***'Foresight: Brain Science, Addiction and Drugs'* project**

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Neuroscience of Drugs and Addiction

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EXECUTIVE SUMMARY

Brain science is at the core of our future understanding of how drugs affect behaviour, and their consequent impact on society. Extraordinary advances in the last three decades have meant that we now understand much about the connectivity of the brain and how its functionality depends on chemical messages passing between nerve cells, or neurons, in the form of neurotransmitters they release which bind to receptors. Psychoactive substances exert their effects by affecting the regulation of neurotransmitters or simulating their actions at their receptors, and subsequently within the nerve cell itself, often in highly specific ways. We understand how many drugs work in molecular terms and where they may work, at least initially, in the brain. Moreover, we now understand in broad terms how different parts of the brain work at a systems level to produce behavioural and cognitive output.

Major advances have been made on two fronts. First, our understanding of the major neural components of the 'reward' or reinforcement system in the brain in animals has improved. This mediates the influence both of events such as food and sex on learning, and of drugs of abuse. Second, understanding has improved in cognitive neuroscience, elucidating how the human brain processes information, particularly within the cerebral cortex. Convergence between these areas is beginning to enable us to understand the neurobiological underpinnings of the effects of psychoactive substances in humans, even within a societal context. For example, the emerging theme of neuroeconomics promises to reveal how the cognitive apparatus of the brain constrains the assumptions of rational decision-making in traditional economic theory. A complementary advance has been the application of some aspects of neural decision-making theory to the explanation of the behaviour of individual substance abusers.

Our burgeoning understanding of how psychoactive substances affect brain function includes a growing realisation of their long-term effects, both neural and behavioural. Vulnerability or susceptibility to some actions of psychoactive substances, including both cognitive enhancement and dependence, appear to depend on individual differences based on genetic or environmental, including developmental, factors. It is becoming clear that the future impact of neuroscience will be realised through interactions with diverse disciplines including cognitive and social psychology, physics, molecular biology and genomics. This expansion of knowledge is influencing our attitudes to such important areas as the treatment of mental illness, the potential for augmenting cognitive function through psychoactive substances, and the study of drug use and abuse. Thus, the concept of addiction itself is undergoing radical change. Although many in society still view drug abuse as a social or moral problem best handled through the criminal justice system, the

growing scientific evidence suggests instead that addiction is a chronic, relapsing and treatable brain disorder that can result from prolonged effects of drugs on the brain.

1. INTRODUCTION

Communication within the brain depends on the release of neurotransmitter substances. Many agents, including drugs but also nutrients and transcranial magnetic or deep brain stimulation, exert their effects through chemical neurotransmission. Many psychoactive drugs work on chemical systems that not only control behaviour, but also respond to behavioural change. Many forms of behaviour, ranging from transcendental meditation to compulsive eating or gambling, may regulate the functioning of the chemical systems of the brain.

In the last 50 years or so, our list of chemical neurotransmitter substances in the brain has lengthened from two to over 60 [1; 2]. The neurotransmitters include amino acids and monoamines and structurally more complex neuropeptides. The list is likely to be extended, leading to further drug development. The discovery of new neurotransmitters goes hand in hand with the mapping of the neurons that contain them in the brain. These substances are not distributed homogeneously in the central nervous system, but are contained within defined tracts and clusters of cells, which may be organized in a complex arrangement to form functional, interconnected brain systems. Moreover, at the synapses between neurons, these substances interact as ligands with complex protein molecules called receptors on the neuronal membranes, to which they bind and thus transduce their chemical signals. There are often several distinct receptor sub-types for a given neurotransmitter, and these are also widely distributed within the brain, generally but not always matching the mapping of the neurotransmitter systems themselves. Further complexity is conferred by variations in protein sub-units making up the receptors. The many functional effects of drugs such as nicotine and benzodiazepines such as diazepam can be attributed in part to different receptor sub-types operating preferentially in different brain regions. The discovery of 'orphan' receptors without obvious neurotransmitter ligands in different brain regions indicates the possibility of further discoveries of new psychoactive substances [3; 4]. In the past, the discovery of psychoactive drugs has often predated the discovery of the endogenous neurotransmitter ligand (e.g. endorphin and enkephalins in the case of opiates such as morphine and heroin, and β-carbolines in the case of the benzodiazepines), as well as the brain receptors upon which they act [1].

The biophysical actions of neurotransmitters at specific receptors range from short-lived electrochemical effects at ion channels to slower cellular signalling via receptors linked to biochemical cascades (e.g. 'second messengers') and gene transcription. The old adage of one neurotransmitter per neuron has long been disproved by discoveries that many of the actions of the 'classical' neurotransmitters, such as acetylcholine (ACh), noradrenaline (NA), serotonin (5-HT) and dopamine (DA), are augmented by co-released peptides [1]. The chemical neurotransmitters affect the functioning of dense, but generally highly organized, sets of connections, conveniently referred to as neuronal networks. They do this either by affecting fast signalling, whether excitatory or inhibitory, within the network, or by slower and spatially more diffuse modulations across the nodes of the network. An individual neuron is subject to many different influences from distinct neurotransmitter systems. The activity of a particular cell and thus of entire networks can be adjusted by variations in the syntax of chemical messages impinging on the cell.

Several neurological and neuropsychiatric disorders have chemical pathologies for which a strategy of pharmacological replacement of deficient systems has been adopted. L-DOPA medication in Parkinson's disease is the classic example, where the loss of DA-containing cells of the substantia nigra leads to the characteristic motor symptoms. L-DOPA remediates some of the cognitive deficits associated with Parkinson's disease [5], but also produces some undesirable cognitive and emotional side-effects, including for some patients a drive to abuse the drug [6]. L-DOPA's therapeutic effects also tend to diminish with long-term treatment, leading to a gamut of other attempts to treat the disorder which includes other dopaminergic drugs, deep brain stimulation, neurosurgery and the

neural transplantation of embryonic nigral cells [7]. Especially in view of the ethical problems posed by the last-named, a future approach will almost certainly involve the use of stem cells engineered to produce DA. A similar approach to the treatment of Alzheimer's disease with cholinergic drug treatments (including nicotine) has proved less successful, although such treatment does improve some functions, notably attention [8]. The future strategy (as with the treatment of stroke) is likely to hinge on neuroprotection, preventing through drug treatment the neuronal loss occurring as a consequence of the initial pathology [9].

Many other disorders that result in cognitive or mood-related deficits are now treated with drugs. These include depression, treated with monoamine reuptake inhibitors such as the selective 5-HT reuptake inhibitors (SSRIs), schizophrenia, treated by DA receptor blockers, and attention-deficit hyperactivity disorder (ADHD), which is treated effectively with amphetamine-like stimulant drugs such as methylphenidate (Ritalin) [10]. A number of cognitive disorders arising from brain dysfunction have been treated on an experimental basis: these include Korsakoff's syndrome (arising from alcoholism), which has been treated with drugs affecting noradrenergic transmission, acute brain injury (treated with DA receptor agonists), and stroke (treated with amphetamine). Whilst the molecular bases of these drugs' actions at the cellular level are well-defined, the mechanistic basis of any of these therapeutic effects is less clear. The most effective anti-psychotic drug, clozapine, is also one of the least specific in pharmacological terms. Anti-depressants such as the SSRIs may work via effects on neurogenesis in the hippocampus [11]. Nevertheless, given the therapeutic efficacy of most of these drugs, and strong evidence from animal models of cognitive function, there is optimism that cognitive and mood-related disorders will continue to respond to interventions based on psychoactive substances.

One of the most promising developments from experimental neuroscience has arisen from a neuronal model of learning called long-term potentiation (LTP). It can occur in subtly different forms in many forebrain regions, but has been investigated most intensively in the hippocampus [12]. LTP crucially depends on the excitatory amino-acid neurotransmitter glutamate, and its actions at the AMPA- and N-methyl-*d*-aspartate (NMDA) receptor subtypes. Several agents affecting glutamate transmission have been developed, including some (such as the AMPA-kines) which have been shown to have positive effects on learning in the laboratory for both normal animals and humans, and have been subject to preliminary clinical trials [13]. Some NMDA receptor antagonists, such as ketamine, have recently been shown to have significant abuse potential [14]. In a more speculative vein, drugs enhancing the transcription factor CREB (cAMP response element binding protein) could also emerge from advances in the application of basic neuroscience [15]

The phenomenon of beneficial effects in normal subjects lacking discernible brain dysfunction is not restricted to drugs affecting glutamate receptors. In specific situations, which may include the infusion of drugs locally to specific brain regions in experimental animals and the engagement of particular cognitive functions, many positive drug effects have been reported for compounds acting on the classical cholinergic, noradrenergic, serotoninergic or dopaminergic systems [16]. Only some of these systems have also been associated with drug dependence. Thus the positive effects of cholinergic drugs on attention and aspects of mnemonic function are not accompanied by mood-altering effects of potential recreational use.

Predicting psychopharmacological efficacy is often confounded by the surprising emergence of new substances which may have initially appeared to be innocuous or which were initially established in some other functional context. The effective anti-narcoleptic modafinil [17] has stimulant-like actions, but does not appear primarily to affect the brain neurotransmitters implicated in the effects of stimulant drugs such as amphetamine and methylphenidate. This drug has mild beneficial effects on tests of short-term memory and planning, as well as an anti-impulsive action, both in normal adults and in patients with

ADHD [18]. Its beneficial effects on vigilance and other aspects of human performance have led to its well-publicised use by the military.

