons, including leptin (released by adipose cells), insulin (secreted by the pancreas), glucagon-like peptide 1 (GLP-1) (released by the intestines) and amylin (released by the pancreas), decrease food intake[178], whereas peripheral signals that stimulate VTA DA neurons, such as ghrelin (released by the stomach and small intestine), increase food intake[179]. VTA DA neurons express receptors for leptin, amylin and ghrelin[180–183]. These homeostatic regulators also stimulate hypothalamic nuclei that project to the DA motive system.

The lateral hypothalamus (LH) and the arcuate nucleus are the main hypothalamic nuclei that regulate food intake and modulate the DA motive system. The LH innervates the VTA[184], and its projections are involved in feeding, energy balance, arousal, reinforcement, and motivated behaviours (reviewed in REF. 185). The LH–VTA projection is composed of neurons releasing glutamate, GABA[186], orexin/hypocretin[187] and neurotensin[188]. Stimulation of the GABAergic LH–VTA projection supports intracranial self-stimulation and facilitates compulsive sucrose seeking[189] by disinhibiting DA neurons and increasing DA in the nucleus accumbens (NAc)[186], whereas stimulation of LH–VTA glutamate projections is aversive. Stimulation of hypocretin (Hcrt; also known as orexin (Ox)) neurons[190] activates DA neurons[187,191] and promotes food intake[192]. Ghrelin stimulates Hcrt (Ox) neurons[193], whereas leptin inhibits them[188]. The arcuate nucleus contains neurons that express pro-opiomelanocortin and inhibit feeding via release of α-melanocyte-stimulating hormone, an agonist for melanocyte MC3 and MC4 receptors[194], which are located in VTA DA neurons and in the NAc[195], and neurons that co-express neuropeptide Y (NPY) and agouti related protein (AgRP), which acts as an inverse agonist of MC3 and MC4 receptors, stimulating feeding[196] while also inhibiting oxytocin neurons in the LH[197,198]. Excitability of AgRP/NPY neurons is decreased by leptin and increased by ghrelin[199,200].

and integrates motivational signals from striatocortical pathways[8]. For the purposes of the present Review, we focus on the DA system, but it is clear that a variety of other neurotransmitter systems — for example, the endocannabinoid, opioid, GABAergic, cholinergic and serotonergic systems — also participate in both drug-seeking and food-seeking behaviours; the interested reader is referred to pertinent discussions of such systems[9,10].

The dopamine motive system

The DA system plays a crucial role in reinforcement[7,11]. Although many other systems are activated in instrumental behaviour (that is, actions performed to reach a goal), it is only the blockade of the DA system that results in the failure or compromised response to respond to a reinforcer[12–20]. Similarly, more recent genetic studies corroborated the critical role of DA in sustaining motivation while providing new insights into the differential roles of the striatum in different forms of motivation and approach behaviours. These studies showed that dopamine-deficient mice displayed a complete lack of motivation for engaging in goal-directed behaviours, including feeding, and that selective restoration of DA signalling in the dorsal striatum rescued motivation and feeding behaviour[12]. Interestingly, in the DA-depleted state, mice were still able to engage in reward-related behaviours[13], which later studies suggested are mediated by a serotonin-dependent compensatory artefact[14]. These early results suggested that DA is a critical gatekeeper that allows output signals to exit the dorsal striatum to facilitate motivated behaviours.

The DA motive system comprises DA neurons in the ventral tegmental area (VTA) that project predominantly to the NAc (located in the ventral striatum), which has traditionally been associated with motivation and reinforcement learning, and DA neurons in the substantia nigra (SN) that project to the dorsal striatum, which has traditionally been associated with action selection, goal-directed behaviour and the emergence of habits[15–17]. However, there is evidence of overlap in their functions, including engagement of the ventral striatum in action selection, habits and goal-directed behaviours[18] and of the dorsal striatum in reinforcement learning[19] (see REF. 20 for review). DA neurons fire either in a stable tonic mode (1–8 Hz), which is fundamental for momentary sensitivity to external stimuli and sets the background dopaminergic tone for behaviour, or in a transient (<500 msec) high-frequency phasic mode (>15 Hz), which is triggered by exposure to salient (reinforcing, novel, unexpected or aversive) stimuli. According to the conventional model, tonic firing causes release of DA from extrasynaptic release sites, where it acts on sensitive (high-affinity) D2 receptors (D2R)[21,22] and determines motivational arousal (sensitivity to external stimuli)[23–27]. Phasic DA firing results in high extracellular DA concentrations[28], which are able to stimulate the low-affinity D1 receptors (D1R) and are associated with the consolidation of recent memory engrams[7] (conditioning to positive and negative reinforcers). Additionally, phasic DA firing concomitantly contributes to D2R signalling[21,22]. However, this is a simplified model that does not incorporate more recent findings revealing that midbrain DA neurons are heterogeneous[29,30], that there are alternative DA firing rates[31] and that phasic DA also participates in alertness and motivation[23,32,33]. Similarly, although a vast number of studies are consistent with the idea that many DA neurons promote reinforcement and conditioned learning through a multipurpose reinforcement-based error-prediction signal[34], there is evidence that both the underlying computational algorithms and neuronal populations are far more complex[23].

The activity of DA neurons in the VTA and SN is influenced by projections from multiple brain areas that control their tonic and phasic firing[35]. Phasic firing requires glutamate stimulation of NMDA and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptors[36] and cholinergic stimulation of muscarinic and nicotinic receptors[37]. Homeostatic signals involved in the regulation of feeding behaviour, coming from peripheral organs and from the hypothalamus, also influence tonic and phasic DA neuronal firing (FIG. 1).

