

# Neural systems of reinforcement for drug addiction: from actions to habits to compulsion

Barry J Everitt & Trevor W Robbins

Drug addiction is increasingly viewed as the endpoint of a series of transitions from initial drug use—when a drug is voluntarily taken because it has reinforcing, often hedonic, effects—through loss of control over this behavior, such that it becomes habitual and ultimately compulsive. Here we discuss evidence that these transitions depend on interactions between pavlovian and instrumental learning processes. We hypothesize that the change from voluntary drug use to more habitual and compulsive drug use represents a transition at the neural level from prefrontal cortical to striatal control over drug seeking and drug taking behavior as well as a progression from ventral to more dorsal domains of the striatum, involving its dopaminergic innervation. These neural transitions may themselves depend on the neuroplasticity in both cortical and striatal structures that is induced by chronic self-administration of drugs.

The nucleus accumbens is well known to mediate the reinforcing effects of drugs, but more recent research emphasizes the role of the striatum as a whole, including the shell and core components of the nucleus accumbens, in the processes leading first to drug abuse and then to addiction. This view has been stimulated by progress in understanding the dopamine-dependent, serial communication between the various domains of the striatum via a cascading loop interconnectivity<sup>1</sup>, and by an improved understanding of associative learning mechanisms that conceive of behavioral output as an interaction between pavlovian and instrumental learning processes<sup>2,3</sup>. In particular, the description of two processes that seem to function partly in parallel, but with the second eventually dominating behavioral output, has led to the concepts of action-outcome and stimulus-response ('habit') learning. Here we elaborate the hypothesis that these behavioral processes can be mapped onto the parallel and serial, dynamic functioning of corticostriatal circuitry (Fig. 1) to mediate the 'switches'<sup>4,5</sup> between drug reinforcement, drug abuse and drug addiction.

## Reinforcement, conditioning and the nucleus accumbens

The reinforcing effects of addictive drugs are multidimensional (Box 1). Drugs act as 'instrumental reinforcers'—that is, they increase the likelihood of responses that produce them, resulting in drug self-administration or 'drug taking' (defined in Box 2). Environmental

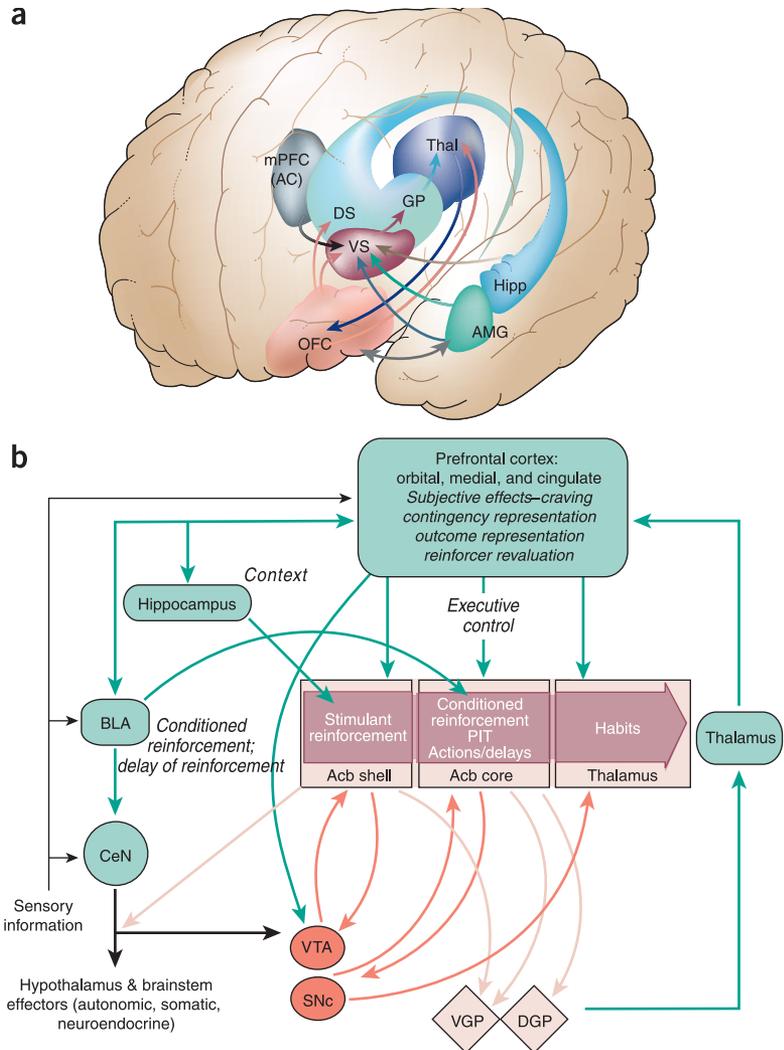
stimuli that are closely associated in time and space with the effects of self-administered drugs gain incentive salience through the process of pavlovian conditioning (Box 2). Drugs produce subjective or 'discriminative' effects, which include the sensing of autonomic activity ('feelings') or distortions in sensory processing. Stimulant drugs such as cocaine and amphetamine (along with others) also exaggerate the perceptual impact or incentive salience of environmental stimuli, especially those that already predict important environmental events, which are known as conditioned stimuli (CSs). We postulate that any combination of these effects may constitute the 'rewarding' effect of a drug—that is, the subjective effects produced by attributions made about the conditioned stimuli. In particular, we argue that it is the sense of expectancy, or perhaps even more importantly, the sense of 'control' over such interoceptive and exteroceptive states, including the overall level of arousal accompanying them, acquired through action-outcome learning (Box 1) that constitutes instrumental drug reinforcement.

