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Misdeed of the need: towards computational accounts of transition to addiction

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Drug addiction is a complex behavioral and neurobiological disorder which, in an emergent brain-circuit view, reflects a loss of prefrontal top-down control over subcortical circuits governing drug-seeking and drug-taking. We first review previous computational accounts of addiction, focusing on cocaine addiction and on prevalent dopamine-based positive-reinforcement and negative-reinforcement computational models. Then, we discuss a recent computational proposal that the progression to addiction is unlikely to result from a complete withdrawal of the goal-oriented decision system in favor the habitual one. Rather, the transition to addiction would arise from a drug-induced alteration in the structure of organismal needs which reorganizes the goal structure, ultimately favoring predominance of drug-oriented goals. Finally, we outline unmet challenges for future computational research on addiction.

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Introduction

Drug addiction is a behavioral disorder that affects millions of persons worldwide and thus represents an important public health problem whose resolution requires a concerted effort at different levels, from policy to clinical and basic research, *en passant* by theoretical and computational modelling.

At the individual level, addiction can be characterized by compulsive seeking and taking of the drug that induces harmful consequences [1]. To avoid confusion, it is important to define at the outset what is meant by compulsive drug-oriented behaviors and how these might differ from mere habits (i.e., learned behaviors that are no longer goal-directed) [2,3]. To be compulsive, a behavior must somehow be executed in presence of a persistent desire or willingness not to engage in that behavior. A compulsive drug user is a person who takes drugs despite his/her own desire and effort not to take it. In general, the desire to resist the compulsive behavior arises from knowledge or awareness of its negative consequences. This compulsivity goes beyond just seeking the drugs and also extends to how much of the drug is consumed once the person begins consumption. In general, people with addiction (as opposed to recreational drug users) tend to consume more than they initially intend, even if they know that such increased consumption can cause important negative consequences (e.g., drinking too much at a dinner party may result not only in lost friendships but also in lost lives) [4]. In addition, as the transition to addiction unfolds, the behavioral repertoire or spectrum of a person with addiction becomes impoverished in favor of a predominance of drug-related behaviors and thus at the expense of other important occupational and social nondrug activities, a phenomenon particularly evident with illegal drugs [5]. At the same time, this does not mean that a person with addiction behaves as a zombie-like creature [6,7]. In fact, the behaviors deployed to seek and secure access to the drug of choice can remain flexible, forward-looking, and purposeful [8•,9,10]. This highlights two key aspects of behavior in drug-addicted individuals that pose a challenge to the mathematical modeller interested in modelling addiction: (1) compulsive, yet flexible, drug seeking and (2) impaired control over drug consumption once the drug is obtained despite knowledge of the negative consequences.

At the neurobiological level, drug addiction has been intensively studied over the past 40 years mainly because animal models exist that reproduce in a simplified manner several key behavioral aspects of addiction: increased motivation to seek the drug, escalating drug consumption, apparent indifference to the negative consequences of drug use, and post-abstinence relapse-like behavior (i.e., generally, post-extinction reinstatement of drug seeking behavior) (Box 1). This work has progressively led to a brain circuit view of addiction where addiction would basically reflect loss of prefrontal top-down control over

Box 1 Animal models of drug addiction

Most animal models of drug addiction discussed in this Opinion article involve the intravenous (i.v.) drug self-administration paradigm [49]. Briefly, in this paradigm, an individual animal with an indwelling i.v. catheter is connected to a drug infusion system and placed in a setting (generally a small operant cage) where it has access to a response operandum (e.g., a lever) that controls the drug infusion system. Thus, by responding on the operandum, the individual can self-administer a drug by the i.v. route which allows the drug to produce its effects rapidly. Importantly, the conditions of access to the drug (e.g., access duration; dose; type of drugs) are generally not under the control of the individual but of the experimenter. In addition, though animals are not physically coerced to take the drug, they nevertheless have no access to other competing, nondrug behaviors during drug access. These environmental conditions must always be kept in mind for a valid interpretation and extrapolation of animal drug self-administration data [45]. The i.v. drug self-administration paradigm has been versatilely used to model different stages and/or features of drug addiction [2,32]. Here is a short list of relevant animal models.

Initiation of drug use

During this stage, an initially drug-naïve animal discovers for the first time and eventually learns that responding on the operandum produces drug effects. It is also during this stage that the individual learns about the nature and time course of these effects. It then exploits this information to learn to titrate or regulate its drug intake around some preferred level or drug reward set-point. Potentially Accounted for by RL computational accounts (e.g., [37], among others).

Maintenance of drug use

After an initial increase of drug intake during initiation of drug use, an individual maintains its intake at a relatively constant level over time ceteris paribus During this maintenance stage, the daily pattern of drug use is typically biphasic: it begins by a brief bout of rapid drug intake (i.e., loading) and then transitions to a slower, highly regular pattern of intake [26]. These cannot be accounted for by standard RL accounts, but by control-theoretic models (e.g., [26]), and the homeostatically regulated reinforcement learning (HRRL) [27].

Escalation of drug use

If the daily duration of access to the drug is extended after stabilization of drug intake during a prior maintenance stage, this can trigger a rapid escalation of drug intake that eventually levels off to a new, higher stable level of intake [2]. Importantly, during extended access to the drug, an individual animal is not only more likely to escalate its drug consumption; it also works harder and takes more risk to seek and to obtain the drug; and, finally, it becomes more vulnerable to relapse after abstinence (see below). Accounted for by the HRRL model of addiction [16••].

Abstinence from drug use

Once an individual animal has initiated and escalated its drug intake, it would continue to self-administer the drug indefinitely, except if its drug use behavior was no longer accessible (i.e., forced abstinence), if its drug use behavior was punished (i.e., punishment-induced abstinence) [50], if its drug use behavior competed with an alternative nondrug-rewarded behavior (i.e., alternative reinforcement-induced abstinence) [51], or, finally, if its behavior was no longer rewarded by drug delivery (i.e., extinction) [52]. Except for the nondrug-reward alternatives case, the other patterns can be explained by most of the RL-based and HRRL model.

Post-abstinence relapse

Importantly, an individual will relapse after abstinence if the factors that precipitated abstinence in the first place are discontinued. For instance, if the drug is again available after extinction or if punishment is discontinued, then the individual returns to its pre-abstinence level of drug intake. Interestingly, however, when the period of forced abstinence is sufficiently prolonged, this leads to an incubation-like increase in the motivation to seek the drug [53] and an intense re-escalation of drug intake [31]. Accounted for by HRRL model of addiction [16••].

the activity of the subcortical brain circuits that drive drug seeking and that regulate drug consumption [11,12•]. One may thus have arrived at a stage of progress where the field of addiction is poised to benefit from more formal computational accounts. Such benefits include quantitative testing of the validity of addiction theories within the formal confine of algorithmic and dynamical computational models [13]. Intriguingly, however, recent computational research on addiction has begun to challenge the view that progression to addiction may be a result of a complete withdrawal of goal-oriented system from decision making in favor some habitual system [14•,15]. Rather, as we will argue in this Opinion article, such progression would arise from a drug-induced alteration in the structure of organismal needs which, in turn, would reset or reorganize the goal structure of the individual, ultimately leaving only the drug-oriented needs and goals controlling behavior [16••]. However, before discussing this novel line of research, we will first provide a brief overview of more classic reinforcement-based computational models of addictive behavior (Figure 1).