DA inputs to the ventral and dorsal striatum innervate two types of primary GABAergic projection neurons (medium spiny neurons or MSNs) as well as GABAergic and cholinergic interneurons. Most research has focused on MSNs, which express either D1R (although they can also co-express D3R) or D2R[38,39]. MSNs that express D1R signal through the direct striatocortical pathway and are stimulated by DA, whereas MSNs that express D2R signal through the indirect striatocortical pathway and are predominantly inhibited by DA[23,40,41].

Relapse
Spontaneous recurrence or reinstatement of a learned behaviour after a given period of extinction, such as the reinstatement of compulsive drug use or the reinstatement of eating behaviours that lead to the reversal of diet-induced weight loss.

Addiction
A chronic brain disease associated with disruption of reward and motivation, memory and conditioning, executive and self-regulation, mood and stress neurocircuitry, the risk of which implicates environmental, genetic and social factors.

Reward
The subjective salience value of an object, stimulus or situation that has the potential to induce goal-oriented behaviour.

Motivation
A brain process triggered by intrinsic and/or extrinsic drivers that induce an animal or a person to move towards a goal.

Box 2 | **Homeostatic signals and drug reinforcement**

Homeostatic signals that influence the excitability of ventral tegmental area (VTA) dopamine (DA) neurons can influence sensitivity to drugs. For example, downregulation of leptin enhances, whereas its upregulation interferes with, cocaine reinforcement[201,202]. Similarly, saccharin exposure, which increases leptin receptor (LepR) mRNA in the nucleus accumbens (NAc) and VTA, impairs cocaine-conditioned place preference[201]. Cocaine decreases leptin levels, thus attenuating leptin's role in antagonizing its reinforcing effect[202]. Leptin-deficient mice have reduced dopamine D2 receptors (D2R) in the striatum, which is reversed by leptin[203], and just as D2R are required for leptin to reduce food intake, LepRs are required for D2R to reduce the reinforcing effects of cocaine[201]. In contrast, leptin administration in mice after alcohol withdrawal increased alcohol consumption[204], and in humans, increases in plasma leptin following alcohol (or nicotine) withdrawal were associated with craving and relapse[205]. Similarly, glucagon-like peptide 1 (GLP-1) reduces the reinforcing effects of various drugs[206], and GLP-1 analogues have been proposed as treatment for addiction[207]. In contrast, ghrelin enhances the reinforcing effects of drugs in rodents[208], and in humans, higher ghrelin levels were associated with greater risk of relapse to smoking[209]. Ghrelin might modulate drug reinforcement through constitutive ghrelin receptors in the VTA and/or by their heteromerization with D1R[210] and D2R[211]. Gut microbiota might also contribute to hunger signals[212] and to obesity[213] through metabolism of nutrients and their influence on mood[214,215] and the DA motive system[177,216,217].

Because hormonal effects are slow, they are more likely to influence the motivation to obtain the drug[202,218–223] than to change the reinforcing experience of taking the drug. Hormonal effects can also come under habitual control: leptin, for example, decreases progressively before expected cocaine intake[202], whereas ghrelin increases when the animal is expecting food but not when the next meal occurs without any predictive cues[224].

Reinforcer
An event or stimulus that, once delivered, increases the probability of repeating the act that it follows; this term can apply to both food and drugs. Painful and aversive stimuli can also act as reinforcers but instead they increase the probability of avoiding the behaviours or circumstances that preceded the stimuli. Novel stimuli can also act as reinforcers by engaging attentional systems.

Tonic
Slow and gradual. Receptors activated by a tonic input typically adapt slowly throughout the stimulation period, conveying information about its duration.

Phasic
Sudden and transient, conveying information about sudden changes in stimulus intensity and rate and promoting rapid adaptation to the stimulus.

Striatum
A key region of the limbic system, dysfunctions of which have been associated with the pathophysiology of addiction and obesity.

Because DA receptors can act either by themselves or in heteromers[42], their specific effects when DA binds to them are difficult to determine. For example, in the NAc, high-affinity D3R are co-expressed with D1R, with which they heteromerize, enhancing their signalling[43]. In general, for the motor system, the direct pathway causes movement and is stimulated by DA binding to D1R, whereas the indirect pathway, in which the binding of DA to D2R is predominantly inhibitory, inhibits movement[41]. These opposing effects of DA, namely, stimulation of the direct 'go' pathway and inhibition of the indirect 'no-go' pathway, provide a foundation for how DA facilitates movement[44] and why both pathways are needed to initiate motor behaviour[45,46]. Assuming that a similar organization exists for the motive system, one can hypothesize that the reinforcing effects associated with increases in DA reflect stimulation of the direct pathway via D1R — the system for long-term potentiation of synaptic memory — and its presumed inhibition of the indirect pathway, which is aversive[44,47]. These opposing effects of DA provide a potential mechanism for how DA facilitates reinforcement (stimulates reinforcement while inhibiting aversive signals)[44,48], with maximal reinforcement occurring when both D1R and D2R are stimulated simultaneously[44,46,48]. However, this model does not incorporate more recent findings showing that the striatopallidal pathways in the ventral striatum are not as well segregated as those in the dorsal striatum[49]. Moreover, even in the dorsal striatum, the canonical model of the indirect and direct pathways might be an oversimplification[50].

Dopamine neurons in the VTA also send projections to the amygdala, hippocampus and prefrontal cortex, which participate in the encoding and retrieval of conditioning to drug or food cues[51]. The prefrontal cortex is also a target through which the striatal direct and indirect pathways modulate executive function, including salience attribution, choice behaviours and self-regulation (FIG. 1) (review REF. 52).