These effects indicate again the possibility of cognitive enhancement in intact individuals. Increasing evidence of individual variability in intellectual function in normal subjects that occurs as a function of genotypical variation [19] and in association with factors such as fatigue or under-arousal in the work-place, may promote self-medication. But although modafinil emerged from a scientific programme of drug development, we do not know how it works. The fact that modafinil is not widely abused indicates that it is feasible to dissociate stimulant from reinforcing actions of drugs of abuse. Whether this dissociation arises from the pharmacokinetic actions of the drug, which is relatively slow-acting, or its distinct neurochemical actions, is a theoretically, as well as practically, important issue.

Self-medication prompted by a perceived need to elevate the activation of particular brain neurochemical systems might also affect other domains of forebrain functioning. The need to enhance activation of the dopaminergic reinforcement ('reward') system might explain why individuals use cocaine and other psychomotor stimulants that operate primarily through this system. Such a view is consistent with evidence that euphoria produced by drugs such as cocaine and methylphenidate may depend on initially low levels of striatal DA (D2) receptors, as revealed by positron emission tomography, which may be indicative of low basal mood states [20] (Figure 1). It may also be relevant to the identification of individuals who indulge in certain behavioural addictions such as gambling [21]. Whether these individual differences arise from genetic or environmental influences is still to be determined.

2. NEUROPSYCHOLOGY OF REINFORCEMENT LEARNING AND ADDICTION

Motivated action can be examined by studying instrumental conditioning, the process by which animals alter their behaviour when there is a contingency between their behaviour and a reinforcing outcome [22]. Reinforcement learning [23-25] has been studied for a long time [22; 26-30]. At its most basic level, it is the ability to learn to act on the basis of important outcomes such as reward and punishment. Events that strengthen preceding responses are called positive reinforcers, while events whose removal strengthens preceding responses are called negative reinforcers [31]. If reinforcers are defined by their effect on behaviour, then, to avoid a circular argument, behaviour cannot be said to have altered as a consequence of reinforcement [31]. However, to explain behaviour rather than merely describe it, internal processes such as motivation must also be accounted for. Central motivational states, such as hunger and thirst, account parsimoniously for a great deal of behavioural variability [32-34]. For example, water deprivation, eating dry food, hypertonic saline injection, and the hormone angiotensin II all induce a common state — thirst — that has multiple effects. Thirsty animals drink more water, drink water faster, perform more of an arbitrary response to gain water, and so on. The ideas of motivational state entered early theories of reinforcement. For example, it was suggested that events that reduce 'drive' states such as thirst are positively reinforcing [28]. However, on its own, this simple model cannot account for many instrumental conditioning phenomena, let alone 'unnatural' reinforcement such as drug addiction.

Modern neuropsychological theories recognize that many processes contribute to a simple act such as pressing a lever to receive food or a drug [35]. Rats and humans exhibit goal-directed action, which is based on knowledge of the contingency between one's actions and their outcomes, and knowledge of the value of those outcomes. These two representations interact so that we work for that which we value [35; 36]. Environmental stimuli provide information about what contingencies may be in force in a given environment [37-39]. Remarkably, the value system governing goal-directed action is not the brain's only one. This 'cognitive' value system exists alongside [40] the valuation

process that determines our reactions when we actually experience a goal such as food, termed 'liking', 'hedonic reactions', or simply 'pleasure' [41]. Under many normal circumstances the two values reflect one another and change together. However, the fact that they are different means that animals must learn which outcomes are valuable in a given motivational state, a process referred to as incentive learning. For example, rats do not know that to eat a particular food while sated is not as valuable as to eat the same food while hungry until they have actually eaten the food while sated [42].

Just as there is more than one value system, there is more than one route to action and not all action is goal-directed. With time and training, actions can become habitual [43], that is, elicited by direct stimulus–response (S–R) associations. S–R habits are less flexible than goal-directed action, because their representation contains no information about what the final outcome will be, and cannot alter quickly if the desirability of a particular outcome changes. But they may help reduce the demands on the cognitive, goal-directed system in familiar settings.

Stimuli that predict reward may become conditioned stimuli (CSs), associated with the reward (unconditioned stimulus, US) through Pavlovian associative learning. Pavlovian CSs can influence instrumental behaviour directly (Pavlovian–instrumental transfer, PIT) and can serve as the goals of behaviour, termed conditioned reinforcement [35; 36; 44-46].

Seen in this context, the major neuropsychological theories of drug addiction — none of them mutually exclusive — can be summarized:

2.1 Direct positive effects of drugs; self-medication; tolerance

Drugs are taken for their positive effects. These may include euphoria, enhanced social experiences, enhanced intellectual or attentional performance, and an enhanced effect of other reinforcers such as food or sex [2; 47-49], as indicated in the accompanying Foresight review on Pharmacology and Treatments (**cite Technology Foresight review:** by Morris et al., 2005).

An aspect of this may be that people 'self-medicate' to achieve a desired level of mood, social performance, and so on [49-53], although the extent to which this occurs is debated (e.g. [53; 54]). Furthermore, the effect of the drug depends upon the user's expectations [55] and prior mood, and varies between people [56; 57].

Tolerance to pleasant drug effects may build up, requiring the user to take more drugs to achieve the same effect. Tolerance can be due to a decrease in drug bioavailability ('metabolic tolerance'), a reduction in the number or responsiveness of receptors or intracellular mechanisms ('pharmacodynamic tolerance'), or a compensatory mechanism ('behavioural tolerance') [2]. Tolerance may develop with chronic use, but in the case of cocaine, can develop in a single session [58], perhaps explaining cocaine 'bingeing'. Metabolic tolerance is seen to barbiturates, ethanol and opiates [2]. Pharmacodynamic tolerance is seen to a wide range of drugs including barbiturates, ethanol, opiates, amphetamine, cocaine, nicotine, and caffeine [2]. Behavioural or conditioned tolerance has been observed to opiates, ethanol, nicotine, benzodiazepines, and other drugs [59-63]. Since conditioned tolerance may be situation-specific [63] and the lethality of drugs may be increased if the environment changes, the opponent process model of addiction [64; 65] suggests that a key component of addiction is the development of behavioural [66] and neuroanatomical [67; 68] tolerance, which can counteract the effects of the drug [69].

2.2 Conditioning and sensitization

CSs associated with the pleasant aspects of drug-taking may act to promote drug-taking. Drug-associated cues including mood states, people, locations, and abuse paraphernalia may induce some of the primary effects of drugs [70], but can also induce craving in addicts, and trigger relapse [71-74]. Addicts may also work directly for drug-associated stimuli (conditioned reinforcement), leading them in turn to the drug itself.

Sensitization ('inverse' or 'reverse' tolerance) occurs when repeated doses of a drug enhance one or more of its effects. Prototypically, moderate, spaced doses of amphetamine enhance the subsequent locomotor response to it [49; 75; 76]. Sensitization can exhibit environmentally-specific conditioned properties [77], and changes in drug pharmacodynamics [78]. It has been suggested that the ability of drug-associated CSs to promote drug-seeking or craving also sensitizes as a consequence of repeated drug-taking [75; 79].

2.3 Withdrawal and conditioned withdrawal

Some drugs, notably the opiates and alcohol, produce powerful physical withdrawal syndromes. Thus, it is possible to consider addiction within the framework of both rewarding and aversive consequences [80]. Withdrawal symptoms are improved by the drug, so the drug is taken to escape from withdrawal [47; 48]. However, demonstrations that the neural substrates mediating physical signs of dependence are separate from those of reward [81] support earlier behavioural evidence that physical dependence is not a necessary correlate of opiate addiction. In withdrawal, incentive learning operates for drugs of abuse just as for natural reinforcers. Just as hunger increases the hedonic impact of food [82], which teaches the animal that it is more worth working for food when it is hungry [36], rats learn that heroin has a high value in the state of opiate withdrawal [83]. Hedonic impact may be a 'common currency' for determining the value of widely varying reinforcers [84]. Environmental stimuli may become associated with withdrawal [85-88] and CSs for withdrawal may then provoke drug-taking just as withdrawal itself does [47; 48].

Drugs such as cocaine that do not produce obvious physical withdrawal syndromes may nonetheless have unpleasant after-effects on mood [72; 89-92], which may promote drug-taking in the same way that physical withdrawal does. 'Opponent process' theories [64; 93-96] use the idea that a long-lasting unpleasant process opposes the euphoric effects of drugs, and that with chronic use, the euphoric effects diminish while the dysphoric process comes to dominate, leading to drug-taking via negative reinforcement.

2.4 Habit learning

Drugs may activate habit-learning systems so that actions that led to the drug are reinforced directly, creating powerful stimulus-resonse habits or 'involuntary' responding [97-101]. A hallmark of habitual responding directly is that it persists stimulus-response habits even if the reinforcer's value is reduced [35]. Habits are sometimes thought of as 'compulsive' responding when they occur at an abnormally high level, since they do not depend on the current value of the goal. Alcohol seeking may primarily reflect habitual responding [102], and while cocaine-seeking can be goal-directed [103], under some circumstances responding for cocaine can be more habitual than responding for natural reinforcers [104]. Similarly, soon after acquisition, cocaine-seeking is readily suppressed by an aversive CS, but this suppression is lost after prolonged experience of cocaine [105]. Craving and habits both capture something of the casual definition of addiction as 'compulsive' behaviour (e.g. [106-108]).

2.5 Individual vulnerability

People who become drug addicts may be more vulnerable than other people to one or more of these neuropsychological effects, as well as being more predisposed to try drugs of abuse in the first place. Vulnerability to drug effects is discussed in greater detail in Section 6.

