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Neural and psychological mechanisms underlying appetitive learning: links to drug addiction

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The complexity of drug addiction mirrors the complexity of the psychological processes that motivate animals to work for any reinforcer, be it a natural reward or a drug. Here, we review the role of the nucleus accumbens, together with its dopaminergic and cortical innervation, in responding to reinforcement. One important contribution made by the nucleus accumbens is to the process through which neutral stimuli, once paired with a reinforcer such as a drug, have the capacity to motivate behaviour. This process may be one of several contributing to addiction, and it may be amenable to pharmacological intervention.

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Abbreviations

Acb	nucleus accumbens
AcbC	nucleus accumbens core subregion
CeA	central nucleus of the amygdala
CS	conditioned stimulus
DA	dopamine
NMDA	<i>N</i> -methyl- <i>D</i> -aspartate
PKA	protein kinase A

Introduction: the psychology of action

The study of motivated action is the study of instrumental conditioning — the process by which animals alter their behaviour when there is a contingency between their behaviour and a reinforcing outcome [1]. Instrumental conditioning is neither psychologically nor neurally simple. Rats and humans exhibit goal-directed action, which is based upon knowledge of the contingency between one's actions and their outcomes, and knowledge of the value of those outcomes; these two psychological processes interact so that we work for that which we value [2,3]. However, this value system is not the brain's only one. Remarkably, this 'cognitive' value system that governs goal-directed actions (sometimes termed 'instrumental incentive value') can be distin-

guished and dissociated [4] from the valuation process that determines our reactions when we actually experience a goal such as food — termed 'liking', 'hedonic reactions', or simply 'pleasure' [5] — although under normal circumstances the two values reflect each other and change together. Just as there is more than one value system, there is more than one route to action. Not all action is goal-directed; with time and training, actions can become habitual [6] — that is, elicited in relevant situations by direct stimulus–response mechanisms. Environmental stimuli have effects beyond eliciting motor responses, however; stimuli that predict reward may become conditioned stimuli (CSs) through Pavlovian associative learning, and Pavlovian CSs can motivate behaviour directly and can serve as the goals of behaviour [7].

Drug addiction, in some way an 'abnormal' set of motivated behaviours, reflects the complexity of instrumental conditioning itself. Addiction is multifactorial. Some drugs of abuse undoubtedly have a positive hedonic impact; pleasurable events come to have high instrumental incentive value, and so drugs are taken in part because they are liked — at least initially. Many, if not all, addictive drugs produce a physical and/or psychological withdrawal state when intake ceases. In general, the instrumental incentive value of reinforcers does not intrinsically depend on motivational state, but comes to do so as a consequence of hedonic experience [3]. Hunger, a natural motivational state, increases the hedonic impact of foodstuffs [8] and this in turn teaches the animal that it is worth working for those foodstuffs more when it is hungry [3]. Similarly, opiate withdrawal reflects a 'new' motivational state that the animal can perceive interoceptively; the state of withdrawal perhaps enhances the hedonic impact of opiates, and this in turn teaches the animal that it is worth working more for opiates — that opiates have a higher instrumental incentive value — when it is in a state of opiate withdrawal [9]. The hedonic impact of a reinforcer may therefore be a 'common currency' for determining the value of widely varying reinforcers (for example [10]). Responding for drugs of abuse can become habitual [11] (sometimes thought of as 'compulsive' responding when it occurs at an abnormally high level, as it does not depend on the current value of the goal). Finally, stimuli that have become Pavlovian CSs by virtue of their association with a drug can motivate behaviour (for example [12]). One key challenge for the neuroscience of addiction is to understand how these basic mechanisms influencing motivated behaviour operate within the brain, and to establish if and how

drugs of abuse have effects qualitatively or quantitatively different from those of 'natural' reinforcers. Here, we discuss some of the striatal and cortical systems that affect responding for reinforcement and the manner in which they might influence and be influenced by drug addiction.

Neural underpinnings of instrumental conditioning

Several limbic cortical and subcortical structures play a role in assessing the value of reinforcers and of stimuli that predict them, and in actions directed at obtaining those reinforcers or stimuli [7[•]]. The contribution of key elements of this circuitry, including the amygdala and orbitofrontal cortex, are discussed by Holland and Gallagher and Matsumoto and Tanaka (this volume), and in this review we will therefore restrict our discussion primarily to the role of the nucleus accumbens (Acb) and its dopaminergic innervation (also discussed by Schultz, this volume).