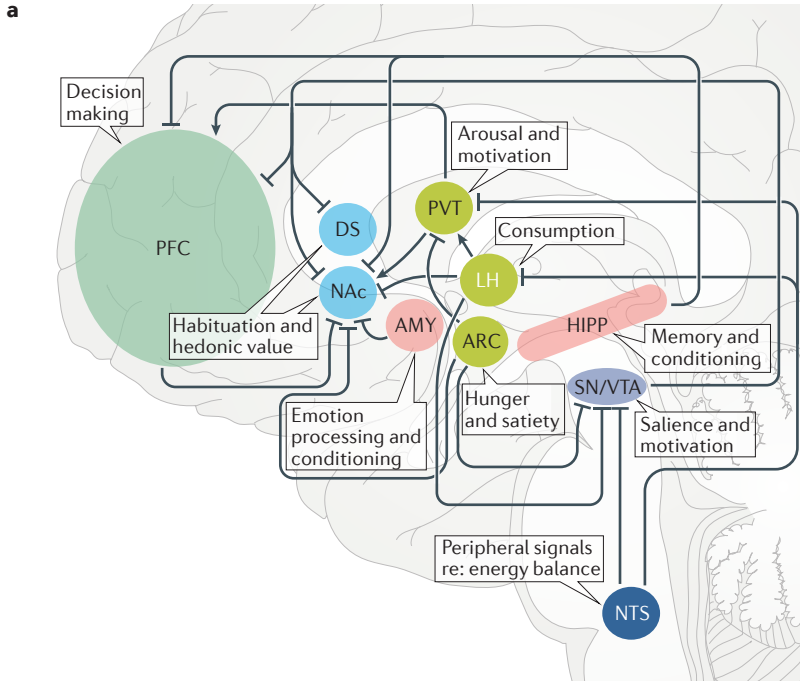
Neuroadaptations in the DA motive system

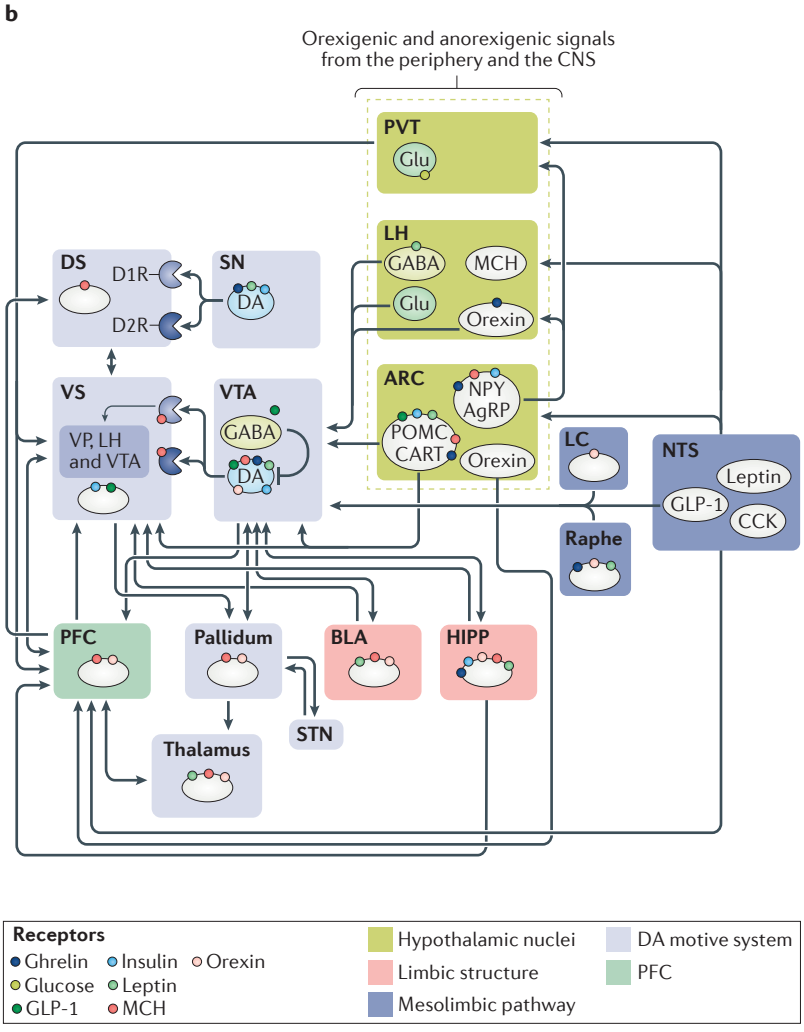
Stimulation of D1R by food and drugs serves a reinforcing function[44]; it consolidates the memory traces of reward reception and the events that immediately preceded it[7,53]. Because of D1R activation, through each exposure to a reinforcer or predictor, the animal will remember more (in subsequent trials) about the associated internal and external stimulus conditions[1,54], coming to identify progressively earlier predictive stimuli. The magnitude of the motivational extracellular DA levels — a product of both internal and external stimulus conditions — determines the sensitivity of the animal to the cues that signal an expected reinforcer[55,56]. The DA level that determines motivational arousal — the state of the animal before it contacts the reinforcer — ranges between 4 nM (REF. 57) and 20 nM, which are the minimum concentrations that can be measured by fast-scan cyclic voltammetry, when reinforcement predictors are encountered[58,59].

The motivating level of arousal during reinforcement seeking is maintained until the animal receives a reinforcer or a predictor thereof, which elicits a burst of neuronal firing that further enhances conditioned learning. However, once conditioned learning has occurred, the DA neurons no longer fire upon receipt of the reinforcer and instead fire when exposed to the predictive stimulus[1]. Presumably, as a meal is consumed, the concomitant changes in metabolic factors — for example, increases in leptin and decreases in ghrelin — reduce the sensitivity of the DA motive system for the food and its predictors. Indeed, imaging studies show decreased sensitivity of brain reward regions to food after satiety (including the midbrain, striatum and medial orbital frontal cortex) in healthy controls, which is consistent with this interpretation[60,61].