CSs that predict natural reinforcers, such as a light that predicts food, can have several effects on behavior, in addition to eliciting pavlovian (that is, automatic or reflexive) elements of approach and consummatory behavior. The locomotor stimulation produced by psychomotor stimulants such as amphetamine and cocaine may arise in this way. CSs can have motivational effects: for example, increasing rates of responding for food when the CS is presented unexpectedly (called pavlovian-instrumental transfer, PIT; Box 2)<sup>2</sup>. These motivational effects of CSs can be ascribed to a hypothetical process of pavlovian arousal, which serves to energize or activate responding, whether in terms of enhanced locomotor activity or increasing rates of instrumental (operant) behavior. Considerable evidence now shows that the midbrain dopamine neurons show fast phasic burst firing in response to such CSs<sup>6</sup> but may also be active, at least in their tonic mode, under other circumstances in response to such factors as unpredictability<sup>7</sup>, novelty, stress and

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**Figure 1** Representation of limbic circuitry, with tentative localization of functions involved in drug addiction. **(a)** Key connectivities in human brain (redrawn from ref. 90). **(b)** Limbic cortical-ventral striatopallidal circuitry. (i) Processing of conditioned reinforcement and delays by basolateral amygdala and of contextual information by hippocampus. (ii) Goal-directed actions involve interaction of prefrontal cortex with other structures, possibly including nucleus accumbens but also dorsomedial striatum. (iii) 'Habits' depend on interactions between prefrontal cortex and dorsolateral striatum. (iv) 'Executive control' depends on prefrontal cortex and includes representation of contingencies, representation of outcomes and their value and subjective states (craving and, presumably, feelings) associated with drugs. (v) Drug craving involves activation of orbital and anterior cingulate cortex, and temporal lobe including amygdala, in functional imaging studies. (vi) Connections between dopaminergic neurons and striatum reflect 'spirals'—serial interactions organized in a ventral-to-dorsal cascade. (vii) Reinforcing effects of drugs may engage stimulant, pavlovian-instrumental transfer and conditioned reinforcement processes in the nucleus accumbens shell and core and then engage stimulus-response habits that depend on dorsal striatum. Green/blue arrows, glutamatergic projections; orange arrows, dopaminergic projections; pink arrows, GABAergic projections; Acb, nucleus accumbens; AMG, amygdala; BLA, basolateral amygdala; CeN, central nucleus of the amygdala; VTA, ventral tegmental area; SNc, substantia nigra pars compacta. GP, globus pallidus (D, dorsal; V, ventral); Hipp, hippocampus; mPFC, medial prefrontal cortex; AC, anterior cingulate cortex; OFC, orbitofrontal cortex; VS, ventral striatum; DS, dorsal striatum; Thal, thalamus. Modified from refs. 91,92.



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food deprivation<sup>8</sup>. For this reason, we have previously used the term 'activation' to describe the important role of the mesolimbic and mesostriatal dopamine systems in behavioral output, to distinguish it from general changes (such as in EEG) associated with the term 'arousal'<sup>8</sup>. Thus, in terms of drug abuse, in addition to obvious direct influences of drugs such as cocaine on extracellular dopamine, it might be feasible in certain circumstances to detect the effects of CSs themselves on striatal dopamine function. In testing this hypothesis, we have found that unexpected presentations of drug-paired CSs elicit dopamine release in the core but not in the shell region of the nucleus accumbens<sup>9</sup>. Consistent with these data, selective lesions of the nucleus accumbens core<sup>10</sup> or infusions of NMDA or dopamine receptor antagonists into the nucleus accumbens core during training<sup>11</sup> greatly retard the acquisition of pavlovian approach responses, whereas infusions of NMDA or dopamine D1 receptor antagonists into this region after a training trial disrupt the consolidation of this response into memory<sup>12</sup>. Lesions of the nucleus accumbens core also abolish PIT<sup>13</sup>, and increasing dopamine in the nucleus accumbens shell potentiates PIT<sup>14</sup>.

Therefore, it might logically be thought that pavlovian approach is involved in maladaptively attracting humans toward sources of addictive drug reinforcers, and that drug-associated CSs that occur unexpectedly invigorate their efforts to seek and take or 'want' drugs as emphasized in the incentive salience theory of addiction<sup>15</sup>. However,

neither phenomenon (neither approach to a CS predictive of a drug, nor enhancement of drug seeking by the unexpected presentation of a drug-associated CS) has been clearly demonstrated in laboratory studies of drug seeking or relapse<sup>16–18</sup>, although both are readily seen in animals responding for natural rewards. It may be that the experimental conditions for demonstrating these phenomena in a drug seeking setting have not yet been optimized, but it may also be that the behavioral influence of CSs associated with drugs and natural reinforcers differ fundamentally in this regard<sup>19</sup>. The neural basis of pavlovian approach behavior and PIT has been reviewed extensively elsewhere<sup>19,20</sup> and will not further be considered here, as it relates exclusively to studies with CSs associated with high-incentive natural reinforcers.