2.6 Comparison of drug-taking to alternative activities

From a behavioural-economic perspective, addicts weigh up the benefits and costs of drug-taking. They may do so rationally [109; 110], or may exhibit decision-making flaws characteristic of humans, such as focusing inappropriately on short-term rather than long-term goals and being inconsistent in their choices [111-117]; see Section 10.

Drug addicts may be predisposed to act even more for short-term benefit than other people, or drugs may induce decision-making deficits [20; 118-125]. There is some evidence that self-control deficits may be a reversible consequence of cigarette dependence [121; 123].

None of these theories, or indeed levels of explanation, is adequate on its own [126]. For example, although heroin may be taken to alleviate withdrawal, heroin self-administration can persist in the absence of withdrawal [81; 127], and although heroin has euphoric effects, humans will work for doses that they cannot subjectively distinguish from a placebo [128]. To seek a single theory of drug addiction is to miss the point that drugs of abuse have many effects, people take drugs for many reasons, and those reasons vary between people.

3. THE NEURAL SYSTEM BASIS OF REINFORCEMENT LEARNING: RELEVANCE TO NATURAL MOTIVATION AND DRUG ADDICTION

Considerable progress has been made in establishing some of the mechanisms by which neural structures respond to appetitive and aversive events. To some extent these structures can be compared directly to the psychological processes known to influence animals' responding for rewards.

A number of limbic cortical and subcortical structures in the brain play a role in assessing the value of reinforcers and of the stimuli that predict them, and in actions directed at obtaining those reinforcers or stimuli [44] (Figure 2). Their relevance to addiction has been considered many times before (e.g. [49; 129]), and influential theories of addiction have postulated that drugs of abuse 'short-circuit' or 'hijack' the neural mechanisms underlying reward or motivation [80; 130-133].

3.1 The role of DA in the nucleus accumbens in motivation and learning

The discovery that rats would work hard to stimulate regions of their brain electrically (intracranial self-stimulation, or ICSS) [134] was historically important. Many sites that support ICSS lie on the path of dopaminergic neurons from the substantia nigra pars compacta (SNc) and ventral tegmental area (VTA) to limbic sites including the ventral striatum (nucleus accumbens, Acb), and ICSS is substantially reduced after Acb DA depletion [135]. The rate at which rats learn to respond for ICSS is correlated with the degree of potentiation of synapses made by cortical afferents onto striatal neurons, a potentiation that requires DA receptors [136]. The discovery that deep brain stimulation and transcranial magnetic stimulation can influence cognition, affect and motor performance in humans means that we cannot discount this means of altering brain function. Deep brain stimulation of the subthalamic nucleus has been successful with severe Parkinson's disease, and may have applications in obsessive compulsive disease

and clinical depression [137] but care is needed as the stimulation can be self-administered, and in the case of Parkinson's disease, dramatic emotional sequelae have been reported [138].

3.2 DA; motivation, reward and pleasure

An early suggestion was that Acb DA mediated the pleasurable aspects of reward [139-141]. There is now strong evidence against this simple idea. Certainly, DA is released in response to appetitive reinforcers (e.g. [142-152]), intra-Acb DA agonists are reinforcing [153], animals may adjust their drug-taking to maintain high Acb DA levels [154], and some aspects of naturally- and drug-reinforced responding depend on Acb DA (e.g. [155-162]). However, Acb DA does not mediate 'pleasure' [20; 147; 163; 164], though its release may correlate with activity in other systems that do, and reinforcement operates in its absence [155; 165]. Measured by microdialysis techniques, DA is also released in response to aversive stimuli, CSs that predict them, and other salient stimuli (see e.g. [149; 166; 167]), which would be consistent with a more general motivational role. CSs that have been paired with reward also elicit approach [168]; this effect also depends on the Acb [169-171] and its DA innervation. DA may also be involved in learning this approach response, again perhaps under the control of the central nucleus of the amygdala (CeA) [130; 159; 172-174] (see Figure 2). Acb DA also contributes directly to subjects' motivation to work hard [156-158].

Hedonic assessment of rewards themselves, or 'liking', does not depend on dopaminergic processes [147; 160; 175; 176]. Instead, it involves opioid mechanisms in the nucleus accumbens shell (AcbSh) and other systems in the pallidum and brainstem [177; 178]. Intra-Acb μ opioid agonists also affect food preference, increasing the intake of highly palatable foodstuffs including fat, sweet foods, salt, and ethanol [179-183], while chronic ingestion of chocolate induces adaptations in endogenous Acb opioid systems [184]. However, the notion that 'pleasure' can be mediated by receptors in a sub-cortical nucleus is perhaps too simple. Activity in this circuitry is probably subject to further processing in cortical (particularly prefrontal cortical) circuits, before attribution and accompanying subjective commentary [49].

3.3 DA and learning

The notion that DA 'stamps in' the learning of stimulus–response connections has considerable support. It has acute effects that modulate corticostriatal transmission, and also lasting effects. The combination of presynaptic and postsynaptic activity normally induces long-term depression of corticostriatal synapses, but if the same pattern of activity is paired with a pulse of DA, then the active synapses are strengthened [185]. Natural reinforcers, drugs of abuse, and CSs that predict either, trigger increases in DA release in the Acb [146-150]. DA neurons fire to unexpected rewards, or to unexpected stimuli that predict reward [142-145]. DA neuron firing may be a teaching signal used for learning about actions that lead to reward [143]. The Acb similarly responds to anticipated rewards [186-197]. Other parameters of tonic DA neuronal firing may signal reward uncertainty, possibly relevant to the understanding of gambling behaviour [198; 199].

Targets of DA neurons certainly influence instrumental behaviour. Structures that learn from the DA 'teaching signal' probably include the dorsal striatum and PFC (see Figure 2), but much attention has focused on the Acb. Blockade of *N*-methyl-D-aspartate (NMDA) glutamate receptors in the nucleus accumbens core (AcbC) has been shown to retard instrumental learning for food [200], as has inhibition or over-stimulation of protein kinase A (PKA) within the Acb [201]. Concurrent blockade of NMDA and DA D1 receptors in the AcbC synergistically prevents learning [202]. Once the response has been learned, subsequent performance is not impaired by NMDA receptor blockade within the AcbC [200]. Furthermore, infusion of a PKA inhibitor [201] or a protein synthesis inhibitor [203] into the AcbC after instrumental training sessions impairs subsequent performance,

implying that PKA activity and protein synthesis in the AcbC contribute to the consolidation in memory of instrumental behaviour.

However, it is clear that the Acb is not required for simple instrumental conditioning but rather is implicated in providing extra motivation for behaviour, especially when such motivation is triggered by Pavlovian CSs, or when reinforcers are delayed or require substantial effort to obtain. Rats with Acb or AcbC lesions acquire lever-press responses on sequences of random ratio schedules at normal or slightly reduced levels [204; 205] and are fully sensitive to changes in the action–outcome contingency [204-206]. Thus, the Acb is not critical for goal-directed action (see [44]). 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 [207; 208] and is required for Pavlovian CSs to provide a motivational boost to responding [174; 205], i.e. for PIT. PIT has sometimes been termed 'wanting' [79; 209], although 'wanting' could equally refer to the instrumental incentive value underpinning true goal-directed action or Pavlovian arousal itself. PIT can be further enhanced by injection of amphetamine into the Acb [209] and depends on DA [160], possibly under the control of the CeA [174]. Other motivational effects of Pavlovian CSs also depend on the Acb, for example, the capacity of CSs to act as conditioned reinforcers of instrumental behaviour.

The neural basis of conditioned reinforcement has been investigated using the 'acquisition of a new response' procedure, in which subjects work only for a conditioned stimulus that has previously been associated with a natural reinforcer such as food or water. From these studies, it is clear that the basolateral amygdala (BLA) and AcbC are important in the ability to respond normally for conditioned reinforcement [169; 210-212]. 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 a number of processes that require motivation [213]. Functional neuroimaging evidence supports this conclusion in humans [191; 214].

3.4 Action–outcome contingency knowledge, planning and value: the prefrontal cortex and amygdala

The prefrontal cortex (PFC) (specifically, prelimbic cortex) is required for rats to represent the contingencies between actions and their outcomes [215; 216], and acquisition of instrumental responses on a simple schedule is disrupted by blocking NMDA and DA D1 receptors in the PFC [217]. This is relevant to evidence from cognitive neuroscience that sectors of the human PFC are important for volitional processes (see Section 8.13 and Figure 2).

The PFC is also involved in extinction [218], the cessation of responding when a CS or response is no longer paired with reinforcement. Extinction is not 'unlearning' but involves the learning of new, inhibitory associations (see [219; 220]). Lesions of the ventral medial PFC interfere with the extinction of Pavlovian conditioned freezing in the rat [221-223]. The PFC interacts with the amygdala, an important site of CS–US association in this task (see [224; 225]), and may suppress conditioned freezing when it is no longer appropriate [218; 226-228].

The orbitofrontal cortex (OFC) is part of the PFC with a particular role in the assessment of reinforcer value. It has bidirectional connections to the amygdala and both are heavily implicated in the retrieval of the value of primary reinforcers based on information from CSs [44; 229-232]. In humans, the OFC and amygdala are also activated during extinction of Pavlovian conditioning [233]. The amygdala regulates the DA signal to the Acb [44; 130; 174; 234; 235]. Goal-directed action requires that action–outcome contingencies interact with the incentive value of goals [35; 36] and the connection between the amygdala and the PFC [236] may provide this functional link [237-240].