In the case of drugs, a different set of processes seems to be at work. Here, when DA levels are overly elevated, further stimulation of the system appears to be unreinforced. The evidence suggests that once DA levels are more than doubled, the conditioned reinforcer predictors become ineffective until the DA levels fall into the normal range, at which time the animal will resume drug self-administration[62]. At least for the case of stimulant drugs (that is, cocaine and amphetamines), this is likely to reflect saturation of DA receptors, at which point any extra drug will not make a noticeable difference in the strength of the reinforcer, although it will affect the duration of receptor saturation. These differences might explain why the risk of loss of control with repeated exposure to drugs is much higher than with reinforcing foods[63].

However, under conditions of extinction, when the reinforcement predictor is repeatedly uncoupled from the associated reinforcer, the DA motive system is silenced at the point in time when the food or drug was previously delivered. With repeated experience





of the predictor in the absence of reinforcement, the incentive value of the predictive cue is reduced, which can eventually lead to an almost complete extinction of the response tendency. However, if the reinforcer is re-introduced in the original surroundings, the response can be almost immediately reinstated[64]. This helps explain relapse both towards overeating behaviours following a period of dieting and towards drug taking following a period of abstinence.

The molecular mechanisms underlying the long-term plastic changes that accompany the establishment of conditioned responses are not fully understood, particularly with regard to non-drug reinforcers. There is some evidence that consolidation of conditioned responses to reinforcement-predictive cues is associated with the strengthening of glutamatergic[65–67] and perhaps cholinergic[68] inputs into DA neurons in the VTA[66] and SN[65]

Figure 1 | **Dopamine motive system. a** | A simplified representation of the major neural nodes that control food intake in the brain, labelled according to their broadly defined functions. Some of the main pathways that regulate their coordinated actions are also indicated. **b** | The dopamine (DA) motive system (shown in light blue), centred around the substantia nigra (SN) and ventral tegmental area (VTA), integrates peripheral and central mechanisms driven by homeostatic signals (their functions are described in BOX 1, and their receptors are indicated here as colour-coded dots) and environmental stimuli that result in goal-directed actions. The hypothalamus is central to energy balance, and several nuclei are involved in energy regulation (for example, the arcuate (ARC) and lateral hypothalamus (LH), which project to the paraventricular thalamus (PVT) (shown in apple green), which, in turn, serves as a main relay to these hypothalamic regions). These nuclei integrate orexigenic and anorexigenic signals from the periphery and the CNS and convey them to the DA motive system. By contrast, top-down inhibition of drug and food seeking depends heavily on the prefrontal cortex (PFC; dark green), including the orbitofrontal cortex, the anterior cingulate cortex and the dorsolateral and inferior prefrontal cortices. The amygdala (AMY), specifically the basolateral amygdala (BLA), ascribes emotional attributes and, together with memory, learning and habituation circuitry (which includes the hippocampus (HIPP)), generates conditioned responses. This circuit is subject to strong influence coming from cortical and mesolimbic input, where neurons in the nucleus of the tractus solitarius (NTS; dark blue) integrate peripheral satiety signals (for example, leptin, cholecystokinin (CCK) and glucagon-like peptide 1 (GLP1)) and convey the information forward (to the locus coeruleus (LC), raphe, and beyond) to modulate the sensitivity of upstream networks. Thus, orexigenic and anorexigenic peripheral signals directly influence not only hypothalamic nuclei but also mesocorticolimbic structures (BLA, prefrontal areas and HIPP). Conversely, many classical neurotransmitters (DA, cannabinoids, opioids, GABA and serotonin) also influence the neurons within the hypothalamic nuclei. Receptors for some of the major homeostatic ligands are colour coded so as to readily identify some of their key sites of expression. DS, dorsal striatum; MCH, melanin-concentrating hormone; NAc, nucleus accumbens; STN, subthalamic nucleus; VS, ventral striatum.

and of glutamatergic corticostriatal inputs onto MSNs[69]. These changes involve modifications in the membrane expression and in the subunit composition of AMPA and NMDA receptors in DA neurons (mostly investigated in the VTA) and their projections into the NAc and dorsal striatum[70,71]. These changes render DA neurons and their projection targets in the striatum more sensitive to excitatory glutamatergic stimulation from the prefrontal cortex, amygdala and hippocampus[72], increasing their reactivity to reinforcement-predictive as well as to aversive and novel cues[73]. It has been hypothesized that these neuroplastic changes disrupt the balance between striatal D1R and D2R signalling with stronger relative downregulation of DA's effects on D2R than on D1R[74]. It has also been proposed that these neuroadaptations render prefrontal regions, which are modulated by the striatocortical pathways and are necessary for salience attribution and executive function, more reactive to conditioned stimuli and less able to inhibit prepotent responses[52].

The plastic changes associated with food-related behaviours have not been the focus of as much research to date, but growing interest is beginning to provide new insights. For example, wild-type mice showed increased spine density in the prefrontal cortex, hippocampus and nucleus accumbens after a cycle of palatable food-driven operant training, an effect that was abolished in δ-opioid receptor (DOR) knockout mice[75]. Interestingly, these same DOR knockout mice displayed reduced motivation for cocaine and cue-induced relapse after acquiring operant cocaine self-administration behaviour[76]. Meanwhile, another group showed that a similar high-calorie operant training paradigm robustly activated the mesocorticolimbic extracellular-signal-regulated kinase (ERK) signalling pathway in a cannabinoid receptor 1 (CB1)-dependent fashion[77]. This is an interesting finding because pharmacological blockade of the ERK (or NMDA) pathway had previously been shown to attenuate cocaine-induced neuroplastic changes in MSNs in NAc and putamen[78]. Thus, at least some of the homeostatic and/or hedonic processes triggered by palatable foods appear capable of inducing structural and behavioural alterations that are reminiscent of those linked to drug addictive-like behaviours. There is abundant evidence that these processes rely heavily on endocannabinoid[77] and opioid[79,80] signalling pathways; thus, considerable progress is likely to emerge from studies of the communication between these two systems[81] and their intersections with the DA motive system[82].