In certain circumstances CSs can also function as conditioned reinforcers. Conditioned reinforcement occurs when stimuli that were initially motivationally neutral, such as a light, become reinforcing in their own right via association with primary reinforcers such as food or drugs. These stimuli help to maintain instrumental responding by bridging delays to the ultimate goal, such as food or cocaine, and affect the responses to D-amphetamine on a delayed gratification task<sup>21</sup>. It is well known that drugs such as amphetamine, nicotine and (under certain circumstances) opiates greatly increase responding with conditioned reinforcement. For example, infusion of amphetamine into the nucleus accumbens increases the acquisition of responding for a

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## BOX 1 THE SIGNIFICANCE OF SUBJECTIVE RESPONSES IN REINFORCEMENT MECHANISMS

Precisely what is a reinforcer, and why might a drug of abuse have reinforcing properties? These fundamental questions remain difficult to answer definitively. Early theories of motivation, as described in any textbook of psychology, suggested that reinforcers produce (i) drive (or need) reduction operating according to a homeostatic regulatory model, (ii) memory consolidation (for example, of the association of a conditioned stimulus predicting a reinforcer) or (iii) incentive-motivational effects by which the expectation of a reinforcer (mediated presumably by its representation in the brain) evokes appropriate preparatory (appetitive) responses, such as approach behavior or physiological adjustment that constitutes a sequence of motivated behavior terminated by consummatory behavior (such as eating food or sexually mounting a female in heat) usually elicited by the reinforcer. There is clearly some truth in each of these accounts, and it is no surprise that they are reflected in contemporary theories of drug addiction<sup>15,88,93,94</sup>. These theoretical schemes do not, however, refer directly to subjective responses or 'feelings' associated with drug effects, although an eventual explanation will have to accommodate these.

The incentive-motivational class of theories has often been assumed to emphasize the hedonic properties of the reinforcer, especially when there is no obvious deficit or need state: for example, reinforcers such as intracranial electrical self-stimulation of the brain, cocaine, sucrose or novel objects. This conceptualization has led to the use of terms such as 'reward' and 'liking' that connote subjective responses associated with reinforcers (generally their post-presentational consequences, which can become associated with incentive-motivation via conditioning). Although these subjectively loaded terms refer to hypothetical processes of attribution that are associated with reinforcement, the processes themselves have never been identified or localized to particular brain regions or networks. This is in part because they have been confounded with the more implicit processes of reinforcement itself. For example, the use of the term 'reward' for 'reinforcement' might have led to the possibly mistaken view that those structures subserving reinforcement, such as the nucleus accumbens and its dopaminergic innervation, also mediate 'reward'<sup>95</sup>, including its subjective, attributional aspects. It is clearly much harder to test the hypothesis that the nucleus accumbens is implicated in 'reward' than 'reinforcement'. Similarly, the identification of 'hedonic' responses associated with

acceptance and rejection reflexes<sup>96</sup> may have led to confusion in separating those structures associated with attribution from those involved in controlling the reflex itself. Whereas it is clear that the latter reside in the brainstem, it seems less likely that subjective attribution does. This analysis, however, is consistent with the view that processes constituting reinforcement can be dissociated: for example, those mechanisms controlling appetitive behavior, such as instrumental lever pressing and locomotor approach behavior that generally occur remote from the reinforcer in space and time, and the consummatory responses associated with its proximal occurrence. Subjective responses associated with reinforcement are similarly dissociable. However, this is likely to be testable only in cases of motivated behavior in humans, and it is compatible with the often erratic capability of verbal expressions of craving for drugs. This should not at all be construed to mean that we discount emotional subjective responses and the brain mechanisms mediating them in the analysis of affective behavior. Such responses have to be translated into a (usually subvocal) verbal code, but might also involve nonverbal representations. These processes are presumably the product of interactive cortical mechanisms. Burgeoning evidence links the orbitofrontal cortex to the sensory representation of reinforcers as well as their value and the relative utility of different courses of action producing them. However, the neural mediation of those aspects of the reinforcer conveying its hedonic properties remain elusive because the use of functional neuroimaging procedures thus far has confounded the sensory properties of a reinforcer with hedonic subjective responses associated with it. We assume that these subjective responses arise in some way as a *post hoc* 'commentary' on the sensory representation itself. Defining sensory properties of reinforcers is more difficult than initially seems. For food, it must involve a combination of gustatory, olfactory, somatosensory (textural) and visual elements<sup>97</sup>. The visual aspects obviously gain their hedonic properties through conditioning. However, it is likely that we have to learn about virtually all of the hedonic properties of food and that even tastes and smells may not be as 'unconditioned' as hitherto believed. In addition, the hedonic effects of food may not arise simply from the exteroceptive stimuli themselves but from their capacity to evoke visceral changes, such as alterations in heart rate and other autonomic responses, 'sensed' as 'feelings' by mechanisms that depend on the insular cortex<sup>98</sup>.

food-related conditioned reinforcer<sup>22</sup>. This behavior depends on two major influences; the nucleus accumbens core mediates the effects of the conditioned reinforcer<sup>10</sup> via its afferent inputs from limbic cortical structures<sup>19</sup> (see below). By contrast, the mesolimbic dopamine projection, especially to the nucleus accumbens shell<sup>10</sup> mediates the response rate-increasing or psychomotor stimulant effects of the drug, hypothetically by simulating the behaviorally activating effects of pavlovian arousal and affecting the incentive salience of the conditioned reinforcer. This dopamine-dependent potentiation of conditioned reinforcement is a key component of the reinforcing effects of stimulant drugs such as cocaine, amphetamine and nicotine and likely other drugs as well.