Positive versus negative reinforcement models of drug addiction

Classic computational models of addiction concern almost exclusively cocaine addiction and fall into two main classes: positive reinforcement and negative reinforcement models of drug addiction [17••]. In the former, the progression to addiction is mainly caused by a supernormal, monolithic positive reinforcement signal that is generated artificially by the direct pharmacological action of the drug on brain dopamine signaling. Such an abnormal dopamine reinforcement signal in downstream brain targets would modulate action and/or value learning processes in favor of drug use and at the expense of other behaviors [18•]. Recently, the sufficiency of dopamine neurons stimulation in addiction has been tested in mice that could self-stimulate their Ventral tegmental area (VTA) dopamine neurons [19]. This set of conceptual

theories has been picked up and formalized by a large class of models based on the reinforcement learning algorithms (see below).

The second class of models assigns the key role, not to positive reinforcement, but instead to negative reinforcement of drug use [20,21]. Here drug use would be mainly maintained by escape and avoidance of the negative affective state that occurs during drug withdrawal. Importantly, avoidance of drug withdrawal requires prior learning that stopping drug use causes a painful withdrawal state and that such occurring state can be escaped by retaking the drug. With repeated experience, the drug user would progressively learn to seek and take the drug, not only to escape withdrawal once in, but also to try to avoid it. Continuous avoidance of a dreaded, albeit non-occurrent, drug withdrawal may contribute to explain why people with addiction pursue drug use despite the negative consequences. Though people can causally attribute drug withdrawal with cessation of drug use, there is no positive evidence that nonhuman animals can make such complex inferential attribution, despite many attempt to show this [22]. This is not saying that nonhuman animals are incapable of avoidance learning, they clearly can [23]. Here what is at stake is the ability to learn that not doing a discrete behavior is the cause of a slow, delayed change of internal state [24,25].

Computational models based on negative reinforcement theories of addiction have been much less numerous, probably because they do not benefit from a coherent algorithmic normative framework. In fact, most of the negative reinforcement models stem from classical control theory and pharmacology, and are focused almost exclusively on modelling the patterns of drug consumption once established [26]. In addition, these models are not strictly speaking neurocomputational and rely heavily on an outdated view of homeostasis that attributes a dominant causal role to negative feedback physiological processes, with no or little role to important predictive or prospective regulatory processes [27,28•]. These models have been previously described in several previous reviews and will not be reviewed here in detail because of space limitation [29,30]. We will only limit our attention on recent neurocomputational models that have focused on the process of acquisition and the transition to escalation of drug use.

Several important stages in the transition to addiction can be recapitulated in animal models (see Box 1). Basically, in the standard drug self-administration setting, animals are given an opportunity to perform a behavior (e.g., press a lever; nose poking a hole in a wall) to receive an intravenous dose of drug. If the drug dose happens to be reinforcing, then animals will learn to repeat the behavior. This results in an escalation of drug intake over time that eventually levels off at a certain level [31]. The speed with which drug intake escalates and the final level at which it stabilizes depend on many different factors, including the individual characteristics, the dose available, and the daily duration of drug access [2]. Once drug intake becomes stable post-escalation, animals behave actively to defend drug intake around an individual-specific level in response to changes in several parameters, at least within a certain range of values. This suggests that drug intake is somehow a regulated variable [26]. It is not drug intake per se that is regulated but the resulting effects on the brain. We recently argued that the goal that animals may pursue during cocaine self-administration is to maintain a sustained increase in the Nucleus Accumbens (NAc) dopamine D1-receptors (D1R) neuronal output activity via a sustained high dopamine level. In this model, escalation of cocaine self-administration would result from a chronic decrease in NAc D1R neuronal activity. Animals would increase cocaine intake to maintain NAc dopamine at a higher level than before escalation in an attempt to compensate for a decrease in NAc D1R neuronal activity [16••].

In the standard drug self-administration setting, drug-seeking motivation can be measured by frustrating the pursuit of the drug goal [2,32,3]. Researchers have developed many different approaches to study drug seeking. For instance, this can be achieved by progressively increasing the amount of effort required to obtain the drug, such as, in the classic progressive ratio procedure where the response requirement per unit of reward is raised systematically after each reinforcer [33]. Alternatively, this can be achieved by interposing an intermediate drug seeking behavior that is different and that conditions access to the drug taking behavior [34]. One advantage of the latter approach is that it allows one to study in the same individuals the factors that control drug seeking versus drug taking.

Again, we can conceptually organize computational models of drug-seeking and taking into two classes: positive reinforcement and negative opponent process models. In the former, focusing on the role of dopamine as a learning signal in the reinforcement learning algorithmic theory of motivation and the latter focusing on dopaminergic opponency under direct drug action and its progressive drive to re-dress its deregulation. In a sense, the positive reinforcement models can capture how one might learn to initiate drug-seeking while the latter can describe how the pattern of self-administration unfolds under various drug availability schedules. An obvious challenge for research is to develop more general models with the potential to explain drug self-administration across all major addiction stages, including drug intake escalation (see Box 1), and further to pin-point the specific mechanisms by which addictive drugs alter the functioning of the dopaminergic circuitry. A further challenge is to go beyond subcortical dopaminergic circuitry to take into

account the executive brain systems that control its activity in a goal-directed manner and whose controlling functions are thought to be impaired in people with addiction. In a word, the challenge is to develop computational models that can formalize and synthesize the neural mechanisms for the transition to the addictive state.

A key outstanding issue concerning the transition from non-disordered drug use to addiction is the role of the biological adaptations seen under the chronic presence of the drug. A variety of alterations have been documented, such as, for instance, decreased function of brain reward pathways and concomitant increased responsiveness of brain stress pathways [11,12•]. Yet, it remains to be shown if these are the cause of the transition to addiction or mere consequences of such transition, with the brain reacting to protect its function from the continued presence of the drug. Put differently, do the biophysical effects of the drug lead to the aberrant behavior, or does the aberrant behavior with the drug consumption outcomes lead to the biological neuroadaptation? Another auxiliary question is how might the neuroadaptations caused by drug use contribute to the difficulty to quit drugs? These are some of questions that could be approached by multi-level computational models that combine circuit-level dynamics of brain function together with algorithmic approaches to formalize motivated behavior and its modulation.

Here we review the recent advances in the computational neuroscience literature along the positive and the negative reinforcement computational models of drug-related behavior. We then argue how an appropriate computational synthesis of the two approaches may provide at least partial answers to the open issues regarding the transition to addiction.