The contribution of the Acb to instrumental learning is still not fully understood. Blockade of *N*-methyl-D-aspartate (NMDA)-type glutamate receptors in the Acb prevents rats from acquiring a lever-press response on a simple (variable ratio 2) schedule, even though the same treatment does not affect performance of a previously learned response [13]. Concurrent blockade of NMDA and dopamine (DA) D1 receptors also synergistically prevents learning [14]. Learning of this kind is known as free-operant instrumental learning because the subject is free to perform the operant (response) at any time. It depends upon successful performance of the response, successful and timely collection of the reinforcer, and a normal mechanism to associate the two. Therefore, a drug may interfere with instrumental learning either because the receptor blockade directly impairs a learning process itself or because it interferes with the performance of some behaviour, such as promptly collecting the food, that is itself required to learn the lever-press response normally. Likewise, pharmacological manipulations, like neurotoxic lesions, could in principle induce 'compensatory' (or other) changes in activity in other brain regions. However, in elegant experiments Kelley and co-workers have shown that infusion of a cyclic adenosine monophosphate (cAMP)-dependent protein kinase A (PKA) inhibitor [15] or a protein synthesis inhibitor [16^{••}] into the Acb core subregion (AcbC) after instrumental training sessions impairs subsequent performance. This implies that PKA activity and protein synthesis in the AcbC contribute to the consolidation of instrumental behaviour.

Although these results indicate that the Acb is involved in the multifactorial process of instrumental learning, its specific contribution to this set of processes is not clear. Certainly many aspects of instrumental responding do not require the Acb. Destruction of the Acb neither prevents

rats from detecting changes in the contingency between actions and outcomes nor prevents them from responding to changes in goal value [17,18]. Thus, the Acb is not critical for goal-directed action [7[•]]; rather, it appears to be critical for some aspects of motivation that promote responding for rewards in real-life situations. For example, the Acb plays a role in promoting responding for delayed rewards [19] and is required for Pavlovian CSs to provide a motivational boost to responding [17,20]. The latter effect is termed Pavlovian-instrumental transfer — or sometimes 'wanting' [21,22], although this term could equally refer to the instrumental incentive value underpinning true goal-directed action. Pavlovian-instrumental transfer can be further enhanced by injection of amphetamine into the Acb [21] and depends on DA [23]. Pavlovian CSs also serve as goals for behaviour (i.e. serve as conditioned reinforcers), and although lesions of Acb subregions do not prevent animals responding for conditioned reinforcement entirely [24], enhancement of DA neurotransmission within the Acb can boost the efficacy of conditioned reinforcement [24–27]. Studies of the role of Acb DA in schedules involving high work requirements (that require subjects to perform a lot of work in order to obtain reinforcement) also support the view that Acb DA contributes directly to subjects' motivation to work [28[•],29]. In naturalistic situations, rewards are frequently available only after a delay, require considerable effort to achieve, and are signalled by environmental stimuli; thus, the Acb is central to several processes that require motivation.

Pavlovian CSs that have been paired with reward also elicit approach — that is, animals approach stimuli that predict reward. This effect, known as 'autoshaping' [30], depends on the Acb [24,31,32], its DA innervation [33[•]], and on information arriving at it from the anterior cingulate cortex [32], which could serve to discriminate stimuli that have previously been paired with reinforcement from those that have not [34]. Although this entire system must be intact for performance of an autoshaped approach response, additional structures appear to play a role specifically in learning to approach rewarded stimuli. Loss of Acb DA has a much greater impact if it occurs before the task is learned than afterwards [33[•]], which suggests that DA contributes to learning in this task. Destruction of the central nucleus of the amygdala (CeA) dramatically impairs rats' ability to learn this task [35] yet has no effect once the task has been acquired [36[•]], implying that for this task, the CeA contributes solely to learning. One possibility is that it does so by regulating the DA innervation of the Acb [20,37].

At a cellular level of analysis, the rate at which rats learn an arbitrary response that delivers electrical stimulation to the substantia nigra is correlated with the degree to which similar electrical stimuli potentiated synapses made by cortical afferents onto striatal neurons in the same animals

when anaesthetised, a potentiation that requires DA receptors [38]. DA has acute effects to modulate corticostriatal transmission, but it also has lasting effects; it is most likely that the combination of cortical (presynaptic) and striatal (postsynaptic) activity induces long-term depression of corticostriatal synapses, but if the same pattern of activity is paired with a large phasic increase in DA, then the active synapses are potentiated [39]. Furthermore, acquisition of instrumental responses on a simple schedule is also disrupted synergistically by concurrent blockade of NMDA and DA D1 receptors in the prefrontal cortex (PFC) [40], a region that is known to be required for rats to represent declaratively the contingencies between instrumental actions and their outcomes [41]. By contrast, hedonic assessment of rewards themselves, or 'liking', does not depend on dopaminergic processes [23,42–44]; instead, it appears to involve opioid mechanisms in the Acb shell subregion (AcbSh) and other systems in the pallidum and brainstem [45,46].