The effects of conditioned reinforcers, perhaps especially drug-related conditioned reinforcers, are pervasive and profound. For example, they support the learning of new drug seeking responses (**Box 2**), an effect that persists for at least two months without any further experience

of self-administered cocaine and that is resistant to extinction of the original CS-drug association<sup>23</sup>. Drug-associated conditioned reinforcers also help to maintain responding under second-order schedules of reinforcement (**Box 2**), where drugs are provided only after a prolonged time interval, thus more realistically modeling drug seeking behavior<sup>24</sup>. Responding in the interim is maintained by the presence of drug-associated CSs that are presented as a consequence of instrumental seeking responses (**Box 2**). The CSs must be presented as conditioned reinforcers (that is, their presentation must depend on the animal's behavior); merely presenting them unexpectedly fails to increase drug seeking<sup>18</sup>. This seems to contradict the 'incentive salience' model of drug seeking behavior, which would predict enhancement from pavlovian, or unexpected, presentations of the CS.

Drug self-administration behavior, including drug seeking under second-order schedules of reinforcement, initially involves action-

## BOX 2 DEFINITION OF KEY TERMS

**Positive reinforcer.** An event that increases the probability of a response on which it is contingent. For example, drug infusions increase the probability of lever pressing for the drug; alcohol ingestion increases the probability of licking or drinking.

**Negative reinforcer.** An event that when omitted or terminated increases the probability of the response on which it is contingent. For example, withdrawal symptoms precipitated by scheduled administration of naloxone in morphine-dependent animals, which can be avoided by lever pressing to postpone the naloxone.

**Incentive.** A stimulus that elicits approach behavior (positive incentive) or withdrawal behavior (negative incentive). A conditioned incentive acquires such properties via pavlovian conditioning. Incentives and conditioned incentives may also function as reinforcers and conditioned reinforcers, respectively, depending on environmental contingencies.

**Pavlovian (or classical) conditioning.** The process by which a conditioned stimulus (CS), such as a tone, after a number of pairings, comes to elicit conditioned responses like salivation that are normally elicited by an unconditioned stimulus, such as food. Such conditioned responses are normally considered to be involuntary reflexes. The pairings require the onset of the CS to occur before the unconditioned stimulus (temporal contiguity) and a positive temporal correlation (predictive contingency) between the two events.

**Conditioned reinforcer.** A stimulus that acquires its reinforcing properties (positive or negative) by pairings with other, generally primary, reinforcers such as food, drugs, sex or electric shock. A stimulus can function as a conditioned reinforcer or discriminative stimulus in the same situation.

**Contingency.** A consistent temporal relationship between two (or more) events that reduces the uncertainty of the subsequent event: for example, a situation in which a tone always occurs at the same time as a shock.

**Operant.** A response on which the presentation of a reinforcer is contingent, such as lever pressing. Such behavior is either called 'instrumental' in obtaining a goal (or 'outcome' or 'reinforcer'), or else it is a voluntary action. The learning of such behavior is termed instrumental conditioning.

**Action-outcome learning.** When instrumental actions are goal directed, the actions (lever pressing) are made with the intention of obtaining the goal. The actions are sensitive to devaluation of the goal: for instance, an animal that has learned to lever-press for food will respond much less or not at all for that food if it is devalued either by making the animal ill after ingesting the food, or by pre-feeding it to satiety with the same food. This is called 'reinforcer devaluation'. It is easy to devalue ingestive reinforcers, but it is much more difficult to devalue intravenously self-administered drugs such as cocaine.

**Stimulus-response or 'habit' learning.** In habit learning, instrumental performance is acquired through the association of responses with stimuli present during training. It therefore reflects the formation of stimulus-response associations, and reinforcers primarily serve the function of strengthening the stimulus-response association but do not become encoded as a goal. Therefore, devaluing the reinforcer does not affect instrumental responding acquired by habit learning.

**Pavlovian-instrumental transfer (PIT).** Appetitive pavlovian stimuli (associated with positive reinforcers such as food) can greatly enhance instrumental responding for the same reinforcer when presented unexpectedly (independent of the instrumental response), and this defines the pavlovian-instrumental transfer effect. PIT has been interpreted as evidence that CSs exert a motivational influence over instrumental performance.

**Drug taking and drug seeking.** 'Drug taking' is a term used to describe drug self-administration when the drug is readily available: for instance, following each lever press or the simple drinking of alcohol ('continuous reinforcement'). The subject does not need to forage, or to work, for the drug, nor does it need to mediate delays in acquiring it; that is, it does not actively need to 'seek' the drug.

'Drug seeking' can be studied in a number of ways. A 'second-order schedule of drug reinforcement' (in contrast to continuous reinforcement) emphasizes the role of drug-associated conditioned reinforcers in maintaining drug seeking behavior over relatively prolonged periods<sup>24</sup>. Rats or monkeys (and also humans) are initially trained to self-administer cocaine or heroin under a simple, continuous reinforcement schedule, each drug infusion being paired with a light CS (simple drug taking). Subsequently, the animal responds for periods of time (usually 15 minutes, but occasionally up to an hour) for each infusion of drug, and responding during that period is maintained by response-dependent presentations of the CS, which act as conditioned reinforcers of the instrumental seeking responses; omission of the contingent CS results in a marked decrease in drug seeking. This behavior models aspects of drug seeking in the real world, in which drugs are not immediately available, and drug-associated stimuli reinforce and maintain drug seeking.