Disruptions of striatocortical pathways may also favour compulsive food intake; this notion is supported by findings that D1R antagonists block, whereas D2R-like antagonists increase, the reinstatement of food-seeking behaviour[83–85]. Moreover, leptin's inhibition of feeding is blocked by D2R antagonists but not by D1R antagonists, and its hypophagic effects are attenuated in mice lacking D2R[86]. Repeated exposure to sugar disrupts DA striatal pathways, resulting in an enhanced propensity to consume large quantities of sugar, a behaviour that is associated with increased DA stimulation of D1R in the dorsal striatum[87]. Diets high in fat have also been shown to reduce the expression of D2R in the dorsal and ventral striatum[88–90] and to decrease extracellular DA levels in the dorsal striatum[91]. Additionally, D1R and D2R striatocortical pathways have been implicated in the energy expenditure component of weight gain and obesity. Specifically, both optogenetic stimulation of the direct pathway (akin to DA stimulatory effects through D1R expressing MSNs) and optogenetic inhibition of the indirect pathway (akin to DA inhibitory effects through D2R-expressing MSNs) facilitated locomotor activity[92]. Although this interpretation is consistent with the assumption that DA is inhibitory when it binds to D2R[41], some have questioned this assumption. Regardless of the interpretation, the reduction in striatal D2R expression in obesity could further facilitate weight gain by reducing physical activity. We propose as a possible explanation that in the case of food, a consistent increase in the frequency of calorific feeding may have effects on the DA system similar to those of the infrequent, but much stronger, effects of addictive drugs.

It is proposed that the neurocircuitry involved in the transition from goal-directed behaviour to loss of control and compulsive drug seeking in addiction involves a shift in behaviour from conscious control, which is dependent on the NAc, to automatic stimulus–response habits, which are under the control of the dorsal striatum[93]. In the case of food (shown for ingestion of sugar), separate striatal subregions modulate gustatory reinforcement, which involves the NAc, and energetic reinforcement (after ingestion), which involves the dorsal striatum[94]. Indeed, animals do not survive if DA signalling is permanently interrupted by DA depletion in the dorsal striatum because the animals lose the motivation to eat altogether[94]. Similarly, brain imaging studies in humans have corroborated the role of dorsal striatal DA increases in the motivation to acquire food (that is, food wanting)[95].

Overlapping neurocircuitry

Three common complaints reported by individuals addicted to drugs and by obese individuals are (i) a lack of control over drug taking or eating, (ii) the consumption of drugs or food without achieving satiety and (iii) an increased preoccupation with drugs or food, respectively[96,97]. What drives these changes?

The lack of control over drug taking or eating is driven in part by weakening of prefrontal regulation of behaviours. The prefrontal disruption in some instances might have preceded the disorder, rendering the individual more vulnerable to loss of control over reinforcement seeking[98,99]. However, repeated exposure to drugs or to food with high fat and/or sugar content downregulates D2R in the striatum[5], which is necessary for prefrontal regulation[100,101]. In addiction[53] and in obesity as well as in binge eating disorders[102–105], brain imaging studies have reported decreased D2R expression and DA release in the dorsal and ventral striatum, which has been associated with reduced activity in prefrontal regions[101,106–108] (FIG. 2). However, other studies in obesity have reported D2R upregulation or no changes[109,110]. The extent to which changes in D1R contribute to prefrontal impairment in addiction or obesity have been much

Dorsal striatum
A region of the striatum associated with habits or stimulus–response learning.

Ventral tegmental area
(VTA). A cluster of midbrain neurons that sends dopaminergic projections to both limbic and cortical areas, thus playing a central role in reward-related and goal-directed behaviours. Note that while it has been traditionally believed that the VTA underlies reinforcement, recent optogenetic studies indicate that the SN also participates in this phenomenon.

Ventral striatum
A region of the striatum that contains the nucleus accumbens and is predominantly associated with reward and motivation.

Substantia nigra
(SN). A cluster of midbrain dopamine neurons that is predominantly associated with movement and involved in habit formation. More recent optogenetic studies also implicate it in reward functions.

Medium spiny neurons
A GABAergic striatal cell type of critical importance because of its pivotal roles not only in motor control, habituation and motivated behaviour but also in psychiatric disorders such as Parkinson disease, Huntington disease, schizophrenia and addiction.

Direct striatocortical pathway
Striatal pathway in which D1R-expressing (striatonigral projection) medium spiny neurons project from the striatum to the internal globus pallidum and the substantia nigra reticulata, which disinhibit thalamic excitatory neurons to the frontal cortex, facilitating movement.