3.5 Relevance to drug addiction

It has been suggested that these motivational and learning processes are particularly significant in some addictions, and their modification may have therapeutic potential. The existence of dissociable parallel brain systems mediating the associative control over addiction sits comfortably within the classic dichotomy of behavior into Pavlovian [241] or instrumental learning [30]. A number of influential theories of addiction have postulated the existence of multiple parallel processes, each with its own independent, but interacting, neural system [80; 130-133].

DA systems are affected by virtually all of the major classes of drugs of abuse, ranging from the psychomotor stimulants to opioids, alcohol and nicotine, as well as by natural reinforcers such as food. Some abused drugs are particularly potent in this regard. 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 [242; 243]. Sensitization occurs following psychostimulant administration directly into the VTA, which induces hypersensitivity to DA in the Acb [244] and enhances the response to Pavlovian CSs associated with reward [79; 245; 246]. In animal models of drug-seeking behaviour controlled by drug-associated stimuli [212], lesions of the AcbC or disruption of its glutamatergic neurotransmission reduce drug-seeking [247; 248], probably by reducing the motivational impact of the CSs. DA D3 receptors are particularly concentrated in the Acb and amygdala [249], and D3 receptor antagonists [250; 251] and partial agonists [252; 253] reduce cue-controlled cocaine seeking or relapse to cocaine-taking in animal models. 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 [250; 251]. It is not yet clear to what extent sensitization contributes to human addiction [254], but it has been suggested that a sensitized response to drug-associated cues contributes to drug craving — that this 'incentive motivational' system becomes sensitized [75]. In present animal models, drug sensitization enhances responding for food, or responding to CSs for food [79; 246; 255], but in human addiction, responding for non-drug reinforcement declines relative to that for drug reinforcement [256]. However, pre-treatment with psychomotor stimulants results in animals being willing to work harder for cocaine and this may reflect an effect of sensitization on the motivation to seek drugs [257].

The well known ability of psychomotor stimulants to potentiate conditioned reinforcement [258], depends upon the integrity of the dopaminergic innervation of the Acb, especially the AcbSh [169]. This might be one possible basis for understanding why psychomotor stimulant drugs are themselves reinforcing; they enhance the reinforcing effects of environmental stimuli. The importance of conditioned reinforcers is that they allow the mediation and maintenance of long chains of behaviour, including drug-seeking behaviour, over delays to primary reinforcement.

Although potent as conditioned reinforcers when presented contingently, CSs paired with drug infusions do not increase drug-seeking when presented noncontingently to animals [259-261]. Thus, conditioned reinforcement appears to be reliant on the contingency between the response and the CS, irrespective of the motivational value of the US [262]. Indeed, the reliance of drug-seeking and taking on drug-associated conditioned reinforcers is underscored by further findings that cocaine self-administration is lower in the absence of any contingent CS [263]. Indeed, nicotine self-administration in animals is difficult to acquire in the absence of conditioned reinforcers [264], suggesting that conditioned reinforcers may form part of a powerful stimulus complex, along with the drug, in maintaining drug use. Similarly, conditioned reinforcement maintained by CSs previously paired with oral alcohol can be persistent [265] and the ability to maintain responding is independent of the drug [266], suggesting that this type of drug-seeking has a habitual quality. The impact of conditioned reinforcement on drug-seeking is persistent and relatively impervious to extinction. It can maintain responding independently from the drug with which it was paired, suggesting that it may depend upon a separate neural system from that which mediates the effects of the drug itself [265; 267].

In experimental models of addictive behaviour in which drug-associated conditioned reinforcers support and maintain prolonged bouts of seeking behaviour [212], the functional integrity of a neural system involving the BLA and AcbC is of major importance (see Figure 2). Thus, lesions of the BLA or AcbC, but not the AcbSh, greatly impair the acquisition of cocaine-seeking behaviour [268; 269]. There is also neurochemical specificity in these BLA and Acb mechanisms. DA receptor blockade, but not AMPA receptor blockade in the BLA, reduces established cue-controlled cocaine seeking. The reverse is true in the AcbC, where AMPA, but not DA receptor, blockade has this effect [270]. It has additionally been established that disconnection of the BLA and AcbC by blocking DA receptors in the BLA on one side of the brain and AMPA receptors in the AcbC on the other has the same effect of dramatically reducing cocaine seeking [270]. These data provide the strongest evidence that the BLA and AcbC function serially as components of a neural system that mediates these conditioned influences on drug-seeking (see Figure 2).

In functional imaging studies of human drug addicts, the amygdala is consistently activated by exposure to cocaine-, heroin-, food- and sex-associated stimuli in a way that is correlated with drug craving (e.g. [239; 271]). Other regions commonly activated by drug-associated stimuli include the anterior cingulate cortex, OFC and occasionally the Acb [271-274]. These data show that in both animals and humans, limbic cortical-ventral striatopallidal circuitry is associated with emotional learning and in processes related to drug craving, addiction and relapse.

3.6 Habits and the dorsal striatum

The development of stimulus–response habits may depend on dorsal striatal plasticity [275], which may in turn depend on DA receptors [136; 185]. The balance between habits and goal-directed behaviour may also be regulated by the prelimbic and infralimbic cortex [276], subdivisions of the rat PFC. Recent functional neuroimaging data in humans supports the hypothesis that the ventral and dorsal striatum are also involved differentially in Pavlovian and instrumental learning [277].

Dorsal striatal DA release to CSs is a correlate of well-established cocaine-seeking [148]. By contrast, such DA release is not seen in the AcbC region [278]. Consistent with the electrophysiological data [145], DA release is only observed there when the CS is presented in a surprising context. Comprehensive studies of chronic cocaine self-administration in monkeys indicate a progressive involvement of limbic, association and sensorimotor striatal domains, with autoradiographic changes evident first in the ventral, and then in the dorsal striatum [279; 280]. These data support the notion that there may be a stage of stimulus–reward or action–outcome learning that precedes stimulus–response habit learning. These phases may be mediated respectively by the ventral and dorsal striatum, either successively, or more probably in a temporally overlapping manner, possibly via the recently characterized 'cascading' neural connectivity that links these different corticostriatal loops [281] (see Figure 2). Thus, drug addiction is conceived in terms of a switch between these modes of learning, operating across the corticostriatal circuitry, from ventral striatal (i.e. Acb) to dorsal striatal domains.

4. NEUROBIOLOGY OF RELAPSE

A key feature of drug addiction is the high propensity to relapse, even after protracted periods of abstinence. The prevalent animal model of relapse utilizes the so-called extinction-reinstatement procedure recently reviewed by Shaham and colleagues [282] in a double issue of *Psychopharmacology* (volume 168, issues 1-2) devoted to this subject. The usual form of this procedure is to train rats to press a lever to self-administer a drug and then to extinguish the instrumental act of lever pressing by omitting drug infusions. Following extinction, three manipulations generally accepted to be of importance in

precipitating relapse in abstinent human drug addicts can 'reinstate' drug-seeking responses by increasing lever pressing although the drug remains unavailable. They are exposure to drug-associated stimuli, experimenter-administered drug, or 'stress,' usually an electric shock to the feet. However, extinction of the instrumental act of drug self-administration is not generally a means by which human addicts achieve abstinence. Abstinence is more likely to arise through an active decision to abstain or through abstinence imposed by the law or by treatment. Moreover, since the extinguished response is so readily reinstated, it is unlikely that extinction training will provide an effective clinical approach to treatment. Extinction of the acquired properties of drug-associated stimuli through their non-reinforced exposure has been attempted as a therapeutic strategy, but with limited success [283; 284], most likely because cue exposure in the clinic is unlikely to reduce the properties of drug cues in the original drug-associated environment.

Neurobiologically, these ways of inducing relapse in the extinction-reinstatement model depend upon both common and discrete elements of limbic cortical-ventral striatopallidal circuitry. Most studies have involved the reinstatement of cocaine-seeking behaviour, but there are also studies with heroin and nicotine.

4.1 Drug-cue-induced reinstatement

The neural basis of cue-induced reinstatement has been reviewed extensively [282; 285]. It is prevented by reversible or permanent inactivation of the BLA and reversible inactivation of the dorsal mPFC [285-287]. Inactivation of the OFC also attenuates cue-induced reinstatement of drug seeking [288]. Systemically injected D1 and D3 DA receptor antagonists block cued reinstatement [261; 289], as do intra-BLA, but not intra-Acb, infusions of D1 DA receptor antagonists [290] — consistent with the effects of D1 and D3 DA receptor antagonism in the BLA on cocaine-seeking measured under a second-order schedule [270]. Perhaps surprisingly, inactivation of the Acb does not attenuate cue-induced reinstatement [285], yet this structure is important for conditioned reinforcement and other Pavlovian influences on instrumental behaviour, while AMPA receptor blockade attenuates cocaine-seeking under a second-order schedule [248]. Although limbic cortical-ventral striatopallidal systems are implicated in the conditioned control of drug-seeking and reinstatement after extinction, much remains to be established in terms of the processes occurring in cortical and subcortical structures and the ways in which different subsystems interact. While the BLA mediates reinstatement following exposure to discrete, cocaine-associated stimuli, the hippocampus may underlie the motivational impact of contextual stimuli (see Figure 2). Theta-burst stimulation of the hippocampus, a form of experimental deep brain stimulation, has been shown to reinstate extinguished cocaine-seeking in a manner that depended on glutamate transmission in the VTA. It was suggested that this might mimic the process by which reinstatement occurs when animals are placed in a context associated with drug-taking, rather than in response to discrete cocaine cues [291]. Indeed, dorsal hippocampal inactivation attenuates context-induced reinstatement of drug seeking, as does inactivation of the dorsal mPFC [292]. These data are in accord with the suggestion of a differential involvement of the amygdala in conditioning to discrete, and the hippocampal formation in conditioning to contextual stimuli [293; 294]. Moreover, electrophysiological and *in vivo* neurochemical studies have demonstrated that hippocampal, amygdala and PFC projections interact in the Acb in a way that is modulated by mesolimbic DA and that, in turn, can modulate the release of DA [295-299]. Thus, hippocampal, amygdala and PFC mechanisms may influence drug-seeking through their convergent projections to the Acb, perhaps competing for access to response strategies subserved by different cortical-striato-pallido-thalamo-cortical re-entrant loops (see Figure 2). The mPFC is clearly important in reinstatement — whether induced by cues, contexts, drugs or stress — following extinction of the instrumental seeking response [292; 300]. Determining the psychological process that the mPFC subserves in these settings is an important goal.