Modification of this dopaminergic motivational process may have therapeutic potential, as it might contribute to addiction in several ways. Relapse is common in many forms of drug addiction, which could in part be because detoxification does not extinguish the ability of drug-associated cues in the addict's environment to trigger craving and relapse to drug-taking [47]. Such cues might have motivational effects because they act as conditioned reinforcers (such that addicts work for them) or through Pavlovian-instrumental transfer (such that simply encountering them triggers or enhances drug-seeking); cues that previously signalled drug availability are especially potent in this respect [48]. As the motivational impact of reward-associated cues depends on the Acb and its DA innervation [7,17,20,21,24–27,31,32,33], modulation of Acb or DA neurotransmission could be useful to reduce the motivational impact of drug-associated cues. In animal models of drug-seeking behaviour controlled by drug-associated stimuli [49], lesions of the AcbC or disruption of its glutamatergic afferent innervation reduce drug-seeking [50,51], probably by reducing the motivational impact of the CSs. It may also be possible to target the mesolimbic DA system with some specificity to reduce drug seeking. DA D3 receptors are particularly concentrated in the Acb and amygdala [52], and both D3 receptor antagonists [53,54] and partial agonists [55,56] reduce cue-controlled cocaine seeking or relapse to cocaine-taking in animal models, and have potential for clinical use.

Differences between drugs of abuse and natural reinforcement

Clearly, 'natural' reinforcers, such as food and sex, have their effects in very similar ways to 'artificial' reinforcers, such as drugs of abuse; there may be no sharp dividing line between the two. A behavioural economic view would liken addiction to that situation in which demand

for a particular reinforcer (drug) has become relatively 'inelastic' — that is, it remains high in the face of increased price or other costs associated with drug-taking [57–60]. Yet this could represent a quantitative rather than a qualitative difference in reinforcement: below a certain level of food intake, there is also inelasticity in the demand for food. As Kelley and Berridge [46] recently noted, drugs could activate the same circuits as natural rewards, perhaps in a more potent manner; they could create new states, such as the motivational state of withdrawal, and/or they could differentially affect the balance of processes (such as habits, goal-directed actions, and cue-induced motivation) that normally contribute to responding for natural rewards. Neurobiologically, how might natural and drug reinforcement be differentiated?

Both food and drugs of abuse increase Acb DA, but the DA response to drugs of abuse may not habituate to the same extent as that to food [61]. Some manipulations that reduce drug-seeking or reinstatement of drug-taking in animal models, such as DA D3 receptor antagonists, do not reduce food-seeking in a similar manner [53,54]. However, there are also differences in the effects of, and neural basis of responding for, highly palatable and less palatable foods — relevant to the semantically difficult question of whether or not one can be said to be addicted to food, or a particular subset of foods. Manipulations of the opioid system affect food preference: intra-Acb administration of μ opioid receptor agonists (putatively modulating hedonia [45]) increases the intake of highly palatable foodstuffs including fat, sweet foods such as sucrose and saccharin, salt, and ethanol [62,63–66]. In addition, chronic ingestion of chocolate induces adaptations in endogenous Acb opioid systems [67].

Sensitisation might also differentiate drug from non-drug reinforcement. An influential contemporary theory of addiction emphasises the role of drugs in sensitising an incentive motivational system [68]. There is no doubt that repeated exposure to drugs can induce an enhanced (sensitised) response to the locomotor effects of the drug [68], to Pavlovian conditioned stimuli [22,69] and conditioned reinforcers [70]; sensitisation to amphetamine can also cause increased responding for amphetamine under a progressive ratio schedule [71]. Yet it is intriguing that many studies investigating the effects of drug sensitisation on cue-controlled behaviour have shown enhanced responding for natural rewards or responding to natural-reward-related stimuli following sensitisation to drugs [22,69,70], rather than an enhanced response to drug-related stimuli. By contrast, a primary characteristic of human addiction [72] is that responding for non-drug reinforcement decreases relative to that for drug reinforcement (whether because the value of, or motivation to seek, the drug increases or the value of non-drug reinforcers decreases), rather than increasing motivation to seek natural reinforcers, as seen in many animal studies of

sensitisation. Cross-sensitisation can occur between different classes of drugs; are there situations in which repeated exposure to some types of natural reinforcer produces sensitisation to the effects of either natural rewards or drugs? It remains to be definitively established to what extent sensitisation contributes to human addiction [73].