The 'reinstatement of drug seeking' after extinction of the instrumental seeking response (*i.e.*, the decrement in responding caused by non-delivery of the drug)<sup>99</sup> or the maintenance of drug seeking responses in the absence of drug<sup>100</sup> are widely used procedures because they model a critical aspect of drug addiction: namely, the propensity to relapse after sometimes prolonged periods of withdrawal (or abstinence). The ability of drug-associated conditioned reinforcers to maintain or reinstate drug seeking responses may actually increase with the duration of withdrawal<sup>100</sup>. Not only drug-associated stimuli but also injections of the drug itself and stressors can all reinstate drug seeking measured in this way. The subject has been reviewed extensively and is not considered in detail here<sup>59,60</sup>.

Recently, another method of measuring drug seeking has adapted the 'acquisition of a new response' procedure, in which the ability of a drug-associated CS to support the learning of a new instrumental seeking response is measured<sup>23</sup>. This procedure models another feature of conditioned reinforcers: namely, their ability to act as goals themselves and thereby support the learning of new behavioral strategies directed toward obtaining the primary reinforcer—in this case, a drug. This behavior is remarkably persistent, as is drug seeking in drug-addicted individuals.

**Discriminative stimulus.** A stimulus in the presence of which responding is reinforced according to some schedule of reinforcement. For example, drug cues can act as discriminative stimuli (*i.e.*, can set the occasion) for behavioral responding that is maintained by drug reinforcement.

outcome learning (**Box 2**), before extended training additionally leads to the formation of stimulus-response ('habit') associations that help maintain responding<sup>20,25</sup>.

### Interacting roles of striatal subregions in reinforcement

The experiments discussed above and further below show that the nucleus accumbens core, as distinct from the shell, is important in the maintenance of instrumental behavior involving delays in the provision of cocaine, in particular in the capacity of CSs to bridge that delay. This conclusion begs the question of where the drug exerts its primary reinforcing effects. One possibility is the nucleus accumbens shell, which is connected to the full network of descending neural influences over reflexive autonomic and motor responses<sup>26,27</sup> (**Fig. 1**). This idea is consistent with evidence that this region is necessary for the direct psychomotor stimulant effects of the cocaine, including response rate-enhancing and locomotor activity effects<sup>10</sup>. Some of the unconditioned effects of food reinforcers may be similarly mediated via the nucleus accumbens shell, though involving mechanisms specifically associated with opiate, rather than dopamine, receptors<sup>27</sup>. Cocaine (and other drugs) have positive reinforcing effects when infused response-dependently directly into another region of the ventral striatum, the olfactory tubercle<sup>28</sup>. We do not wish necessarily to draw a sharp distinction between the unconditioned and conditioned aspects of reinforcement, as we have already pointed out that these may merge into one another. It is possible, for example, that conditioning to interoceptive aspects of reinforcers, such as taste or smell, does depend on the shell or other regions of the ventral striatum<sup>29</sup>, whereas the core is especially associated with exteroceptive (for instance, visual) conditioning<sup>19</sup>.

Important issues to be resolved include how the contributory factors such as pavlovian arousal and instrumental reinforcement, including conditioned reinforcement, are integrated within the nucleus accumbens circuitry. Perhaps the most obvious mechanism could stem from the cascading loop circuitry by which output from the nucleus accumbens shell can influence the functioning of the ascending dopamine projections to the core, and similarly, from the output of the core via the substantia nigra to other domains of the dorsal striatum<sup>1</sup> (**Fig. 1**). Thus, several phenomena, such as the potentiation of conditioned reinforcement by stimulant drugs and pavlovian-instrumental transfer during instrumental learning, could arise from the sequential operation of the drug's impact in the nucleus accumbens shell, influencing processing of CSs in the core. By a similar token, such sequential operations may result in drug seeking (action-outcome learning) that seems to depend on the interaction of the dorsomedial striatum<sup>30</sup> with its afferents from specific regions of the medial prefrontal cortex (mPFC)<sup>31</sup>. Extended training leads to the development of habits, where the emphasis is on slow stimulus-response learning mechanisms with less involvement of the goal itself<sup>25</sup> (**Box 2**). Data for food-maintained habits suggest that yet another sector of the striatum, the dorsolateral striatum, is implicated in habit learning<sup>32</sup> (see below). These sequential phases of pavlovian and instrumental learning may be especially relevant for the transition from initial drug use to drug abuse, and finally compulsive drug taking and drug seeking behavior.