A selective overview of positive reinforcement models of acquisition of drug seeking

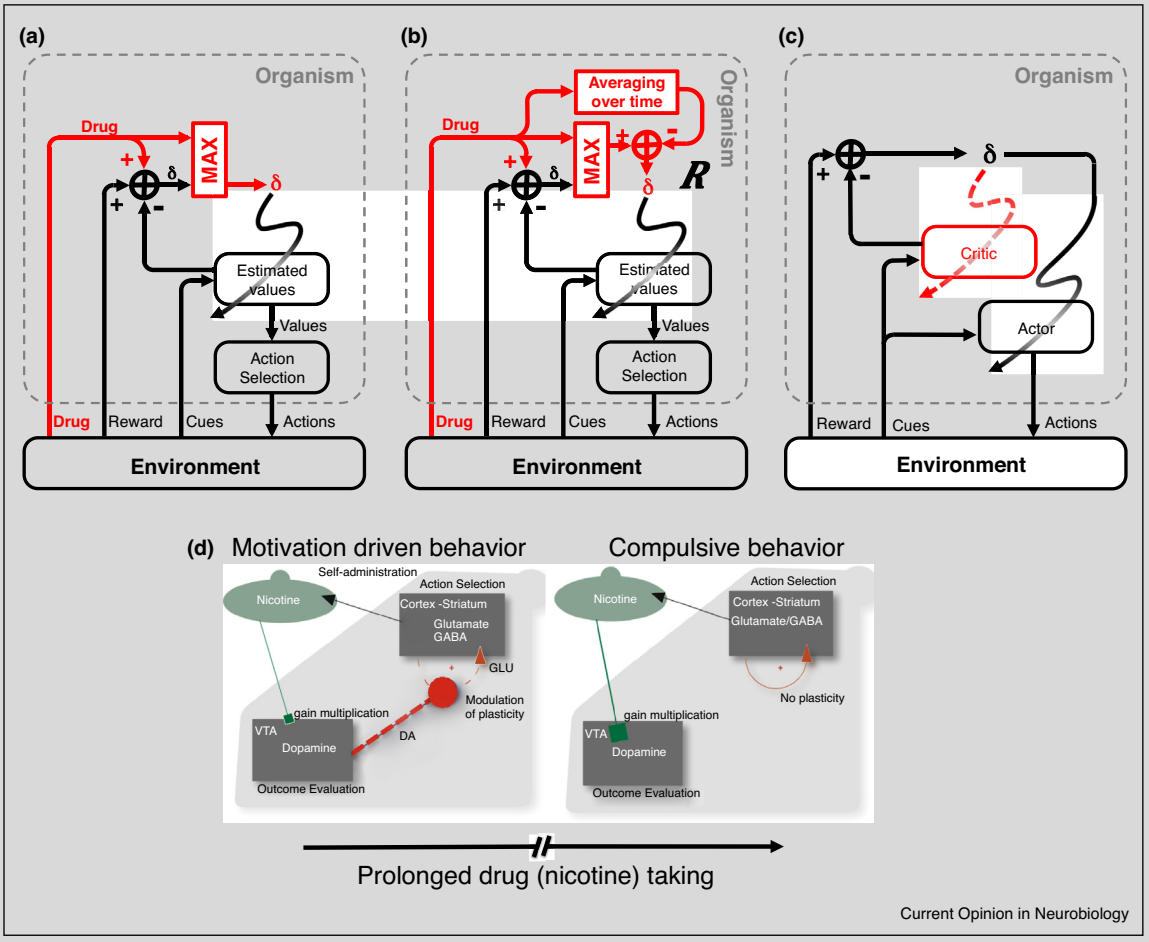
All known drugs act directly or indirectly on the dopaminergic circuitry of the brain to cause fast efflux of dopamine into target brain areas [35]. Most notably, cocaine directly blocks the dopamine transporter and, as a result, provokes increased dopamine transients in the NAc, probably from afferents stemming from the VTA [54]. By extension, since the VTA furnishes direct inputs to a number of brain memory and executive areas (e.g., PFC), such dopamine transients should be seen in those structures. The challenge was to link such neural level effects to the drug-driven onset of self-administration and persistent choice for the drug. Although commented in the reinforcement learning neuroscience literature earlier [36], it was only a decade ago that this challenge was explicitly taken up by a model borrowed from the machine learning techniques. Redish [37] presented an abstract computational model of cocaine addiction. The model was a straightforward extension of the temporal-difference reinforcement learning algorithm (TDRL) (see, e.g., [38] for an overview). The key to this model was that the dopaminergic response to non-drug rewards, both in biology and in the algorithm, converges to zero as the subject learns to expect rewards delivered after the choice. In other words, in the jargon of the field, the phasic dopamine signal in response to the reward delivery is 'learned away' while, the dopamine response is transferred to the reward predicting cue. By contrast, for cocaine delivered contingent on the animal's choice, phasic dopamine signal remains, because cocaine directly increases dopamine signaling. If we take into account the TDRL dogma that phasic dopamine is a learning signal that encodes the error between the received and the expected rewards (a.k.a. reward prediction error; RPE) [36] cocaine acts directly and pharmacologically on the DA circuitry to create a persistent under-expectation of rewards. Interestingly, early data suggested that neuropharmacological effect is mostly, though not entirely, independent from the how the drug-taking is reinforced [39]. This lack of accommodation to cocaine predicted that the learned value of cocaine should keep increasing over repeated use, ultimately overshadowing the values of other reinforcers. Hence, animals allowed to choose mutually exclusively between cocaine and a non-drug reinforcer should inexorably prefer cocaine, regardless of the magnitude of the alternative reinforcer.

The Redish model rested on several assumptions that needed to be reconciled with data obtained in cocaine-addicted individuals. The model postulated hedonic constancy, where the non-drug choice value is not influenced by the prior experience with the drug. This implied that people with addiction should have otherwise normal value-based behavior (except for the drug-related behaviors). This assumption has been difficult to reconcile with the observed long-term decrement in non-drug reward processing in both cocaine-addicted animals and humans [40].

Second, the key assumption of the model — that cocaine-induced dopaminergic responses do not accommodate is disputed by recent experimental evidence of accommodation in phasic dopamine response in extended cocaine taking [41]. Notably, in rats with 24-hour access to cocaine self-administration for 10 days, cocaine rapidly lost its ability to boost the dopamine pathway that innervates NAc, mostly because of a failure to inhibit the dopamine transporter [42]. Furthermore, data showed that important differences occur between the ventral and dorsal striatal release of dopamine: with accommodation of DA response to cocaine in Ventral NAc and a late onset of response in Dorsal NAc in animals who have escalated their drug-intake [41]. Finally, in contrast to the implications of the model, drug choice studies in rodents and nonhuman primates have revealed that cocaine choices are sensitive to the magnitude of the alternative reward

Box 2 Structure of selected computational models of drug addiction.

Figure 1



Several computational models have treated simulation of how drug seeking and taking arises and/or how this process is related to drug-induced adaptations in the dopaminergic system. Most of these models are based on the reinforcement learning algorithms, and the central role for dopamine as the learning signal (the error between expected and received reward). Here we give a graphical representation of the general structure of these models, marking the drug-influenced processes in red. (A) RL model of drug addiction due to Redish [37], where the drug directly affects the d error signal. Note that under drug consumption, a maximum of either the natural reward + drug effect or the drug effect acts as the teaching signal for the value learning. (B) Extended model due to Dezfouli *et al.* [46] does not require the maximum operation, since it keeps track of the long-term average rewards in the environment, and this estimate is directly affected by the drug. (C) In a Actor-Critic model suggested by Takahashi and colleagues [55] exposure to cocaine selectively impairs the dopamine RPE error in the critic thereby blocking the value state-learning and leaving only the Actor to learn. This allows the model to account for the experimental observations. (D) In the dynamical framework for nicotine addiction due to Gutkin and colleagues [58], nicotine-induced receptor activation first increases dopamine response to the drug. This leads to a pathological learning of drug-apporting actions. In the long-term nicotine induces receptor down-regulation, removing the dopamine influence over action selection and leaving the drug-oriented behavior rigid and independent of motivational signals.