The vigour of conditioned reinstatement of cocaine seeking increases with the duration of withdrawal [301], suggesting that neuroadaptations to chronic cocaine self-administration and withdrawal interact with the motivation to seek cocaine when cocaine cues are present in the environment. These findings may provide insight into the possible mechanisms that underlie the persistence or 'incubation' of cocaine-seeking reported to occur over time in abstinent cocaine addicts. The mechanisms underlying this incubation effect have been shown to depend upon the upregulation of the extracellular signal-regulated kinase (ERK) signalling pathway specifically within the CeA [302]. Thus, exposure to cocaine-associated stimuli increased cocaine-seeking and also ERK phosphorylation in the CeA, but not BLA, substantially more after 30 days than after one day of cocaine withdrawal, so the incubation effect was correlated with ERK upregulation in the CeA. Inhibition of ERK phosphorylation in the CeA, but not BLA, after 30 days of withdrawal greatly decreased cocaine-seeking, whereas stimulation of ERK phosphorylation in the CeA, but not BLA, increased cocaine seeking after one day of withdrawal. Thus the mechanisms mediating drug-cue-induced relapse and its enhancement during protracted withdrawal appear to depend upon two dissociable mechanisms in the BLA and CeA, respectively.

4.2 Drug-induced reinstatement

Drug-induced reinstatement by 'priming' (i.e. non-contingent or experimenter administered cocaine or heroin — often given intraperitoneally and not intravenously) can be attenuated by D1-like dopamine receptor antagonists [303]. In neuroanatomical studies it has been shown that drug-induced reinstatement can be blocked by inactivation of the VTA, dorsal mPFC, AcbC and ventral pallidum, called the 'motor subcircuit' by Kalivas and colleagues [285; 286; 300] (see Figure 2). Moreover, DA receptor antagonists infused into the mPFC or AcbSh also attenuate drug-induced reinstatement (see [282]). Antagonists at AMPA, but not NMDA receptors in the ACb, block reinstatement induced by systemic or intra-mPFC cocaine and, by contrast, AMPA receptor agonists infused into the Acb reinstate cocaine seeking [304; 305]. The effects of cocaine or heroin to reinstate extinguished responding are mimicked by systemic injections of D2, but not D1, receptor agonists [306] and by infusions of cocaine, amphetamine or DA itself directly into either the Acb or mPFC [300; 305; 307]. Antagonists at μ opiate receptors prevent the effects of heroin and alcohol, but not cocaine, on reinstatement [303; 308] and a CB1 receptor antagonist has also been shown to prevent the reinstatement effects of cocaine [309].

4.3 Stress-induced reinstatement

Reinstatement can be induced by several stressors, including footshock, food deprivation and also CNS administration of corticotrophin releasing factor CRF; see [282]. Inactivation of the dorsal mPFC prevents footshock-induced reinstatement; this area of the PFC is commonly involved in cued, drug and stress-induced reinstatement [310]. Additional and unique neural circuitry appears to be critical for the effects of stress, including the CeA, bed nucleus of the stria terminalis (BNST) and the noradrenergic medullary tegmentum which innervates these structures [311-313]. Thus, the following manipulations all block stress-induced reinstatement: intra-BNST, but not intra-amygdala, infusions of a CRF antagonist; systemic and intracerebroventricular, but not intra-locus coeruleus, injections of an alpha-2 noradrenergic receptor agonist; intra-BNST and intra-amygdala alpha-2 noradrenergic receptor antagonists; and destruction of the ventral noradrenergic bundle originating in the medullary noradrenergic cell groups (see [282] for review). The CRF-containing projections between the CeA and BNST have also been shown to be a critical link between these structures in mediating stress-induced relapse [282]. Thus, two neural systems implicated in stress responses in general — one utilizing NA and the other CRF — are implicated along with the mPFC in mediating relapse induced by footshock stress in the extinction-reinstatement procedure. The generally accepted mechanism is that stress activates the medullary noradrenergic neurons and leads to activation of the CRF system within the BNST and possibly the CeA (see [282;

285] for reviews). How this subcortical, neuroendocrine mechanism interfaces with the mPFC is not altogether clear, nor is how this impinges on limbic cortical ventral striatopallidal circuitry.

One of the reasons for developing and studying the neural basis of relapse in experimental animals is to develop treatments that will promote abstinence. Intensive experimental investigation of this area has yielded detailed information on the neural systems and neurochemical mechanisms underlying cue-, stress- and drug-induced relapse. An important issue for resolution is the extent to which the effects on reinstatement of cues, drug or stress actually depend upon the prior process of instrumental extinction. If they do their utility in human addiction, where this extinction process does not occur, may be slight. D3 DA receptor antagonists appear to have efficacy in both the cued-reinstatement procedure and ongoing, cue-controlled cocaine-seeking suggesting that this dopaminergic target might affect the conditioned process common to both. In addition, the GABA-B receptor agonist baclofen both attenuates drug seeking that depends upon drug-associated conditioned reinforcers in rats [261] and also attenuates cue-induced activation of limbic cortical areas in cocaine-addicted humans [314]. New pharmacological treatments to prevent relapse may emerge from this rich preclinical data on experimental models of reinstatement in animals.

5. NEUROADAPTATIONS — INTRACELLULAR CASCADES

The chronic administration of drugs of abuse results in the induction of intracellular cascades within the limbic corticostriatal circuitry. Although different drugs act at different receptor targets on the cell surface, there is a degree of convergence in their downstream signalling pathways. Interaction between the drug and its target results in either the opening of a ligand-gated channel, or the activation of a receptor-linked G-protein [315], both of which induce intracellular cascades. One common action of drugs is the activation of the transcription factor CREB and components of the cAMP signalling pathway, such as adenylyl cyclase (AC) and protein kinase A (PKA) [316-327]. CREB regulates the transcription of genes whose promoters contain the CRE element, and is thought to be a site of convergence of intracellular cascades as it can be activated through phosphorylation at serine 133 by several difference protein kinases [328; 329]. Therefore alterations in CREB and the cAMP signalling pathway may represent common neuroadaptations of different drugs of abuse.

Opiates and cannabinoids acutely inhibit adenylyl cyclase and the cAMP signalling pathway [319; 330; 331], resulting in a decrease in phosphorylated CREB [320]. In contrast, acute administration of ethanol and stimulants increases the activity of the cAMP signalling pathway [324; 332]. However, in all cases, there is a common chronic upregulation of the cAMP signalling pathway that is accompanied by tolerance to the acute intracellular response to drugs of abuse [317; 320; 331; 333; 334]. The switch from acute inhibition to chronic upregulation of the cAMP pathway with repeated opioid administration is poorly understood, though it is known to involve adaptations in G-protein properties resulting from their persistent stimulation [335], and neuroadaptive changes in protein kinase systems [336]. Furthermore, few downstream targets have been identified that mediate the functional effects of cAMP and CREB upregulation. Among the proteins whose levels are increased by chronic drug administration in a CREB dependent manner are AC, tyrosine hydroxylase (TH), the rate limiting enzyme in DA synthesis, and the opioid peptide dynorphin [317; 318; 337-339]. Dynorphin stimulates κ-opioid receptors, resulting in an inhibition of DA release [340], and the effects of CREB upregulation on drug reward are blocked by κ-opioid antagonists [317; 333]. Dynorphin mRNA levels are increased in the striatum of cocaine abusers *post-mortem* [341]. Therefore neuroadaptations in cAMP signalling, resulting in dynorphin upregulation, may partially underlie tolerance to the effects of drugs of abuse.

Repeated intermittent administration of addictive drugs results in sensitization of, rather than tolerance to, some of the behavioural and rewarding effects of drugs. The VTA is required for the initiation of behavioural sensitization [342], and long-lasting adaptations in the Acb are correlated with the expression of sensitization [343-345]. Transient increases of GluR1 subunits in the VTA are important for the triggering of sensitization [346]. The resultant persistent increase in calcium signalling and calcium/calmodulin-stimulated (CaM) kinase activation have also been implicated in behavioural sensitization [347]. CaM kinase II stimulates the mitogen-activated protein (MAP) kinase signalling pathway [348], which is known to be involved in sensitization [349]. Sensitization may also be mediated by a chronic drug-induced downregulation of the *Homer* gene family. Developmental genetic knockout of *Homer1* or *Homer2* in drug-naïve rats mimics the sensitized response to acute drug administration observed in rats experiencing withdrawal [350]. Specifically, *Homer* downregulation is critically important in the Acb, as localized antisense-mediated knockdown of *Homer1* expression in the Acb similarly induces sensitization [351], and virally-mediated rescue of *Homer2* in the Acb of *Homer2* knockout mice reverses the drug-sensitized phenotype [350].