Compulsive drug seeking and drug taking are the hallmarks of the definitions of drug addiction (or 'dependence' in the *Diagnostic and Statistical Manual IV*), which is becoming increasingly acknowledged by neuroscientists modeling this behavior<sup>33–35</sup>. In theoretical terms, it seems reasonable to characterize such compulsive behavior as a maladaptive stimulus-response habit in which the ultimate goal of the behavior has been devalued so that the behavior is not directly under the control of the goal<sup>20,25</sup>. Rather, responding is governed by a succession of discriminative stimuli, which also function—when they are

presented as a consequence of instrumental responses—as conditioned reinforcers. Hypothetically, such stimulus-response associative ('habit') learning occurs in parallel with instrumental action-outcome learning but, with extended training, eventually dominates behavioral output. Crucial to drug addiction is the persisting quality of these habits, which has been likened to the subjective state of 'wanting'<sup>15</sup>, but which we would suggest corresponds more obviously to the subjective state of 'must do!'—although this subjective response could arise *post hoc* as a rationalization of the 'out-of control' habitual behavior rather than being the driving influence. These behavioral patterns are maintained by the enhanced significance of drug-associated conditioned reinforcers, which act as discriminative stimuli for continued drug seeking behavior, especially once the drug itself has been taken<sup>18,36</sup>. The obvious analogy is with obsessive-compulsive disorder. It is, of course, possible, as with obsessive-compulsive behavior, that the habitual behavior is maintained in part by negative reinforcement<sup>37</sup>; active avoidance behavior in monkeys can have a similarly persistent quality, especially after treatment with psychomotor stimulant drugs<sup>38</sup>. Two details of this hypothesis are important: it applies to instrumental behavior such as intravenous drug self-administration under a 'drug seeking' second-order schedule, and it is not an example of a procedural skill, such as playing the piano or tying one's shoelace—although it is plausible that such skills result from even more extended training. The analogy with drug addiction would be a persistence or constant reinitiation of such activities.

Evidence for this concept of drug addiction as a maladaptive and persistent habit comes from several sources, which also increasingly point to the dorsal striatum as a major contributor to this form of learning. An operational definition of a habit is that the behavior continues even after the controlling influence of the goal is reduced by devaluation procedures, such as satiation or even poisoning in the case of a food goal (**Box 2**)<sup>39</sup>. The extent to which instrumental behavior is maintained under these conditions reveals the degree of control by stimulus-response mechanisms. This approach has led to the definition of a role for the dorsolateral striatum<sup>32</sup> and its dopaminergic innervation<sup>40</sup> in instrumental habit learning in rats. However, devaluing drugs as reinforcers seems to be quite difficult and probably depends on understanding the precise nature of their reinforcing effects (see above and **Box 1**). This cannot readily be achieved by simple pharmacological antagonism, which does not devalue a reinforcer so much as remove it. In studies of oral cocaine and alcohol self-administration, however, habitual responding—evidenced by resistance to devaluation by gastric malaise—develops more rapidly for a drug than for a food reinforcer<sup>41,42</sup>.

Dopamine release in the nucleus accumbens core and shell, as measured by microdialysis *in vivo*, is not generally coincident with the provision of drug-paired CSs in rats extensively trained under second-order schedules<sup>9</sup>, but such conditioned reinforcers do evoke dopamine release in the dorsal striatum<sup>36</sup>. Thus, although the acquisition of drug seeking under a second-order schedule depends on the nucleus accumbens core, which is part of the ventral striatum, control over performance may ultimately devolve to the dorsal striatum. Indeed, the mixed dopamine receptor antagonist  $\alpha$ -flupenthixol infused into the dorsal striatum greatly reduces well-established cocaine seeking under a second-order schedule, yet it has no effect when infused into the nucleus accumbens core<sup>43,44</sup>. This is consistent with the habit hypothesis and also with the presence of 'error prediction' dopamine neurons innervating the entire striatum, including its dorsal as well as ventral regions<sup>6</sup>. Perhaps of even greater significance is that these findings provide further evidence of devolved control from the shell and core regions of the nucleus accumbens now to include the dorsal striatum, thereby supporting the capability of ventral-to-dorsal unidirectional cascades of information processing mediated by corticostriatal 'loop' circuitry<sup>1</sup>. This proposed sequence of changes

caused by drug-self-administration is further supported by observations in rhesus monkeys self-administering cocaine over an extended period. The downregulation of striatal dopamine D2 receptors, as well as other cellular markers, known to occur in human chronic cocaine abusers<sup>45</sup> can also be observed to occur first in ventral and then in dorsal territories of the striatum in cocaine-taking rhesus monkeys<sup>46–48</sup>.

The findings of both parallel and serial cascading mechanisms of associative learning suggested by these studies require further investigation. They are broadly compatible with functional neuroimaging evidence in humans that the ventral striatum is implicated in pavlovian conditioning and the dorsal striatum with instrumental learning<sup>49</sup>. From the neurocomputational perspective, the ventral and dorsal striatum could conceivably correspond to the ‘critic’ and ‘actor’ components, respectively, of contemporary models of reinforcement learning<sup>49</sup>. The critic learns to predict future rewards, and the actor maintains information about the rewarding outcome of actions; in other words, the interaction of pavlovian and instrumental learning through the intermediary of conditioned reinforcement. However, it would be very misleading to imply that it is only the striatum that is implicated in these aspects of learning. First, of course, the striatum is also implicated in performance, involving the retrieval of appropriate stimulus-response rules and goal representations. Second, the striatum is only one part of a much more extended network defined by its intimate, roughly topographical inputs from limbic cortical structures, such as the basolateral amygdala, the hippocampus and the prefrontal cortex, that are primarily focused on the ventral striatum and discrete regions of the dorsal striatum, as well as from neocortical areas.