[43,44]. In fact, choice studies in rodents have systematically found that when faced with a choice between a stimulant drug and a palatable food or drink, the vast majority of rats prefer the food alternative over the drug in a variety of conditions and even after a long history of drug self-administration and drug intake escalation. Only a minority preferred the drug despite the opportunity to engage in a different nondrug activity [43]. This robust finding does not square well with Redish's model or with any other dopamine-based computational models of addiction, and therefore, remains an unexplained apparent anomaly [45].

Although open and vulnerable to criticism, Redish's model has nevertheless stemmed a whole line of research into addictive behavior and mechanisms that is squarely

based on formal learning algorithms and connects directly with learning theory. For example, Dezfouli *et al.* [46] have expanded on the basic hypothesis to ameliorate a rather unrealistic unbounded increase in the value of the drug choice, by using an average reward reinforcement models and arguing that the drug increases the value of drug-cues and choices, but also depresses the average expected rewards from the environment. Takahashi and colleagues [55] have focused on cocaine induced impairments in reversal learning that was observed in an odor go/no-go task: cocaine sensitized animals were significantly impaired in reversing strategies. Electrophysiological measurements also showed that selectivity of cue representations was shifted in these animals from ventral to dorsal striatum [56]. Takahashi and colleagues proposed that these behavioral changes and neurophysiological adaptations induced by cocaine can be accounted for computationally by a pathology of the critic in the actor-critic RL framework. Here the actor in the drug-exposed case was left intact, while the learning of state-value associations in the critic was suppressed. In this case, the training signal sent to the actor was not the RPE but only the current reward. This biased the learning processes towards over-learning of positive valued-states in the Actor and promoted habitual non-flexible behaviors. In the author's own words, cocaine sets the 'coach awry' and let the 'actor run loose'. Authors further implied that this critic-less computation in the striatal circuitry could explain drug-induced inability to correctly make intertemporal choices, with the immediate rewards being chosen over the more valued delayed rewards.

In an application of RL models to human addictive behavior, Garbusow and colleagues [48•] showed that drug-addicted subjects (alcoholics) are more prone to Pavlovian Instrumental Transfer (PIT) effects — where drug-predicting Pavlovian cues start to drive addicted subjects instrumental choices — and that this augmented PIT is related to alcoholics proneness to relapse after abstinence. This approach was nicely expanded upon in Huys *et al.* [57] with a particular suggestion that drug-addiction may be particularly prevalent in 'sign-tracker' individuals, whose behavior is governed by pure value-driven decisions (consistent with model-free RL algorithms) as opposed to 'goal-trackers' who pay more heed to the nature of the outcomes (consistent with model-based RL). At the same time computational models of the intertemporal choice, so called discounting models, have been used in fMRI studies to show that addicted subjects tend to have faster reward discounting — thereby focusing on more proximal outcomes, as compared to bigger delayed outcomes [47]. Hence they appear impulsive in their choices.

Yet, these studies have not addressed several higher cognitive aspects associated with addiction, such as lack of self-control despite explicit knowledge of the negative consequences of drug taking. This was recently partially addressed by Keramati and Gutkin [27] who used a hierarchal RL model to show how the drug-driven percolation of exaggerated value of the drug through the ventral-dorsal cortico-striatal loops may lead to a correct evaluation of drug-related consequences at the top of the decision hierarchy where abstract plans (or goals) are represented, but have a pathologically high valuation of the drug-choices at the lower parts of the decision hierarchy where concrete implementation of actions is encoded. In other words, the biological effects of the drug, building up along the dopaminergic spiral connectivity that cascades reinforcement signal down the ventro-dorsal cortico-striatal hierarchy may leave the abstract assessment of the drug consequences intact, yet their actions will inevitably be biased towards seeking the drug. Interestingly, this chimes in directly with self-reports in drug-addicted people, and even with the first point in the Alcoholics Anonymous 12-steps 'We admitted we were powerless over alcohol — that our lives had become unmanageable'. This model also identifies, how the lower levels of the decision hierarchy might usurp control over behavior under drug-action, and pin points specific vulnerability points in the cortico-strial system where the pharmacological action of the drug should lead to the observed effects: notably (a) the midbrain dopaminergic projections to striatum that encode RPE, and (b) the midbrain GABAergic interneurons that receive striatal GABAergic disinhibition and synapse on dopaminergic neurons. What this model leaves moot is how the mismatch in the values at the high (abstract plans) and low (concrete actions) levels of hierarchy may entrain a potential withdrawal of behavioral control from the higher to lower levels and thereby, leaving the behavior to be fully controlled by the lower habitual-like processes, while leaving the individual perfectly aware of what and why they should not be taking drugs.

The unifying element of all of these models is their central emphasis on phasic dopamine signaling and its computational role in reinforcement of behaviors. In a sense, all of these models focus on how addictive drugs (and mostly cocaine) usurp the common currency of environmental experiences that drive our motivation and behavior. Interestingly in these models, drug-driven neuroadaptations are taken into account only in passing. A promising attempt to put together neuroadaptations and dopamine driven reinforcement was taken up by Gutkin *et al.* [58] neurodynamical framework to explain the mechanisms by which nicotine drives the onset of self-administration and its progression to drug-seeking that is independent of the drug taking consequences. The key for that modelling framework is the ability to simulate a transfer to habitual drug seeking as the direct effect of nicotine on the dopaminergic circuit through activation and desensitization of nicotinic acetylcholine receptors. The increased dopaminergic signaling conditioned on

nicotine consumption allowed for increased selection of the drug-associated actions through a dopamine-gated Hebbian learning. Prolonged exposure to nicotine provoked an opponent process, down-regulating nicotinic receptors, reducing dopamine signaling and effectively decoupling the dopamine module from the action selection circuit: thereby decoupling action from reward evaluation and influence. In the long term, the drug choosing is a glutamatergic process automatic upon cues signaling drug availability. Hence, the key to acquiring drug-taking was a positive reinforcement modulated learning (plasticity), while transfer to addiction was driven by an opponent process. Interestingly, subsequent computational modelling on the level of local circuits in the VTA showed how nicotine alters the computation of the RPE in the VTA by changing the interplay between the glutamatergic inputs, dopamine neurons and GABA neurons in the VTA. Driven by the desensitization of the nicotinic receptors by nicotine, this renders previously neutral stimuli (for which the values has been already learnt) labile again, with and re-opened positive RPE when nicotine is present [59].

The above models are successful in proposing how initial and sustained motivation to seek the drug is formed due to dopamine driven learning. The idea that drug addiction manifests in behavior being controlled by the habitual dopamine-dependent decision system is implicit in these models. The reinforcement learning models due to Redish and Dezfouli *et al.*, Garbow et *al.* and Huys *et al.* are all 'model'-free, hence they implicitly treat addictive behaviors as habitual. In Keramati and Gutkin, the drug induced accumulation of positive value for the drug-seeking choice at the lower levels of the decision hierarchy, points towards these, presumably habitual levels of decision making, taking control over behavior. The model discussed by Takahashi and colleagues, presumes that drug-induced adaptations impair learning in the 'critic', thereby leaving the habitual 'actor' to control behavior, and this theme is echoed by Gutkin *et al.*, where motivation-dependent learning is removed from control over action selection by long-term nicotine. All-in-all the models reviewed above may not explicitly argue for the transfer from goal-oriented to habitual drug-seeking in the transition to addiction, but they certainly are not set up to challenge this view-point.