One neuroadaptation that has attracted particular interest is the upregulation of the chronic Fos-related antigen ΔFosB. Levels of ΔFosB are increased in the Acb for up to four weeks following drug administration [352-354], and ΔFosB is also progressively upregulated with repeated drug administration [355]. This suggests that it is involved in behavioural sensitization, a hypothesis that is strongly indicated by the demonstration that ΔFosB overexpression in the Acb sensitizes behavioural and rewarding responses to cocaine and morphine [356], whereas a reduction inhibits responses to cocaine [357] and *fosB* knockout mice do not develop behavioural sensitization [358]. Therefore, ΔFosB may be a 'molecular switch' [359], that enables the sensitization of responses to drugs of abuse and long-term adaptations underlying addiction that persist through withdrawal. Again, the current challenge is to identify downstream targets of ΔFosB signalling, one of which may be cyclin-dependent kinase 5 (cdk5) [360; 361].

Upon withdrawal from drugs, which may be precipitated experimentally by the administration of an antagonist, there is a further increase in the activity of the cAMP signalling pathway beyond the level observed during tolerance [319; 320]. This reflects a state of dependence upon drugs of abuse, whereby when in withdrawal, the molecular cascades underlying reward are altered, resulting in an amotivational state [317; 333; 362-365]. Mice deficient in CREB display reduced opiate dependence [339; 366; 367] showing that cAMP signalling is important for both tolerance and dependence. A focus for current and future research is the characterization of the downstream targets of CREB, such as dynorphin, that are required for the development of tolerance and dependence.

Neuroadaptations implicated in drug-induced reinstatement (section 4) include the expression of *AGS3* (*activator of G protein signalling 3*), the blockade of which prevents cocaine-induced relapse to cocaine seeking [368], and a lowering of extracellular glumate through reduction of cystine-glutamate exchange, the restoration of which also prevents cocaine-primed relapse [369]. Drug-cue-induced reinstatement exhibits a time-dependent increase through withdrawal, with cue-induced cocaine, methamphetamine, heroin and sucrose seeking behaviours incubating over time [301; 370-372]. Molecular changes that correlate with this incubation effect may be important for cue-induced relapse to drug seeking. With short periods of withdrawal, transient increases are observed in tyrosine hydroxylase activity and cdk5 protein levels in the VTA [373; 374], and more persistent increases in PKA activity occur in the Acb [325; 373; 374]. However, the closest correlate of incubation appears to be the progressive upregulation of BDNF protein in the VTA [375; 376]. BDNF appears to be involved in the persistence of the incubation effect rather than being critical for incubation itself, evidenced by the demonstration that intra-VTA infusion of BDNF protein increases cocaine seeking over and above the incubation-related elevation [377].

BDNF has a well-established role in hippocampal LTP and learning and memory [378-380]. Therefore there is a similarity between the molecular mechanisms of drug addiction and learning and memory that also applies to the other intracellular cascades described, particularly the involvement of CREB [381]. Furthermore, drugs of abuse induce changes in the VTA and Acb that are reminiscent of the influential cellular models of learning and memory LTP and long term depression (LTD) [12]. One important issue that concerns research into both drug addiction and learning and memory is the longevity of both processes. All the molecular neuroadaptations described thus far are impermanent, and though some are indeed long-lasting, none can account for the compulsion and relapse that are observed months or even years after withdrawal. It is increasingly thought that morphological changes in synaptic structure are the only process by which the plasticity underlying both drug addiction and learning and memory can become near-permanent [362]. BDNF is necessary for the neuronal growth and synaptic remodelling associated with learning and memory [379; 380; 382; 383], and its putative role in incubation, as well as sensitization [349; 384], suggests that morphological plasticity may be critically involved in drug addiction.

Many genes have been implicated in synaptic plasticity [355; 385-387], and recently the involvement of *cdk5* in addiction-related permanent plasticity has attracted great attention. *Cdk5* is regulated by ΔFosB [360; 361], providing a link between the longest-lasting molecular adaptation and permanent plasticity [388], while cdk5 mediates the proliferation of striatal dendritic spines in response to chronic administration of cocaine [360; 389]. Such structural changes are likely to involve neurofilaments, which are elements of the cytoskeletal architecture of neurons [390; 391]. There is evidence for hyperphosphorylation of neurofilament proteins both in rodents and in human opiate addicts *post mortem* [392-394]. The mechanisms underlying neuroadaptations in synaptic morphology will be a focus of future research investigating the mechanisms of the long-lasting plasticity mediating drug addiction.

Synaptic morphology can also be altered by the production of new neurons. This neurogenesis is increasingly believed to play a role in drug-induced neuroadaptation. The few studies that have been conducted suggest that chronic exposure to drugs of abuse decreases neurogenesis in the hippocampus [395-399]. A parallel is found in studies of depression, in which decreased hippocampal neurogenesis is observed [11; 400; 401]. In contrast, learning and memory are associated with an increase in hippocampal neurogenesis [402; 403], and one action of antidepressant drugs is to increase hippocampal neurogenesis and neuronal growth [401; 404; 405]. This may suggest a potential avenue for the treatment of addiction. Some antidepressants may work partly by increasing neurogenesis. Antidepressants are sometimes, but not always, effective medications for drug dependence [406; 407].

Though further delineation of the molecular pathways involved in drug addiction will be a focus of future research, an important challenge will be to integrate the resulting information as the same molecular candidates are implicated in several aspects of drug addiction. BDNF is associated with incubation, relapse, sensitization and permanent plasticity. Furthermore, neuroadaptations occur throughout the limbic corticostriatal circuitry. Although molecular changes have been localized to particular brain areas, their relevance to behaviour is only beginning to be determined in a spatially localized manner. Array technology has recently been used both *in vitro* and *in vivo* to produce large sets of information on the upregulation of genes following the administration of drugs of abuse [408-412], but it will be several years before it can be established whether such neuroadaptations are merely correlative, or critical for the development of addiction.

The similarity between the molecular processes implicated in drug addiction and those firmly established in learning and memory will guide future research. One exciting prospect is the possible manipulation of drug-associated memories long after they have been acquired. Studies of fear conditioning have demonstrated that previously learned memories for stimulus-aversive outcome associations can be disrupted in a retrieval-

dependent manner, so that they are not expressed subsequently in retrieval tests [413]. This impairment of the reconsolidation of memories has also been observed in several other learning and memory paradigms [414-418], including a study of appetitive incentive learning [419], and also in humans [420], and may be extended to drug addiction. Drug-associated environmental stimuli elicit strong craving and increase the chance of relapse in abstinent individuals. The potential to reduce the impact of these cues through disrupting the reconsolidation of their association with addictive drugs may be a future avenue of research. Stimulus–addictive drug associations are supported by the same neuroanatomical substrates as both appetitive and aversive associations [235; 421], further underlining the similarity between addiction and learning, and the upregulation of *Zif268* in the amygdala is strongly correlated with the reconsolidation of both stimulus–drug and stimulus–footshock associations [422; 423], providing a prospective target for functional studies. *Zif268* has recently been shown to be a specific marker of the reconsolidation of hippocampal-dependent contextual fear memories [424]. Moreover, it appears that the molecular mechanisms of consolidation and reconsolidation are doubly dissociable, at least in the hippocampus [424] (Figure 3). It may be possible to target the reconsolidation of previously-learned maladaptive memories that are important in drug addiction [425].

6. VULNERABILITY TO ADDICTION

A significant proportion of the population take drugs of abuse at least once in their lifetime. Many individuals are capable of maintaining prolonged recreational use. Only a few develop a true addiction [426]. In the last few decades, the identification of the factors that determine these individual differences in propensity for addiction has become one of the major targets of drug abuse research. Emerging data from both clinical and animal experiments suggest that there exist 'vulnerable' phenotypes and genotypes that are more predisposed to drug abuse [427]. Elucidating the nature of these vulnerabilities could help prevent addiction in the predisposed population.

6.1 Individual differences in humans

Enormous differences in the subjective and reinforcing effects of drugs in humans are well-documented [56; 428; 429]. Individuals who prefer the effects of amphetamine to placebo show increased ratings of euphoria and positive mood, compared to anxiety and depression in subjects that choose placebo over amphetamine [56]. Recent advances in imaging technology have yielded exciting information about the neural correlates of these subjective differences. In one recent report, the intensity of the high induced by methylphenidate was significantly correlated with levels of released DA. Subjects who had the greatest increase perceived the most intense high [430]. Further, the magnitude of decrease in D2 receptor availability is significantly associated with the positive reinforcing effects of the psychomotor stimulant methylphenidate [430] (Figure 1), and release of DA in response to *d*-amphetamine correlates with self-reports of 'drug wanting' and the personality trait of novelty-seeking [431]. In support of these findings, rhesus monkeys with extensive cocaine self-administration history show significant decreases in D_2 receptor densities throughout the striatum compared to monkeys with a history of food reinforcement [279] (Figure 4). These data suggest that pre-existing differences between subjects in the rate of DA release and/or D_2 receptor distribution may play a role in the predisposition to drug abuse. The cause and exact nature of these functional differences is not known.

6.2 Animal models in the study of individual differences

Individual differences in conditioned and unconditioned responses to drugs of abuse have been reliably demonstrated in animals [432]. In particular, the propensity to acquire intravenous self-administration (IVSA) in rats can be predicted by the behavioural reactivity of an individual rat to a stressful situation, such as exposure to a novel environment (e.g. [433-435]). In this model, the propensity to develop drug SA can be represented by dividing animals into subgroups based on their locomotor response to a novel environment. Animals with an activity score above the mean for the entire group, so-called 'high responders' (HRs), show enhanced acquisition of psychostimulant IVSA [433-436] compared to animals with an activity score below the median of the group, the 'low responders' (LRs).