### The basolateral amygdala–nucleus accumbens core system

Selective lesions of the basolateral amygdala or the nucleus accumbens core impair the acquisition of cocaine or heroin seeking under a second-order schedule<sup>50–53</sup>. These studies also show that continuously instrumental responding for cocaine is completely unaffected by core lesions, consistent with other evidence that this region is not directly implicated in instrumental learning *per se*: lesion-induced deficits are found only when the drug infusions are delayed. Thus, the mechanisms underlying drug taking are dissociable from those underlying drug seeking. The effects of lesions in basolateral amygdala or nucleus accumbens are likely to reflect the interacting roles of these structures in conditioned reinforcement<sup>19</sup> and also their roles in mediating delays to reinforcement. Basolateral amygdala lesions, like nucleus accumbens core lesions, increase the choice of small, immediate rewards over larger, delayed rewards—indicating greater impulsivity<sup>54</sup>. The core is also necessary for instrumental learning when there is a delay between the response and the reinforcer<sup>55</sup>. Presumably, it acts by allowing CSs occurring during the delay (either discrete, or forming part of the context) to act as conditioned reinforcers for instrumental responding, leading to the reward.

Using a disconnection procedure (unilateral manipulation of structures within a putative neural system, but on opposite sides of the brain), we have shown the functional importance of serial interactions between the basolateral amygdala and nucleus accumbens core in drug seeking sustained by conditioned reinforcers<sup>43</sup>. Dopamine (but not AMPA) receptor blockade bilaterally in the basolateral amygdala impairs cocaine seeking under a second-order schedule, whereas AMPA (but not dopamine) receptor blockade bilaterally in the nucleus accumbens core has a similar effect. Most importantly, unilateral blockade of dopamine receptors in the basolateral amygdala combined with unilateral blockade of AMPA receptors in the core in the contralateral hemisphere (neither of which has any effect alone) reduces cue-controlled cocaine seeking as much as bilateral manipulations of either structure<sup>43</sup>. These

data indicate that associative information in the basolateral amygdala is translated into goal-directed, drug seeking behavior via its interactions with the nucleus accumbens core (Fig. 1).

Selective lesions of the orbital prefrontal cortex (OFC) also impair the acquisition of cocaine seeking<sup>56</sup> and responding with conditioned reinforcement<sup>57</sup>, but without affecting continuously reinforced cocaine self-administration<sup>56</sup>. The OFC and basolateral amygdala are richly interconnected, as well as projecting to the nucleus accumbens core and overlying anterior dorsal striatum (Fig. 1). The observation that basolateral amygdala and OFC are involved, along with the nucleus accumbens core, in the neural mechanisms underlying the ability to seek drugs over long delays bridged by conditioned reinforcers is consistent with a growing body of data that the basolateral amygdala and OFC cooperate to regulate goal-directed behavior<sup>58</sup>.

Studies of the cued reinstatement of extinguished responding for cocaine (Box 2) have been reviewed extensively elsewhere<sup>59,60</sup>. These also emphasize the involvement in drug seeking of the basolateral amygdala<sup>61</sup>, lateral OFC<sup>62</sup> and nucleus accumbens core<sup>63</sup> as well as dopamine and glutamate transmission in the basolateral amygdala and nucleus accumbens core<sup>64,65</sup>—but in the context of relapse, which is a key aspect of drug addiction.

### Hippocampus—nucleus accumbens system

There is general consensus on the functions of the amygdala, nucleus accumbens core and OFC and their interactions in the control over goal-directed behavior by discrete CSs acting as conditioned reinforcers. In contrast, the hippocampal formation, which is also a major source of glutamatergic afferents to the nucleus accumbens, especially the nucleus accumbens shell<sup>26</sup> (Fig. 1), has received somewhat less attention in studies of drug seeking. Inactivation of the dorsal hippocampus prevents the reinstatement of extinguished responding for cocaine by contextual stimuli, but not by discrete CSs<sup>66</sup>. Theta-burst stimulation of the hippocampus reinstates extinguished cocaine seeking, acting via glutamatergic transmission in the VTA, which was suggested to mimic the way that reinstatement occurs when animals are placed in a context associated with drug taking, rather than in response to discrete cocaine cues<sup>67</sup>. These data are generally consistent with the view that, whereas the amygdala mediates conditioning to discrete CSs, the hippocampal formation underlies conditioning to contextual or spatial stimuli<sup>68</sup> and may therefore underlie the motivational impact of contextual stimuli on drug seeking.

Hippocampal contextual information and amygdala-dependent discrete CSs may compete for control over goal-directed behavior<sup>3</sup>. Thus, amygdala lesions not only impair appetitive behavioral responses under the control of discrete CSs but also result in enhanced control by contextual cues; similarly, hippocampal lesions impair contextual conditioning but can also result in enhanced conditioning to discrete CSs<sup>3</sup> (R. Ito, T.W.R., B.L. McNaughton & B.J.E., unpublished observations). The neural basis of such competition between associative influences on behavior is unclear, but may depend upon the projections of the basolateral amygdala and hippocampus to the nucleus accumbens core and shell<sup>69</sup>. Electrophysiological and *in vivo* neurochemical studies show that hippocampal, amygdala and PFC projections interact in the nucleus accumbens. This interaction is modulated by mesolimbic dopamine and, in turn, can modulate the release of dopamine<sup>70–73</sup>. Indeed, D1 and D2 dopamine receptors differentially regulate the influence of mPFC versus hippocampal afferents on the activity of nucleus accumbens neurons, and this modulation influences performance in appetitive behavioral tasks<sup>70</sup>.