Setting the goal-oriented versus habitual issue aside (for the moment), transition to addiction is characterized not only by the persistent motivation to seek the drug, but also a change in the consumption patterns: from moderate consumption to binging and overconsumption. Furthermore, the RL models leave the neuro-adaptations evoked by the addictive drugs that are linked to negative reinforcement aspects of drug-action outside their formal frameworks.

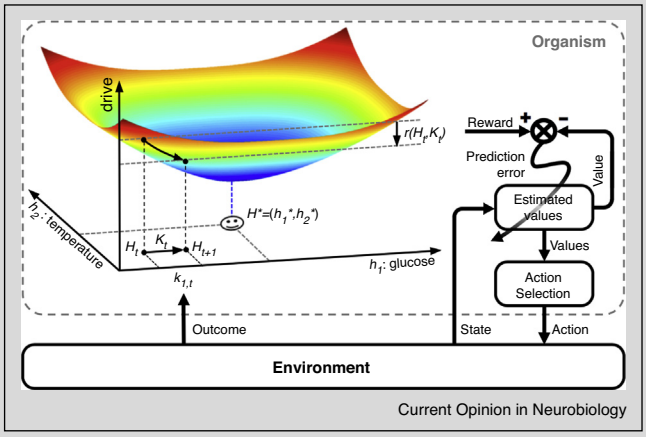
Positive and negative reinforcement components of addiction integrated

To address these issues, our hypothesis is that a complex interplay between the motivational impact of the drug and the neuroadaptations caused by it would explain how the initial motivation for the drug arises together with evolving patterns of consumption. A theory for this interplay would be able to synthesize the two phenomena. In other words, the desire for the drug contributes to render it more rewarding and thus leads to its consumption; the neuroadaptations caused by consumption, in turn, create a need for the drug that alters the structure of rewards focusing on the drug as the most desired or sought by the drug-addicted individual. Here a need merely corresponds to the internal state of a physiologically-deprived or psychologically-deprived organism (e.g., hunger or thirst). An individual may not explicitly know or be aware of such a need, unlike a goal which corresponds to a conscious, explicit representation of a behavioral end-state (e.g., eating that particular food). Importantly, a goal may be geared to fulfill a physiological need, but not exclusively. There are, obviously, abstract or symbolic goals that do not fulfill any physiological need, at least directly. Hence, needs may define goals but not necessarily the other way around (Box 2).

Long-term access to the drug may induce neuroadaptations that act to oppose the positive reinforcing effects of the drug. In other words the drug recruits a relatively slower dynamical opponent process. This idea of dynamical opponency was the central element of a recently introduced model of transition to learned escalation of cocaine dose. This phenomenon where prolonged access to a drug leads animals to radically escalate the amount of consumed drug (per unit time) has been argued to be a model of the transition to addiction [2]. The proposed model is conceptually based on a recently introduced normative framework [27] whose goal was to define the relationship between the concept of reward and organismal physiological internal needs. In fact, following the classical (but albeit almost discarded) drive-reduction theory of motivation, we hypothesized that reward should be defined with respect to the organismal needs: more formally to the deviations the organism is experiencing away from its homeostatic reference point(s). An action that reduces this deviation would produce a reward, whereas actions that increase the deviation would produce punishment. In this framework, the notion of homeostatic deviation and drive are combined mathematically with the RL algorithmic learning. This produced a unified framework where homeostatic maintenance and motivational learning are two sides of the same coin. So the agent learns to predictively choose actions that prevent expected homeostatic challenges (e.g., to stay away from life-threatening states). Furthermore, we showed that within this framework, seeking of maximal rewards is equivalent to maintaining optimal organismal

Box 3 Homeostatic Reinforcement Learning (HRL) theory

Figure 2



In the HRL theory, the organism's internal state at time t, represented by H_t, is a multidimensional vector where each dimension represents the level of one physiologically regulated variable (e.g., glucose level, body temperature, plasma osmolality). Given a hypothetical desired internal state, H^*, known as the setpoint, the HRL theory defines the organim's drive, $d(H)$ as the distance of the current internal state from the setpoint. Accordingly, assuming that a certain outcome changes the internal state along a vector K_t, the rewarding value of this outcome can be de computed as the consequent reduction of drive:

$$r(H_t, K_t) = d(H_{t+1}) - d(H_t) = d(H_t + K_t) - d(H_t)$$

Inspired by the coupling of the hypothalamic homeostatic-regulation system and the brain reward mechanism, the HRL theory proposes that the primary reward as computed above is used by the brain associative learning machinery to structure behavior. This, for example, can happen by computing a reward prediction error (RPE) signal that encodes the mismatch between the realized and the expected drive-reduction consequence of an outcome. This RPE signal can update the value of that action.

The HRL theory mathematically proves that seeking rewards is equivalent to the fundamental objective of physiological stability, defining the notion of physiological rationality of behavior. It also explains why and how animals learn to act predictively to preclude prospective homeostatic challenges, and how erroneous encoding of the nutritional content (i.e., effect on internal state) of an outcome by its sensory properties (e.g., taste and smell) can lead to its overconsumption and thus, disrupting homeostasis.