Further studies show that individual differences in drug intake originate from vertical shifts in the dose–response curve for intravenous cocaine self-administration, and these vertical shifts can be predicted by reactivity to novelty [427]. HR/LR groups also show differences in drug-mediated behaviours, such as increased locomotor response to systemic administration of cocaine, amphetamine, and morphine [437-440], enhanced psychostimulant-induced behavioural sensitization [441-443], and stronger contextual conditioning to drugs [443].

Behavioural differences between HRs and LRs appear to be mediated by differences in dopaminergic neuronal structure and function. For example, HRs show increased cocaine [441], amphetamine [444], and stress [445] -induced DA levels in the Acb, as well as a higher 3,4-dihydroxyphenylacetic acid (DOPAC)/DA ratio in this region [446]. Data from electrophysiological studies demonstrate higher basal firing rates and bursting activity of DA neurons in the ventral tegmental area and, to a lesser extent, the SNc in HRs [443]. Structurally, HRs have increased DAT numbers [441] and greater B_{max} for D1 binding sites [447] in the Acb. Regulatory mechanisms of the mesolimbic DA system also differ between HRs and LRs. Recent data indicate that HRs express lower levels of tyrosine hydroxylase levels and CCK-mRNA, part of the intrinsic inhibitory input to dopaminergic VTA neurons, but higher levels of PPE-mRNA, part of the extrinsic facilitating input to these neurons [448].

These behavioural and neurochemical differences are accompanied by differences in activity of the hypothalamic–pituitary–adrenal axis (HPA), the system primarily activated under stressful situations. Animals designated as HR have higher novelty-induced corticosterone secretion compared to LR rats [446], and self-administration of amphetamine is positively correlated with corticosterone levels after two hours of exposure to stress [446]. The work of Piazza and his colleagues suggests that individual differences in vulnerability to addiction can be modelled in animals, and that these differences are related to altered structure and function of the DAergic and HPA systems. Nonetheless, the developmental cause of these behavioural and neural differences is not known.

6.3 Environmental influences on the developing brain

Environmental experience may contribute to individual differences in vulnerability to drug addiction. Early adverse experience, such as childhood sexual or physical abuse, is one of the most important biological and environmental factors that are associated with vulnerability to substance abuse [449]. The prevailing view is that these stressors influence the development of neural systems that underlie the expression of behavioural and endocrine responses to stress and reward. Although clinical data confirm a relationship between early adverse experience and substance abuse, it is not known whether this relationship is direct or indirect. Recent developments using animal models of early adverse environmental experience have been important in elucidating the causal nature of this relationship.

6.4 Effects of disrupted maternal care

One animal model of early adverse experience takes the form of disrupted maternal care, whereby infant rats experience repeated episodes of prolonged maternal separation (MS) during the first two weeks after birth. This consistently gives rise to profound behavioural, neural, and endocrine differences in adult animals. It leads to increased behavioural reactivity in response to stressors [450-452], and these behaviours are accompanied by altered structure and function of neural regions involved in HPA activation [453-456].

Recent work using these models has attempted to form a causal relationship between disrupted maternal care, reactivity to stressors, and individual differences in susceptibility to drug self-administration [457]. The data suggest that such separation leads to alterations in reward-related behaviours, such as a blunted response to both negative and positive contrast effects [458], attenuated locomotor activity to both a novel environment and *d*-amphetamine [459], and, in maternally separated females, blunted acquisition of a conditioned anticipatory locomotor response to food [460]. MS rats also show altered acquisition and maintenance of cocaine self-administration when tested as adults, with dose and gender-dependent effects [460], and other studies report enhanced acquisition of cocaine self-administration [461]. These behaviours are accompanied by structural differences in the mesolimbic DA system [462]. One recent finding demonstrates that maternal separation leads to an enhancement of both stress-induced sensitization to amphetamine and acute Acb DA release following stress and cocaine [463]. This study also reported increased levels of D3 receptor m RNA in the AcbSh, but not AcbC, of MS rats.

These findings dovetail nicely with data from a nonhuman primate model of disrupted maternal care. When infant rhesus macaques are peer-reared (PR), rather than mother-reared, they exhibit a constellation of neurobehavioural dysfunctions at adulthood, such as reduced exploration and increased fear-related behaviours [464], as well as marked increases in HPA activity following stressful situations [465]. PR rhesus macaques consume more alcohol than mother-reared subjects, but interestingly, acute stress in the form of social separation increases alcohol consumption in mother-reared animals to the level of their PR counterparts [466]. Excessive alcohol consumption in PR animals also correlates positively with plasma cortisol levels [466] and negatively with CSF 5-HIAA concentrations in infancy and adulthood [467]. An interesting recent finding is that a functional variant of the rhesus serotonin transporter-linked polymorphism (rh5-*HTT*LPR) interacts with rearing condition and gender to influence adrenocroticotropic hormone (ACTH) response to stress [468], suggesting differential sensitivity to stress dependent upon a gene-environment interaction.

6.5 Effects of social isolation

Converging evidence suggests that early adverse social experience, like maternal separation, may influence susceptibility to the effects of drugs. Like maternal separation, isolation rearing of infant rats (housed singly in small, opaque cages) leads to disruptions in a variety of reward-related behaviours when these animals are tested as adults. Isolation-reared rats show enhanced stereotypy to *d*-amphetamine and apomorphine [469; 470], are more sensitive to the effects of negative and positive contrast in sucrose intake tests [471], and show increased locomotor activity following administration of psychostimulants [472; 473]. It is also noteworthy that these animals show sustained hyperactivity in a novel environment [462], a finding that converges with data from the maternal separation and HR/LR models. Isolation rearing also increases self-administration of a variety of abused drugs [471; 474-479], depending on dose, being more sensitive to low doses [480-484]

Isolation rearing also alters the structure and function of regions involved in drug reinforcement. It leads to a reduced DOPAC/DA turnover in the frontal cortex, but a

larger turnover in the Acb and striatum [485-487]. Isolation rearing also leads to decreased opiate receptor binding in the frontal cortex, hippocampus, periaqueductal grey, and striatum [488; 489], downregulation of 5-HT in the hippocampus [483; 486; 487; 490-495], and upregulation in catecholamine systems in the Acb [483; 487; 496-501].

6.5 Protective effects of enriched environment

There is some suggestion that the behavioural and neural deficits observed following social isolation rearing or maternal separation may be reversed or altered by some period of enrichment rearing in which the animal is housed in a large, socially and environmentally complex environment. In one recent study, C57BL/6 mice, an inbred strain considered 'addiction-prone' (see below), were more resistant to both cocaine and MPTP following enrichment rearing, and showed different patterns of *c-fos* expression in the striatum compared with mice raised in standard conditions. Further, after MPTP treatment, enriched mice showed less DA loss, less DAT binding, and increased BDNF expression in the striatum [502]. In another instance, environmental enrichment during the peripubertal period completely reversed the effects of maternal separation on both HPA and behavioural responses to stress, with no effect on CRF mRNA expression [503].

6.7 Effects of early drug exposure

Another important question is whether early exposure to drugs of abuse can influence individual differences in propensity to drug addiction. It is well established that prenatal exposure to cocaine, heroin, marijuana, nicotine, and alcohol can have profound effects on cognitive and motor function in adolescence and adulthood [504-509], and there is some suggestion that this exposure influences propensity to addiction [506; 507; 510; 511]. However, longitudinal or retrospective clinical studies are often problematic due to the high incidence of confounding variables. Thus, animal models are important in elucidating the individual contribution of early drug exposure to adult vulnerability to addiction.

Data using animal models suggests that prenatal drug exposure has a profound effect on behaviour and neurochemistry when these animals are tested as adults and that these changes may predispose to addiction. Converging evidence using a variety of techniques suggest that prenatal exposure to alcohol [512-514], nicotine [515-517], opioids [518; 519], or cocaine [520-525] produces persistent cognitive and neural deficits in adults. In particular, these data suggest that prenatal exposure to drugs of abuse leads to downregulation and tolerance in neural systems involved in drug reward.

Although these changes may indirectly influence propensity to addiction, only a few studies have addressed the question of whether prenatal exposure to drugs of abuse affects later drug self-administration. Prenatal cocaine exposure in rodents increases intravenous self-administration for moderate doses of cocaine [526; 527], but the rate of cocaine intake does not differ between cocaine and saline-exposed animals [527]. This result suggests that prenatal exposure to cocaine does not alter the reinforcing value of cocaine, a finding that is consistent with a study examining addiction-prone versus addiction-resistant rat strains [528]. Another important question is whether prenatal exposure to drugs of abuse facilitates the development of drug dependence in general. In one study, prenatal exposure to morphine enhanced rates of heroin and of cocaine self-administration [529].

Adolescence is another period during which the brain undergoes many complex changes that can have a prolonged impact on decision-making and cognitive processes [530; 531]. In addition, adolescents are more likely to experiment with illicit drugs, which may be due in whole or in part to the increase in sensation and novelty seeking that is characteristic of adolescence [532]. Recent clinical data suggest that adolescent exposure to drugs of abuse is associated with increased risk of addiction in adulthood [533; 534].