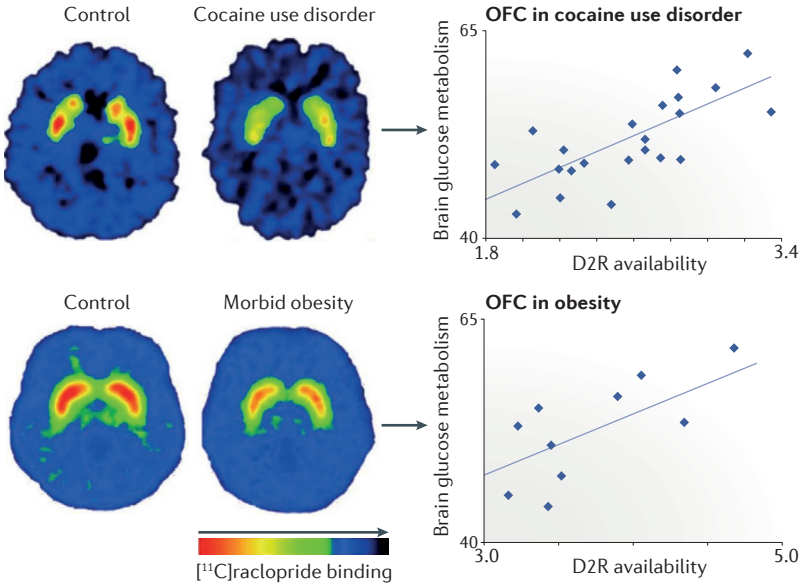


Figure 2 | **Brain images of DA D2 receptor availability in individuals suffering from either cocaine use disorder or morbid obesity along with the images of matched controls.** Left panels: images from a cocaine abuser and a control subject (top row) and averaged images from a group of morbidly obese and control individuals (bottom row) show, on average, significantly lower levels of dopamine D2 receptors (D2R) in their striatum, as determined by PET imaging with [^{11}C]raclopride. The pseudocoloured scale below the images depicts the observed range of [^{11}C]raclopride binding: from dark blue (low binding or low receptor availability) to bright red (high binding or high receptor availability). Right panels: furthermore, these reductions in striatal D2R availability are consistently and dose-dependently associated with reduced glucose metabolism (a marker of brain function) in the orbitofrontal cortex (OFC, shown) and other areas of the prefrontal cortex (that is, the cingulate gyrus). Adapted with permission from REF. 5, Royal Society Publishing.

less investigated. In addiction, D1R have been evaluated only in cocaine abusers, and although D1R levels did not differ from those in controls, they were negatively associated with cocaine choices[111]. To our knowledge, there are no brain imaging studies of D1R in human obesity. The D2R-associated striato-prefrontal pathway (targeting, among others, the orbitofrontal cortex, anterior cingulate gyrus, dorsolateral prefrontal cortex and inferior frontal cortex) is necessary for inhibition of prepotent responses that otherwise result in approach to reinforcement predictors and reinforcers. Indeed, for both addiction[112] and obesity[113], prefrontal activity has been shown to predict clinical outcomes, and disrupted connectivity between prefrontal and striatal regions[114] is a consistent finding in imaging studies of both disorders.

The consumption of drugs or food without achieving satiety is likely to reflect, in part, the reduced sensitivity of the DA motive system to the actual consumption of the reinforcer (drugs or food) in addiction and obesity[115–118]. Indeed, imaging studies have shown a profound attenuation of the DA increases induced by stimulant drugs during intoxication in cocaine addicted individuals[118] as well as a lack of the normal increase in striatal DA during consumption of calories in obese individuals[115]. In this respect, the attenuated DA response to the reinforcer generates a mismatch between the experiences of the expected and the actual reinforcer, which we postulate sustains the motivation to continue consumption of the drug or the food in order to achieve the expected outcome. In the drug world, this pattern of behaviour is described as 'chasing the remembered high'. Alternatively, compulsive drug or food consumption in addiction and obesity, respectively, could reflect perseverative behaviours, perhaps emerging from sensitization to downstream responses to the reinforcer and the downregulation of the D2R striatocortical pathway, which becomes unable to oppose it.

It seems reasonable to speculate that the increased preoccupation with drugs[96] or food[97] is likely to reflect a concomitant reduced sensitivity of the motive system to other stimuli, that is, to non-drugs in addiction[119] (and reviewed in REF. 120) or to non-food reinforcers in obesity[121], reducing the capacity of the individual to be motivated by behaviours that are not related to drugs or food, respectively. Although clinical support for this hypothesis in addicted or obese individuals has not been published, an association between downregulation of tonic DA and of striatal D2R and reduced motivation has been reported in adults with attention deficit disorder (ADHD)[122,123]. This relation, coupled with enhanced sensitivity to conditioned cues — that is, drug cues in addiction[124] and food cues in obesity[125] — which engage ventral medial prefrontal regions that mediate salience attribution (medial orbitofrontal cortex, ventral anterior cingulate gyrus), may help explain the observed preoccupation with drugs and food and the weakened competition from other stimuli. The increased sensitivity to conditioned drug cues has been associated with worse outcomes in addiction (reviewed in REF. 126) and the increased sensitivity to food cues with increased risk of obesity[127,128].

In parallel, there is a transition in the addicted state from seeking the drug for its positive reinforcement towards seeking it to avoid negative reinforcement[97]. This state has been described as the 'dark side' of addiction[129] and is most evident during acute drug withdrawal. This phenomenon has been associated with a high risk of relapse as a means to temporarily escape the aversive state[129]. In heroin abusers, as had previously been shown for rodents[130], the acute withdrawal precipitated by the μ-opioid receptor (MOR) antagonist naloxone was associated with inhibition of DA release in the striatum[131]. Presumably, the lack of D2R inhibition of the indirect striatocortical pathway, which generates an aversive response[47], and the occurrence of changes in systems regulating stress responses (that is, dynorphin, CRF and noradrenaline)[132] contribute to the aversive state of withdrawal. Rodent studies have also documented that exposure to a high-sugar diet renders the animals vulnerable to naloxone-precipitated acute withdrawal[133]. Though such an acute withdrawal process has not been reported in humans, it is possible that a more-subtle withdrawal contributes to relapse in obese individuals[134]. Indeed, increased sensitivity to stress and anxiety and negative mood are prevalent in individuals on food restriction diets[135,136]. It is worth highlighting in this context the extensive preclinical evidence on the role of stress, both acute and chronic, in modulating the sensitivity of an animal to both food and drug reinforcers (see reviews on the topic: REFS 132,137,138).

Indirect striatocortical pathway
Striatal pathway in which D2R-expressing (striatopallidal projection) medium spiny neurons project from the striatum to the external globus pallidum and then to the subthalamic nucleus, which then projects into the internal pallidum and substantia nigra reticulata with a resultant inhibition of thalamic stimulation of the frontal cortex, inhibiting movement.

Heteromers
Receptors consisting of dimers and possibly higher-order entities with unique biochemical and functional characteristics, composed of different monomers from the same or different gene families.