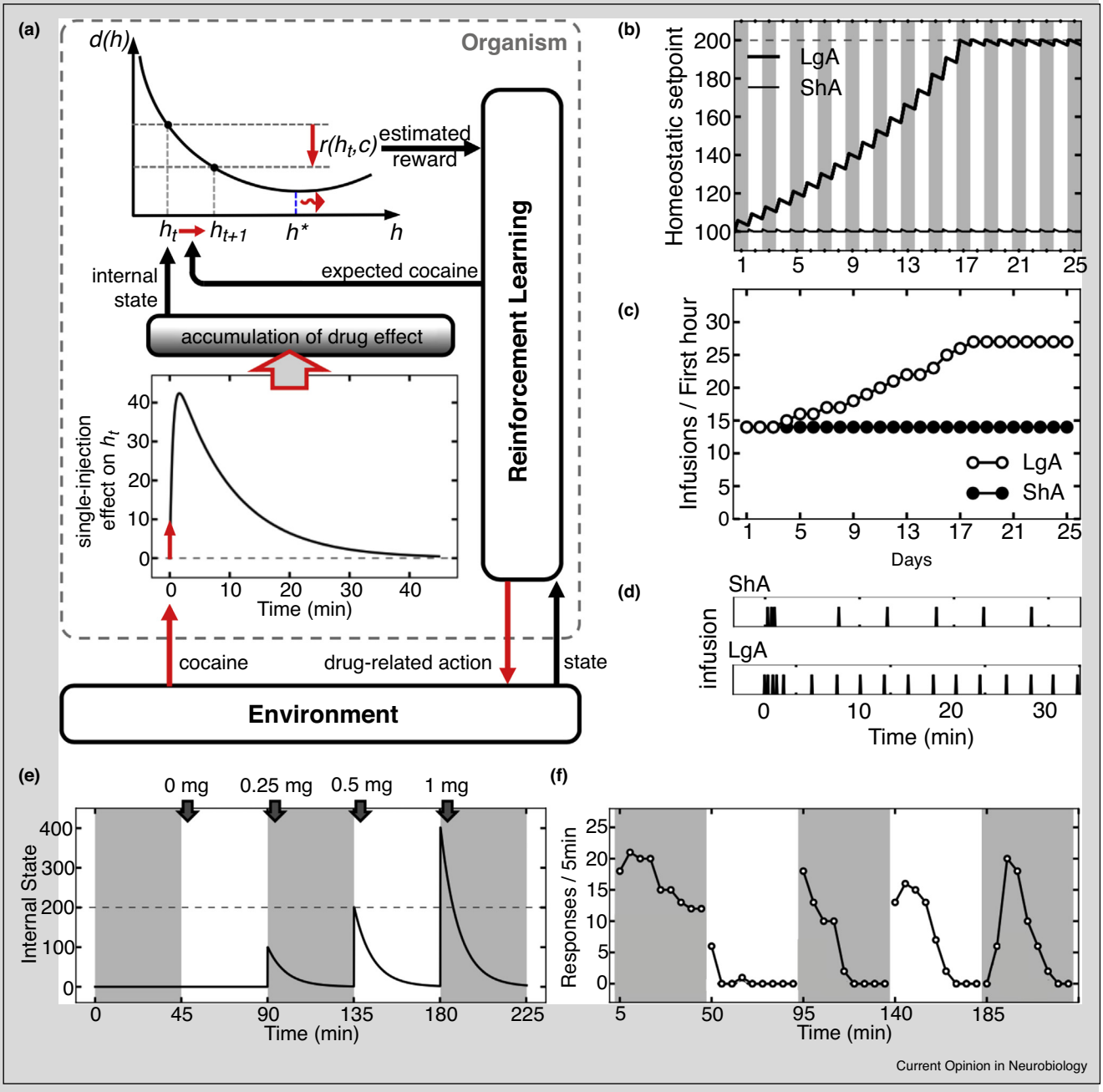
stability (Mathematical details of the Homeostatically Regulated Reinforcement Learning (HRRL) framework are given in Box 3, Figure 2). By taking into account the internal nature of primary 'reward' as being dependent on the organismal physiological state, the HRRL theory can naturally handle a number of behavioral phenomena that have eluded explanation by either the classical homeostatic theories or the standard RL models. Notably, anticipatory responding where animals learn to act proactively to preclude anticipated homeostatic challenges is shown as a clear behavioral marker of the coupling of homeostatic and learning mechanisms. Furthermore, the notions of satiety and overconsumption and their motivational impact are naturally taken into account.

The HRRL framework is intimately related to the concept of incentive salience as defined by Berridge [60]. In fact, the HRRL can be argued to be a normative generalization of the computational model for incentive salience introduced by Zhang *et al.* [61] where the previously learned expected rewards were modulated by an ad hoc internal variable (either multiplicatively or additively). HRRL goes beyond this idea to propose that the reward itself is calculated with respect on the internal state at the time of the action leading to the outcome, hence it is naturally modulated by the physiological state.

In drug seeking and taking context (see Box 4, Figure 3), we hypothesized that the drug has a dual effect: (1) it directly and rapidly affects the dopaminergic circuits of the brain to produce a rapid DA response and thereby altering levels of homeostatically regulated internal variables; (2) neuroadaptations caused by the drug leading to a gradual shift of the homeostatic reference points. Although the rapid dopaminergic effect of the drug has a drive-reduction effect and therefore is rewarding, the allostatic shift pushes this motivation to be abnormally stabilized. Conceptually, the motivation for the drug starts from wanting it (value-based responding) due to a preexisting need state, but then prolonged fulfilling of this need amplifies it. This vicious circle results in a gradual escalation of drug seeking. Eventually the need

Box 4 Homeostatic reinforcement learning theory of cocaine addiction

Figure 3



The HRL theory of addiction proposes that administration of cocaine increases the level of a certain internal variable (h) proportional to the self-administered dose, thereby rendering drug-related actions rewarding. The bottom plot of panel A shows the presumed pharmacodynamics of the internal variable h upon a single injection with the unit dose k. The consequent change in the level of this variable from each time point (t) to the next ($t+1$) is assumed to determine the reward experienced by the animal:

$r(h_t, k) = d(h_{t+1}) - d(h_t)$

In parallel, drug gradually shifts up the setpoint (symbol ⇑ in plot A). This results in a significant setpoint escalation over several days (B) in simulated animals that have daily long access (LgA) to the drug, but not in animals with short access (ShA). The escalated setpoint entails increased rewarding value of the drug due to the intensified need and thereby, higher levels of self-administration (C). To reach the setpoint from their initial deprived level, both groups of animals start the sessions with a burst of SA responding, which is then followed by a steady level that maintains homeostasis (D). These patterns replicate rats' behavior in the cocaine escalation paradigm.

level elevates to such high levels that the strong motivation of fulfilling this need outweighs the punishments associated with drugs and thus, drug-seeking becomes compulsive. Moreover, the slowness of the recovery of this escalated need back to its healthy level keeps abstinent drug users vulnerable to relapse for a very long period such that even an acute exposure to the drug or cues associated with it can revive the partially-extinguished actions that lead to the drug.

Importantly, this HRRL model of addiction suggests that the key hypothetical pathology is NOT in the reward signaling machinery itself (e.g., not in how the RPE is computed by the dopamine circuits), but in how the reward itself is computed by the needs machinery of the brain and how this machinery can be diverted to intensify a preexisting need when chronically exposed to drugs. In this sense, rather than (or in parallel with) framing addiction as a dominance of the habitual over the goal-directed reward-seeking mechanism, the HRRL model shifts the focus onto the reward computation itself and on the machinery that sets needs. The maladaptive needs then entrain a pathological goal structure. No matter what instrumental system is in control over behavior, seeking to reduce an escalating need state may be maladaptive, at least under some circumstances.

Summary and outstanding issues

Current neurocomputational research is consistent with the view that, in people with addiction, the very process of need or goal setting is progressively altered by the erroneous wanting of the drug, based on the initial positive reinforcing effects of the drug. Progressively, the need structure is altered, thereby changing the structure of reward-signaling. So transition to addiction is a pathological interplay between learning based on rewards and how these rewards are defined by the internal machinery of allostatic representation of needs. The key pathology is NOT in the reward signaling itself (e.g., not in how the RPE is computed by the dopamine circuits), but in how the reward itself is computed by the needs machinery of the brain. Hence seeking and taking drugs would lead to a pathological need structure and, in turn, the motivational salience (or value) of the drug-state rapidly takes over the addict's behavior. Despite this misbehavior of value, the overall addictive behavior remains goal-oriented and potentially flexible as long as the goal is to attain the drug. In fact we might speculate that addiction is rather a pathology of goal flexibility: goals to obtain the drug become rigid, unconditional and persistent, eventually taking over the addicts life strategies and defining patterns of behavior.