Dorsal subiculum-lesioned rats are hyperactive in tests of exploratory locomotion, whereas ventral subiculum-lesioned rats show an attenuated locomotor response to amphetamine and impaired acquisi-

tion of cocaine self-administration<sup>74</sup>. Lesions of the ventral subiculum also completely abolish the locomotor response to intra-accumbens infusions of D-amphetamine in addition to blocking the potentiative effect of the same treatment on responding with conditioned reinforcement<sup>75</sup>. These data suggest a key role for hippocampal projections to the nucleus accumbens, especially the shell, in regulating its dopaminergic tone and mediating the psychomotor stimulant effects of drugs such as amphetamine and cocaine<sup>10,53</sup>. We hypothesize that, in psychological terms, hippocampal mechanisms provide the contextual background that defines the motivational arousal upon which goal-directed responding occurs. Inactivating this mechanism at the hippocampus or nucleus accumbens shell level reduces exploration, activity and contextual conditioning and also the potentiation of these responses by psychomotor stimulants—providing, therefore, an additional basis for understanding the reinforcing effects of drugs acting on the dopamine and other systems in the nucleus accumbens (see above).

### The prefrontal executive system

By far the most detailed investigation of the prefrontal cortex (PFC) in drug seeking measures the reinstatement of cocaine seeking after extinction. Inactivation of the dorsomedial part of the PFC prevents the reinstatement of responding elicited by drug cues, contexts, priming injections of drugs or stress<sup>59,60</sup>. Moreover, the involvement of the mPFC in the reinstatement of drug seeking depends on glutamate release in the nucleus accumbens core and also on the integrity of the ventral pallidum, providing clear evidence of the function of specific limbic cortical-ventral striatopallidal circuits<sup>59,64</sup>. Hippocampal, amygdala and mPFC mechanisms may therefore all influence drug seeking through their convergent projections to the nucleus accumbens (Fig. 1), perhaps competing for access to response strategies dependent on different limbic cortical-striatal circuitries<sup>70</sup>.

Lesions of the mPFC (including the prelimbic and infralimbic cortex) result in increased responding for cocaine under a second-order schedule of reinforcement and also enhance the acquisition of cocaine self-administration<sup>76</sup>. However, these effects of mPFC lesions seem unlikely to result from any change in conditioned reinforcement<sup>75</sup> and may reflect instead an impairment in executive control over behavior (including behavioral inhibition processes)<sup>77</sup>. This is consistent with burgeoning neuroimaging and neuropsychological evidence from human studies suggesting that chronic drug abusers show deficits in tests of inhibitory control and decision making<sup>78–80</sup>. Studies using PET, especially, highlight changes in metabolism in the OFC in abstinent drug abusers<sup>45,81</sup>, but despite the involvement of this region in reinforcer processing, few experiments have examined its role in controlling drug seeking behavior in animals. Distinct changes in neuronal plasticity in this region, however, do result from chronic stimulant self-administration<sup>82</sup>.

Overall, we hypothesize that the transition from voluntary actions (governed mainly by their consequences) to more habitual modes of responding in drug seeking behavior represents a transition from prefrontal cortical to striatal control over responding, and from ventral to more dorsal striatal subregions (Fig. 1). Some of that transition may reflect important changes in the balance of activity in those brain regions mediating the executive control over behavior: for example, in the acquisition of action-outcome learning itself, the detection of altered instrumental contingencies with associated changes in subjective attribution, and in related processes of goal revaluation by components of the prefrontal cortex, including prelimbic and infralimbic regions<sup>31,77,83,84</sup>. Impairments in such processes, perhaps arising in part as the direct consequence of toxic drug effects, may contribute to the shift in balance of behavioral control processes toward those promoting habitual behavior. This hypothesis is plausibly supported in

neural terms by neuroimaging data in humans showing reductions in the activity of the prefrontal cortex, including the orbitofrontal region of abstinent addicts<sup>45,81</sup>.

Habitual responding by itself, however, does not capture the persistent, indeed, compulsive aspects of 'out-of-control' drug bingeing; some additional factor seems to be required. In the 'incentive-sensitization' model, the potentiated responding is postulated to depend on drug-induced sensitization of behavior<sup>85</sup>. A related but distinct view is that the drug effect itself may produce the enhanced drive to responding, thus prolonging the duration of a drug taking binge. On this account, sensitization reflects the normal processes of tolerance and inverse tolerance that modify the effects of many drugs. Whether sensitization directly affects instrumental drug self-administration seems less clear, although sensitization can augment responding for conditioned reinforcers enhanced by intra-accumbens amphetamine<sup>86</sup> and increase 'break points' (the highest number of responses rats will make) for cocaine assessed using a progressive ratio schedule<sup>87</sup>. According to the *DSM-IV*, another characteristic of drug addiction is that it persists despite adverse consequences. This, too, has been modeled in rats, which continue to seek cocaine after a prolonged, but not brief, drug taking history in the face of conditioned or unconditioned aversive stimuli<sup>34,35</sup>. Alternatively, as in the case of obsessive-compulsive disorder itself, which has similarly been associated with dysfunctional orbitofrontal-striatal circuitry, it may be necessary to postulate a source of negative reinforcement that maintains responding, for example, through opponent motivational systems also engaged by drug abuse<sup>88,89</sup>. How such systems interact at a neural level with those inducing the habitual appetitive behavior associated with drug addiction remains a central question for future research.

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### COMPETING INTERESTS STATEMENT

The authors declare that they have no competing financial interests.

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