Satiety
A feeling that follows food intake and that leads to meal termination. It is a complex psychological construct that can be linked to physicochemical measures related to stomach distention, blood levels of peptides such as cholecystokinin and glucagon-like peptide-1, peripheral biomarkers associated with meal termination, and neural activity related to sensory-stimulus-specific satiety.

Compulsive
Related to an uncontrollable, often unconscious urge to perform a specific act, often in a repetitive fashion.

Implications for the current obesity crisis

In the modern world, conditioning to the many surrounding food stimuli along with the accessibility of reinforcing food can lead to problems. It is presumably the elevation of DA by the conditioned stimuli that propels us to go after the chocolate (or other conditioned foods). This effect of conditioned stimuli may help explain the deleterious consequences of enhanced advertising for unnecessary high-calorie foodstuffs (that is, those that are surplus to our daily requirements) as well as the push to manufacture foods that maximize their reinforcing value and hence conditioning effects by mixing ingredients with purposefully calibrated (high) concentrations of fat, sugar and salt. For foods, enhanced conditioning for a flavour can be associated with the energy content in the food, namely, its value after ingestion[139]. In addition, food manufacturers use all their skills to induce us to eat more of their products (larger portions) than we need, to which we subsequently become conditioned, so that we build up an expectation not only for the high calorie content of the food but also for the delivery of large portions.

Implications for therapeutics

Current medications for obesity (and for addiction) are limited[140] (TABLE 1) and are based either on interference with food absorption or on interference with the DA motive system. Thus, it is not surprising that some medications in the latter category have also shown promise for addiction treatment. For example, lorcaserin (Belviq®), one of the six FDA-approved obesity medications, is a selective 5-HT_{2C} agonist that promotes satiety and reduces self-administration of cocaine (reviewed in REF. 141), opiates[142] and nicotine[143] in rodents, presumably through the modulatory effect that 5-HT_{2C} receptors have on the firing rate of VTA DA neurons and on DA release in the NAc[144]. Similarly, Contrave®, the FDA-approved drug combination of naltrexone (a MOR antagonist that modulates the firing of VTA DA neurons and the release of DA) and extended-release bupropion (a DA and noradrenaline reuptake inhibitor that also binds to cholinergic receptors), decreases food intake but may also increase abstinence in cigarette smokers and be particularly beneficial for obese smokers[145,146]. Recent preclinical results also suggest that the glucagon-like peptide 1

Table 1 | **Approved anti-obesity drugs.**

Approved anti-obesity drug	Primary mechanism of action	Known or potential interaction with the DA motive system	Potential for therapeutic use in drug addiction
Phentermine (Adipex-P®)	NE transporter inhibitor; appetite suppression mediated by activation of POMC neurons in the arcuate nucleus	An amphetamine derivative, known releaser of DA in the NAc[225,226]	Negative. Rewarding effects in animals[225,226]
Orlistat (Xenical®)	Gastric and pancreatic lipase inhibitor; reduces absorption of dietary fat	Not applicable	Not applicable
Lorcaserin (Belviq®)	Selective 5-HT_{2C} agonist; promotes satiety	5-HT_{2C} receptors modulate forebrain DA neurotransmission and ancillary networks[227]	Positive. Shown to reduce the reinforcing effects of cocaine in rhesus monkey after repeated administration[141]
Phentermine and topiramate (Qsymia®)	• Phentermine: see above • Topiramate: GABA agonist; appetite suppression may be due to modulation of voltage-gated ion channels, increased activity at GABA-A receptors and/or inhibition of AMPA and kainate glutamate receptors	• Phentermine (see above). • Topiramate may regulate mesolimbic DA[228]	• Unclear. • For topiramate, clinical trials have yielded mixed results in cocaine use disorders. A preclinical study showed that topiramate increased cocaine's reinforcing effects and blocked cocaine extinction[229]
Naltrexone and bupropion (Contrave®)	• Naltrexone: opioid receptor antagonist; prevents β-endorphin-mediated negative feedback on α-MSH release • Bupropion: DA and NE transporter inhibitor; stimulates hypothalamic POMC neurons, resulting in decreased food intake and increased energy expenditure	Naltrexone counteracts the reinforcing effects of alcohol and opiates[230]. Bupropion increases extracellular norepinephrine and DA concentrations in several forebrain areas while inhibiting the firing of noradrenergic and dopaminergic neurons in brainstem regions[231,232]	Positive. Naltrexone is an effective treatment for some SUDs and promising for behavioural addictions[233]. Bupropion has been approved as a smoking cessation medication and has been shown to reduce craving[234].
Liraglutide (Saxenda®)	GLP-1 agonist; decreases appetite	New evidence that central GLP-1R activation suppresses phasic dopamine signalling in the NAc core[235]	Positive GLP-1Rs remain viable targets for the treatment and prevention of cocaine seeking, taking and relapse[235,236]. Recent studies have also shown GLP-1R agonists can inhibit alcohol consumption and alcohol-mediated behaviour in rodents[237], which makes them promising candidates for the development of novel treatments of alcoholism in humans[238]

5-HT, 5-hydroxytryptamine (serotonin); AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; DA, dopamine; GLP-1, glucagon-like peptide 1; GLP-1R, glucagon-like peptide 1 receptor; MSH, melanocyte-stimulating hormone; NAc, nucleus accumbens; NE, norepinephrine; POMC, pro-opiomelanocortin; SUDs, substance use disorders. Modified with permission from REF. 140, Elsevier.

agonist liraglutide (Victoza®), which has FDA approval for weight loss, reduces the reinforcing effects of alcohol and may therefore be beneficial for the treatment of alcoholism[147].