Open questions and challenges

Although contributing significantly to our understanding of addiction, the computational models reviewed above leave a large number of open questions. Notably, an important issue that could be resolved with computational approaches is rather mechanistic — how do the neuroadaptations evoked by the drug translate into behavioral and motivational patterns seen in addiction? Meaning, how can we connect mechanistically the neurobiological and pharmacological mechanisms to the behavioral manifestations? The second issue that needs to be addressed is the mechanisms by which drug-seeking and drug-taking induces the alleged pathology of cognitive control and how this leads to compulsive drug-seeking and taking. Is this pathology a disconnection of the prefrontal cortex from the behavioral control machinery? Is this a drug-induced change in the structure of goal representations in the prefrontal cortex or is it, as has been suggested from several studies, a change in the general balance in the competition for control over behavior between the fronto-cortical goal systems and the habitual dopamine-related brain systems?

Conflict of interest statement

Nothing declared.

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References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Hasin DS, O'Brien CP, Auriacombe M, Borges G, Bucholz K, Budney A *et al.*: **DSM-5 criteria for substance use disorders: recommendations and rationale**. *Am J Psychiatry* 2013, **170**:834-851.

2. Ahmed SH: **The science of making drug-addicted animals**. *Neuroscience* 2012, **211**:107-125.

3. Everitt BJ, Robbins TW: **Neural systems of reinforcement for drug addiction: from actions to habits to compulsion**. *Nat Neurosci* 2005, **8**:1481-1489.

Simulating the model also shows that the absence of drug over a period of 90 min (E) results in extinction of drug-seeking behavior (F). Upon an acute injection of priming dose, responding relapses due to the fact that the response-drug association was only extinguished in a 'cocaine-free' mental state, whereas it has remained intact in an 'under-drug' state. Furthermore, when the priming dose is sufficiently high (e.g., 1 mg), reinstatement does not occur instantaneously because the internal state overshoots the setpoint and drug is not rewarding (it does not decease deviation from the setpoint). Thus, the model waits until the internal state drops sufficiently below the setpoint and then starts seeking cocaine. These patterns replicate experimental results in a priming-induced relapse paradigm.

4. Martin CS, Chung T, Langenbucher JW: **How should we revise diagnostic criteria for substance use disorders in the DSM-V?** *J Abnorm Psychol* 2008, **117**:561-575.

5. Volkow ND, Baler RD, Goldstein RZ: **Addiction: pulling at the neural threads of social behaviors**. *Neuron* 2011, **69**:599-602.

6. Hyman SE: **The neurobiology of addiction: implications for voluntary control of behavior**. *Am J Bioeth* 2007, **7**:8-11.

7. Vohs KD, Baumeister RF: **Addiction and free will**. *Addict Res Theory* 2009, **17**:231-235.

8. • Baumeister RF, Vonasch AJ: **Uses of self-regulation to facilitate and restrain addictive behavior**. *Addict Behav* 2015, **44**:3-8.
This paper provides several examples where initiating, maintaining, and even quitting addictive drug use requires self-regulatory, goal-directed capabilities.

9. Hogarth L, Troisi JR II: **A hierarchical instrumental decision theory of nicotine dependence**. *Curr Topics Behav Neurosci* 2015, **23**:165-191.

10. Pickard H: **The purpose in chronic addiction**. *AJOB Neurosci* 2012, **3**:40-49.

11. Koob GF, Volkow ND: **Neurocircuitry of addiction**. *Neuropsychopharmacology* 2010, **35**:217-238.

12. • Luscher C: **The emergence of a circuit model for addiction**. *Annu Rev Neurosci* 2016, **39**:257-276.
This review article summarizes recent research in rodents showing how drug-induced changes in synaptic plasticity and metaplasticity can rewrite the brain circuits involved in drug-seeking behavior and how reversal of some of these synaptic changes can causally influence drug-seeking behavior.

13. Gutkin B, Ahmed SH (Eds): *Computational Neuroscience of Drug Addiction*. Springer Science + Business Media; 2012.

14. • Everitt BJ, Robbins TW: **Drug addiction: updating actions to habits to compulsions ten years on**. *Annu Rev Psychol* 2016, **67**:23-50.
This review article is basically an up-to-date reevaluation of Everitt and Robbins's influential hypothesis (2005) that the transition to drug addiction is fundamentally a transition from goal-directed drug use to compulsive-drug seeking habits.

15. Goldstein RZ, Volkow ND: **Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications**. *Nat Rev Neurosci* 2011, **12**:652-669.

16. •• Keramati M, Durand A, Girardeau P, Gutkin B, Ahmed SH: **Cocaine addiction as a homeostatic reinforcement learning disorder**. *Psychol Rev* 2017, **124**:130-153.
Building upon a recently developed homeostatic reinforcement learning theory [27], this theoretical paper proposes a computational theory of cocaine addiction where cocaine reinforces behavior due to its rapid homeostatic corrective effect, whereas its chronic use induces slow and long-lasting changes in homeostatic setpoint. This theory coherently explains many behavioral and neurobiological aspects of the transition to cocaine addiction, and suggests a new perspective toward understanding addiction.

17. •• Wise RA, Koob GF: **The development and maintenance of drug addiction**. *Neuropsychopharmacology* 2014, **39**:254-262.
Two scientific giants, Roy Wise and George Koob, who contributed to give birth and to shape the field of the neurobiology of drug addiction, expose and discuss their long-standing conceptual opponency about the defining property of addiction positive or negative reinforcement? That was the question.

18. • Keiflin R, Janak PH: **Dopamine prediction errors in reward learning and addiction: from theory to neural circuitry**. *Neuron* 2015, **88**:247-263.
This review integrates different theories and experiments on the function of midbrain dopamine neuronal projections in reward error-prediction-based learning and its hypothetical usurpation by drugs during the transition to addiction.

19. Pascoli V, Terrier J, Hiver A, Luscher C: **Sufficiency of mesolimbic dopamine neuron stimulation for the progression to addiction**. *Neuron* 2015, **88**:1054-1066.

20. Koob GF: **A role for brain stress systems in addiction**. *Neuron* 2008, **59**:11-34.

21. Wikler A: **A psychodynamic study of a patient during experimental self-regulated re-addiction to morphine**. *Psychiatr Q* 1952, **26**:270-293.

22. Lenoir M, Cantin L, Vanhille N, Serre F, Ahmed SH: **Extended heroin access increases heroin choices over a potent nondrug alternative**. *Neuropsychopharmacology* 2013, **38**:1209-1220.

23. LeDoux JE, Moscarello J, Sears R, Campese V: **The birth, death and resurrection of avoidance: a reconceptualization of a troubled paradigm**. *Mol Psychiatry* 2017, **22**:24-36.

24. Lindesmith AR: **A general theory of addiction to opiate-type drugs**. *NIDA Res Monogr* 1980, **30**:34-37.

25. Solomon RL, Corbit JD: **An opponent-process theory of motivation. I. Temporal dynamics of affect**. *Psychol Rev* 1974, **81**:119-145.

26. Ahmed SH, Koob GF: **Transition to drug addiction: a negative reinforcement model based on an allostatic decrease in reward function**. *Psychopharmacology (Berl)* 2005, **180**:473-490.

27. Keramati M, Gutkin B: **Homeostatic reinforcement learning for integrating reward collection and physiological stability**. *eLife* 2014:3.