Another key characteristic of human addiction is that drug taking persists despite considerable adverse consequences, which has frequently been suggested to indicate compulsive or involuntary behaviour. Do drugs of abuse induce habitual, 'involuntary' responding faster than natural reinforcers [74–77]? One hallmark of habitual, as opposed to goal-directed, responding is that it persists even if the reinforcer's value is reduced [2]. Although it has proved difficult to devalue drugs of abuse — perhaps itself a difference between natural and drug reinforcers — some studies attempt to address this issue. While cocaine-seeking can be goal-directed [78], under some circumstances responding for cocaine can be less susceptible to devaluation of the reinforcer (that is, more habitual) than responding for natural reinforcers [79]. Similarly, alcohol-seeking may reflect primarily habitual, rather than goal-directed, responding [80**]. Soon after acquisition, cocaine-seeking is readily suppressed by an aversive CS, whereas following prolonged experience of cocaine, this conditioned suppression is lost (Vanderschuren, Everitt, unpublished). The development of motor habits could depend on dorsal striatal plasticity [81] — indeed, dorsal striatal DA release is a correlate of well-established cocaine-seeking [82] — and the balance between habits and goal-directed behaviour may also be regulated by the prefrontal and infralimbic cortex [83**].

Conclusions

Key questions remain as to what extent food and drug reinforcement are qualitatively or quantitatively different. Is sensitisation of a motivational system a specific property of drugs of abuse that gives them value above that of alternative reinforcers and renders the user hypersensitive to 'wanting' induced by environmental cues signalling the availability of those drugs? Does compulsive (or habitual) responding develop as a consequence of sensitisation, can it develop in the absence of sensitisation merely as a consequence of repeated use (as would be suggested by analogy with food reinforcement), or is habitual responding directly promoted by drugs of abuse, independent of sensitisation? The majority of (say) cocaine users do not progress to a stage of addiction in which cocaine use has major detrimental consequences; are those individuals whose lives are bent to the pursuit of drugs those individuals whose motivational brain systems are vulnerable to being captured by any particularly salient, opioid-, or DA-releasing reinforcer [84,85], including highly palatable foods and gambling, with drugs of abuse simply representing a potent example of this class of reinforcers?

Behavioural economics and animal learning theory offer tools to analyse the psychological processes contributing to addiction. Neurobiological studies are likely to use these tools more and more to establish the functions of brain systems that bring animals closer to reinforcement, and in the process characterise the nature of individual differences that might predispose to addiction and identify potential therapeutic targets.

Update

Two recent studies have shed further light on the way in which habits are acquired and/or expressed. Rats with lesions of the dorsolateral striatum do not acquire habits normally [86*], while the infralimbic cortex may suppress goal-directed actions once behaviour has become habitual [87*].

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The authors trained rats to respond on two levers for food pellets and 10% ethanol solution. Subsequently, either the food pellets or the ethanol was devalued by pairing it with illness induced by lithium chloride. When lever-pressing was subsequently tested (in extinction), rats pressed the pellet lever less if the pellets (but not the ethanol) had been devalued, indicating that responding for pellets was a goal-directed action. By contrast, the rate at which they pressed the ethanol lever was unaffected by devaluation of the reinforcer (although their consumption of the ethanol was reduced). This suggests that responding for ethanol was not a goal-directed action but a stimulus–response habit, whose performance was not controlled by the consequence of the action.

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When rats learn to press a lever for food, their actions are initially goal directed and if the value of the reinforcer is subsequently altered, their responding is sensitive to this. Under certain conditions, extended training can render the response habitual and insensitive to reinforcer reevaluation. In this study, rats were given either limited or extended training before receiving excitotoxic lesions of either prelimbic or infralimbic cortex. Following prelimbic lesions, rats' behaviour was habitual after only limited training, which suggests that they lacked their goal-directed

system. This supports previous evidence demonstrating the necessity of this structure to perceive action–outcome contingencies and thus to execute goal-directed actions. Intriguingly, rats with infralimbic lesions maintained goal-directed responses even after responding had become habitual in sham-operated controls.

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The authors demonstrate that instrumental responding in rats with lesions of the dorsolateral striatum continues to be sensitive to devaluation of the reinforcer (that is, their actions are goal directed) beyond the point at which normal rats' actions have become habitual and insensitive to such devaluation. This provides strong support for the long-held view that the dorsal striatum is critical for habit formation.

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This study follows on from the authors' previous work [83**] by demonstrating that rats can be 'released' from habitual responding by inactivation of the infralimbic cortex; this structure may therefore act to inhibit goal directed action once a habit has been acquired.