On the other hand, rimonabant, a cannabinoid CB1 receptor inverse agonist, which was initially approved in Europe for the treatment of obesity, was subsequently withdrawn because of its side effects; this withdrawal also interfered with its potential development for the treatment of substance use disorders, for which it appeared beneficial[148,149]. In juxtaposition, the increase in bariatric surgeries for the treatment of obesity has revealed an increased risk of alcohol use disorder after the procedure[150,151]. There is also concern that bariatric surgery might increase vulnerability to the reinforcing effects of opioid analgesics[152]. Preclinical studies in rodents have confirmed an enhanced degree of sensitivity to the reinforcing effects of alcohol[153] and opioids[154] after bariatric surgery. Although the underlying mechanisms are unclear, one hypothesis is that there is transference of one addiction (food) to another (alcohol), but it is also possible that changes in metabolic signals (such as ghrelin, leptin and insulin) triggered by the surgery might increase the patient's sensitivity to the reinforcing effects of alcohol or other drugs[155].

There has also been an explosion of non-medication-based strategies with potential benefit for both obesity and addiction. For example, stimulation techniques that target a peripheral nerve (that is, the vagus nerve), external stimulation of the brain (that is, repetitive transcranial magnetic stimulation [rTMS][156,157] and transcranial direct current stimulation [tDCS][158]) or deep brain stimulation (DBS) are currently being tested for the treatment of obesity and of substance use disorders. Indeed, a vagal nerve stimulator was approved by the FDA for the treatment of obesity, while preclinical studies provide evidence that this technique could reduce drug consumption[159]. Preliminary studies with rTMS and tDCS, targeted to the prefrontal cortex, have yielded promising results — more so for food craving than for food intake[157] — as well as for smoking cessation[160] and for the treatment of alcohol[161] and cocaine use disorders[156,162]. Pilot clinical trials of DBS have reported benefits in the treatment of refractory obesity[163] and other eating disorders such as anorexia nervosa and bulimia[164,165] as well as in people with treatment-resistant alcoholism[166].

Research opportunities

Neurobiology of addiction and obesity. Although in this Review we have described the neurocircuitry that is implicated in addiction and obesity, this model is a simplified one whose details are far from elucidated. Similarly, although research has revealed some of the molecular mechanisms underlying long-term potentiation and long-term depression triggered by repeated drug reinforcers, the neuroplastic changes triggered by repeated energy-rich food have been much less investigated. Further work is also required to understand how these neuroplastic changes map onto the behaviours observed in addiction and obesity. This research will benefit from new mapping and imaging tools emerging from the Brain Research through Advancing Innovative Neurotechnologies® (BRAIN) initiative, from access to new transgenic strains and from genetically based stimulation approaches.

Mechanisms of vulnerability to addiction or obesity. Although it is clear that both drugs and food engage the DA motive system and can trigger loss of control and compulsive drug taking or food consumption, it is unclear why this phenomenon occurs only in some individuals and not in others. Similarly, the mechanism(s) that account for vulnerability to a specific reinforcer (food versus a specific drug) other than differences in its availability or accessibility are unclear.

Role of stress in modulating sensitivity to food and drugs. The stress system has a well-established influence on drug and food reinforcement. However, much work is still needed to understand the effects of acute and chronic stress on the DA motive system as a function of developmental stage and gender and their impact on risk of addiction and obesity.

Roles of diet, physical activity, sleep and circadian rhythms in the DA motive system. The importance of physical activity for sustaining weight loss[167] as well as its value in the treatment of substance use disorders, is well recognized[168]. However, the mechanisms underlying inactivity in obesity[169], the influence of physical activity on sensitivity to foods' reinforcing effects[170] and the therapeutic benefits of physical activity in addiction are poorly understood[168]. Similarly, studies have started to reveal the influence of sleep[171] and circadian rhythms[172] in dopaminergic signalling and their relevance to changes in addiction[173], but these studies are still preliminary.

Role of the gut-brain connection in drug reinforcement. As summarized in BOX 1, there is increased recognition that hunger-regulating hormones target the DA motive system and that some of these homeostatic signals also influence drug reinforcement. However, our understanding is still very limited, including how homeostatic signals and diets influence neuroplasticity in the brain's DA motive system.

Role of the microbiome in sensitivity to food reinforcers and in addiction. Our knowledge of the influence of the gut microbiome on obesity[174], while imprecise, has already led to clinical trials to evaluate the benefits of gut microbiota transplants in obesity[175,176], and preclinical studies are starting to evaluate the role of the microbiome in drug reinforcement[177].

Concluding remarks

The dopamine motive system sits at an evolutionary crossroads for neurocircuits and homeostatic signals that control the sensations of hunger and satiety and that motivate our actions. As we continue to explore this intersection, we should expect to discover more effective interventions for correcting the specific deficits in

Optogenetic stimulation and inhibition
A technique that allows the use of an external source of monochromatic light to stimulate or inhibit the activity of cells reversibly and with a high degree of spatiotemporal resolution (typically applied to selected neuronal populations that have been genetically modified to express light-sensitive ion channels).

Gut microbiome
The diverse collection of symbiotic microorganisms (flora) residing in the gastrointestinal tract that perform structural and histological functions and play significant roles in the regulation of host health maintenance and homeostasis.

reinforcement, motivation and self-regulation underlying the enhanced habitual and inflexible responding that characterize disorders such as obesity and addiction. In the meantime, our current understanding of the role of the DA motive system in addiction and obesity highlights the importance of public health interventions promoting environments that protect us from conditioning to drug and obesogenic foods as one of the most effective interventions to prevent and control these disorders.

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Author contributions

N.D.V.: researching data for article, substantial contribution to discussion of content, writing, review and editing of manuscript before submission. R.A.W.: researching data for article, substantial contribution to discussion of content, writing, review and editing of manuscript before submission. R.B.: substantial contribution to discussion of content, writing, review and editing of manuscript before submission.

Competing interests statement

The authors declare that they have no pertinent competing financial interests or any other conflict of interest in relation to the work described herein.

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