28. • Ramsay DS, Woods SC: **Clarifying the roles of homeostasis and allostasis in physiological regulation**. *Psychol Rev* 2014, **121**:225-247.
This fascinating review provides a much needed clarification of the concept of allostasis and how it may be fruitfully distinguished from the more classic concept of homeostasis. The authors also emphasize the importance of behavioral and physiological anticipatory mechanisms in addition to more reactive, homeostatic mechanisms.

29. Ahmed SH, Bobashev G, Gutkin BS: **The simulation of addiction: pharmacological and neurocomputational models of drug self-administration**. *Drug Alcohol Depend* 2007, **90**:304-311.

30. Ahmed SH, Graupner M, Gutkin B: **Computational approaches to the neurobiology of drug addiction**. *Pharmacopsychiatry* 2009, **42(Suppl. 1)**:S144-S152.

31. Ahmed SH, Koob GF: **Transition from moderate to excessive drug intake: change in hedonic set point**. *Science* 1998, **282**:298-300.

32. Badiani A, Belin D, Epstein D, Calu D, Shaham Y: **Opiate versus psychostimulant addiction: the differences do matter**. *Nat Rev Neurosci* 2011, **12**:685-700.

33. Arnold JM, Roberts DC: **A critique of fixed and progressive ratio schedules used to examine the neural substrates of drug reinforcement**. *Pharmacol Biochem Behav* 1997, **57**:441-447.

34. Olmstead MC, Lafond MV, Everitt BJ, Dickinson A: **Cocaine seeking by rats is a goal-directed action**. *Behav Neurosci* 2001, **115**:394-402.

35. Luscher C, Ungless MA: **The mechanistic classification of addictive drugs**. *PLoS Med* 2006, **3**:e437.

36. Montague PR, Hyman SE, Cohen JD: **Computational roles for dopamine in behavioural control**. *Nature* 2004, **431**:760-767.

37. Redish AD: **Addiction as a computational process gone awry**. *Science* 2004, **306**:1944-1947.

38. McClure SM, Daw ND, Montague PR: **A computational substrate for incentive salience**. *Trends Neurosci* 2003, **26**:423-428.

39. Hemby SE, Co C, Koves TR, Smith JE, Dworkin SI: **Differences in extracellular dopamine concentrations in the nucleus accumbens during response-dependent and response-independent cocaine administration in the rat**. *Psychopharmacology (Berl)* 1997, **133**:7-16.

40. Ahmed SH: **Neuroscience. Addiction as compulsive reward prediction**. *Science* 2004, **306**:1901-1902.

41. Willuhn I, Burgeno LM, Groblewski PA, Phillips PE: **Excessive cocaine use results from decreased phasic dopamine signaling in the striatum**. *Nat Neurosci* 2014, **17**:704-709.

42. Mateo Y, Lack CM, Morgan D, Roberts DC, Jones SR: **Reduced dopamine terminal function and insensitivity to cocaine**

following cocaine binge self-administration and deprivation. *Neuropsychopharmacology* 2005, **30**:1455-1463.

43. Ahmed SH, Lenoir M, Guillem K: **Neurobiology of addiction versus drug use driven by lack of choice**. *Curr Opin Neurobiol* 2013, **23**:581-587.

44. Banks ML, Negus SS: **Preclinical determinants of drug choice under concurrent schedules of drug self-administration**. *Advan Pharmacol Sci* 2012, **2012**:281768.

45. Ahmed SH: **Validation crisis in animal models of drug addiction: beyond non-disordered drug use toward drug addiction**. *Neurosci Biobehav Rev* 2010, **35**:172-184.

46. Dezfouli A, Piray P, Keramati MM, Ekhtiari H, Lucas C, Mokri A: **A neurocomputational model for cocaine addiction**. *Neural Comput* 2009, **21(10)**:2869-2893.

47. Wesley MJ, Lohrenz T, Koffarnus MN, McClure SM, De La Garza R II, Salas R *et al.*: **Choosing money over drugs: the neural underpinnings of difficult choice in chronic cocaine users**. *J Addict* 2014, **2014**:189853.

48. • Garbusow M, Schad DJ, Sebold M, Friedel E, Bernhardt N, Koch SP, Steinacher B, Kathmann N, Geurts DE, Sommer C *et al.*: **Pavlovian-to-instrumental transfer effects in the nucleus accumbens relate to relapse in alcohol dependence**. *Addict Biol* 2016, **21**:719-731.
Results show how inappropriate transfer from pavlovian cues to instrumental behavior (PIT) in detoxified alcohol-dependent individuals may be predictive of relapse. Here the alcohol-dependent individuals are argued to be particularly sensitive to pavlovian cues associated with drinking initiating behaviors geared toward obtaining alcohol.

49. Weeks JR: **Experimental morphine addiction: method for automatic intravenous injections in unrestrained rats**. *Science* 1962, **138**:143-144.

50. Panlilio LV, Thorndike EB, Schindler CW: **Reinstatement of punishment-suppressed opioid self-administration in rats: an alternative model of relapse to drug abuse**. *Psychopharmacology (Berl)* 2003, **168**:229-235.

51. Caprioli D, Zeric T, Thorndike EB, Venniro M: **Persistent palatable food preference in rats with a history of limited and extended access to methamphetamine self-administration**. *Addict Biol* 2015, **20**:913-926.

52. Shaham Y, Shalev U, Lu L, De Wit H, Stewart J: **The reinstatement model of drug relapse: history, methodology and major findings**. *Psychopharmacology (Berl)* 2003, **168**:3-20.

53. Grimm JW, Hope BT, Wise RA, Shaham Y: **Neuroadaptation. Incubation of cocaine craving after withdrawal**. *Nature* 2001, **412**:141-142.

54. Phillips PEM, Stuber GD, Heien MLAV, Wightman RM, Carelli RM: **Subsecond dopamine release promotes cocaine seeking**. *Nature* 2003, **422**:614-618.

55. Takahashi Y, Schoenbaum G, Niv Y: **Silencing the critics: understanding the effects of cocaine sensitization on dorsal and ventral striatum in the context of an actor/critic model**. *Front Neurosci* 2008, **2**:86-99.

56. Takahashi Y, Roesch MR, Stalnaker TA, Schoenbaum G: **Cocaine exposure shifts the balance of associative encoding from ventral to dorsolateral striatum**. *Front Integr Neurosci* 2007, **1**:11.

57. Huys QJM, Tobler PN, Hasler G, Flagel SB: **The role of learning-related dopamine signals in addiction vulnerability**. *Prog Brain Res* 2014, **211**:31-77.

58. Gutkin BS, Dehaene S, Changeux J-P: **A neurocomputational hypothesis for nicotine addiction**. *Proc Natl Acad Sci* 2006, **103**:1106-1111.

59. Graupner M, Gutkin B: **Modeling nicotinic neuromodulation from global functional and network levels to nAChR based mechanisms**. *Acta Pharmacol Sin* 2009, **30**:681-686.

60. Berridge KC: **From prediction error to incentive salience: mesolimbic computation of reward motivation**. *Eur J Neurosci* 2012, **35**:1124-1143.

61. Zhang J, Berridge KC, Tindell AJ, Smith KS, Aldridge JW: **A neural computational model of incentive salience**. *PLoS Comput Biol* 2009, **5**:e1000437.