Not unlike the data from prenatal exposure papers, studies using animal models suggest that rodents with adolescent exposure to drugs such as methylphenidate [535; 536], nicotine [516; 537-539], cannabinoids [540], MDMA (ecstasy) [535; 541], and alcohol [542; 543] also show behavioural and neural changes indicative of tolerance to these and other drugs, which persist into adulthood. Adolescent-exposed animals tested as adults show a behavioural and neural profile that is different from adult animals administered a similar drug regime (e.g. [539; 540]). This suggests differential long-term neuroadaptive responses to drugs, possibly related to immature or still-developing plasticity mechanisms in the PFC. One potential confound for these studies is that the majority of them look at effects of non-contingent drug administration during the periadolescent period on later adult behaviour and neurochemistry. Future studies should aim at exploring how self-administration drug experience during adolescence influences drug-mediated behaviours and neural changes when tested in adulthood.

6.8 Genetic factors involved in vulnerability to addiction

Individual differences in genetic make-up critically influence susceptibility to addiction. Although some aspects of vulnerability may to unique for specific substances, most known genetic influences are common to all drugs of abuse. Recent estimates suggest that genetic components explain 40-60 per cent of overall vulnerability to addiction [544-546]. These data do not support single-gene models for the inheritance of addiction vulnerability. Contributions from allelic variations in several genes are likely to be involved. Genetic components do not necessarily impact upon the initiation of drug use, but instead influence progression from regular use to dependence [544; 546]. Recent data are yielding information on which chromosomal regions, genes, haplotypes, and allelic variants provide exactly what genetic influence on vulnerability to drug abuse.

Although there are numerous candidate genes influencing addiction and addictive behaviours, human studies have generally focussed on identifying genes associated with dopaminergic function. A number of studies report a significant association between substance dependence and polymorphisms of dopaminergic receptor genes (DRD1, DRD2, DRD3, DRD4). Subjects with a history of drug use show increased frequency of homozygosity for the restriction polymorphism Dde 1 of the DRD2 gene [547], and several studies have demonstrated a link between the presence of the A1 allele of the DRD2 Taq 1 polymorphism and drug dependence [548-550]. Polymorphisms of the DRD3 gene have recently been identified in 96 rat strains and substrains [551], although there is good evidence that this gene does not play a major role in the genetic vulnerability to alcoholism [552; 553]. Novelty-seeking, a personality trait often observed in addicts, is significantly associated with the 7-repeat allele of the DRD4 exonic polymorphism [554].

Individual differences in genetic polymorphisms have functional outcomes. Individuals homozygous or heterozygous for the 7 (or longer) repeat allele (DRD4 L) report significantly higher craving after consumption of alcohol compared to individuals classified as DRD4 S [555]. Further, although olanzapine reduces craving for alcohol in both DRD4 S and DRD4 L individuals, it only reduces cue- and alcohol priming-induced craving in DRD4 L individuals [556].

6.9 Animal models used in the study of genetic neurovulnerability to addiction

The role of genetic factors in contributing to drug-related behaviours can be examined using inbred rodent strains, which, in contrast to outbred strains, provide a stable genotype. Two inbred rat strains that differ in responses to drugs of abuse are Lewis (LEW) and Fischer 344 (F344) rats. In comparison to F344 rats, LEW rats show greater behavioural responses to several drugs, including oral self-administration [557-559], intravenous acquisition of self-administration of morphine [560] and cocaine [561], place conditioning [562; 563], and locomotor sensitization [563; 564].

These strains also differ in properties of their mesolimbic DA systems. LEW rats have lower basal extracellular DA metabolite levels in the Acb [564; 565] and lower numbers of spontaneously active DA neurons in the VTA [566]. They also show a more prolonged elevation of DA levels in the ventral striatum following acute cocaine administration [564; 565]. At a biochemical level, LEW rats express higher levels of tyrosine hydroxylase in the VTA, but lower levels in the Acb, than F344 rats [567]. Finally, strain differences are also observed in HPA function. Although F334 have higher basal and stress-induced levels of glucocorticoids, LEW rats show a more prolonged elevation of corticosterone following exposure to a stressor [568].

Differences in susceptibility to the reinforcing properties of cocaine, amphetamine, morphine and ethanol have been described among inbred strains of mice [569-572]. A number of studies have demonstrated that mice belonging to the inbred strains C57BL/6 (C57) and DBA/2 (DBA) differ in their behavioural and neural responses to drugs of abuse [570; 573-578]. The data suggest that the C57 genotype can be characterized as 'drug-preferring' and the DBA genotype as 'drug-resistant'. Sensitivity to the unconditioned locomotor effects of amphetamine [569] and level of locomotor activity in a novel environment [576] are both susceptible to the influence of environmental manipulations such as food restriction when measured in these strains. These data provide information on genetic-experience interactions, and suggest a possible homology between these phenotypes and psychostimulant-induced place preference [576].

6.10 The influence of gender on vulnerability

Epidemiological data suggest a greater prevalence of substance use disorders among men, but recent surveys show increased rates of substance dependence in women [579; 580]. These reports are supported by recent evidence that drug-dependent women are more vulnerable to the deleterious effects of drugs and show a faster progression to drug dependence. Women have a more pronounced subjective response to psychostimulants [581-583], become more rapidly addicted to cocaine, heroin, and alcohol [584-587], and experience greater perceived severity of withdrawal from addictive substances such as nicotine [588]. Additionally, despite often having a shorter experience with drugs of abuse than men, substance-dependent women show either a comparable or increased severity of addiction [589; 590], as well as a faster progression to treatment entry [591].

Analogous differences are observed in experimental animals. Female rats show enhanced acquisition, but not necessarily maintenance, of drug-taking behaviour [592-595], and increased vulnerability to relapse [596; 597]. Although there are consistent sex differences during the acquisition phase of stimulant self-administration, the data are more equivocal with other abused drugs [598]. The discrepancies may be due in part to dose differences. Sex differences are more apparent when low doses are used [587; 594; 599]. In maternal separation, peer-reared, and social isolation models of early adverse environmental experience, female rodents show different behavioural and neural effects [452; 600; 601].

The nature of sex differences in vulnerability to drug abuse is not known. Although it is probable that psychosocial factors have an impact, converging evidence from animal studies suggest that fluctuating ovarian hormones have an important role in these differences. There is little experimental work done in this domain in humans, apart from the finding that the subjective response to amphetamines is increased during the follicular phase of the menstrual cycle [602; 603]. In rats, cocaine self-administration varies across the oestrous cycle [604], and high doses of oestradiol facilitate cocaine self-administration [605]. Moreover, the enhanced acquisition of cocaine self-administration in female rats is abolished in ovariectomized animals, but can be reversed with administration of oestradiol [606]. These data suggest that oestogens facilitate dopaminergic function [607-609].

7. HARMS CAUSED BY DRUGS OF ABUSE

It is almost axiomatic that a suitably high dose of a psychoactive substance, administered either acutely or chronically, is likely to have deleterious effects. These can be transient or long-lasting, and impact on one or more of the body systems, including the brain itself. When the effects involve brain regions implicated in volition and executive control, such as the PFC, such damage may exacerbate the drive to abuse and addiction and retard attempts at rehabilitation.

Types of drugs vary in their toxicity. This issue is crucial to the regulation of drug use, but the definition of adverse drug effects is difficult and controversial. It is sometimes problematic to infer the causal effects of psychoactive substances in polydrug abusers and to distinguish them from possible premorbid factors present in the user prior to drug use. Studies in experimental animals which control the exposure to specific doses of particular drugs [e.g. 610; 611] avoid many of these difficulties, but may be compromised by the difficulty of comparing drug doses between species and selecting for investigation the doses most relevant to human drug users. Moreover, when the studies are limited to the influence of sensitising regimens of drug administration on fine details of neuronal organization, such as dendritic branching in different regions of the rat PFC, the effects are sometimes apparently inconsistent with toxic effects, reflecting instead possible effects on neuronal plasticity. Thus, repeated treatment with psychostimulant drugs produces long-lasting increases in dendritic branching and spine intensity in some brain regions [612]. However, it has also been reported that such effects subsequently limit the promotion of synaptic plasticity bestowed by housing in enriched environments [613]. Functional imaging studies of human abusers may likewise reveal abnormal patterns of brain activation (see Section 8.1.2), but in the absence of evidence of cognitive impairment in neuropsychological tests, the significance of these may be unclear.

Notwithstanding these difficulties, much is now known about the toxic sequelae of chronic drug use, whether on the brain itself or on behaviour and cognition, based on the evidence of post-mortem neuropathology, neuroimaging and neuropsychology [614] (see also Section 8). Thus, among the stimulant drug class, high doses of methamphetamine can produce long-term neurochemical and structural changes, including neurotoxic effects on DA- and 5-HT-containing neurons in several animal species [615; 616]. It also reduces markers of DA and 5-HT function in the human brain, *post mortem* studies indicating a reduction in the striatal DAT and reductions in 5-HT markers within the OFC [617]. This evidence is complemented by recent evidence of changes in striatal markers following chronic cocaine self-administration in monkeys (Figure 4) [279; 280]. However, an abiding question is whether such changes are permanent and whether they generalize to drugs of the same class, such as d-amphetamine and cocaine. It appears that chronic exposure to these agents can be associated with loss of grey matter in the PFC, impaired signs of brain activation in functional imaging, and impairment in certain aspects of cognition, including memory and executive function [125]. Similarly, the balance of evidence indicates some toxic effects of MDMA ('ecstasy') on 5-HT neurons based on studies using different techniques on rats, monkeys and humans [618; 619]. It may be significant that, in monkeys self-administering (generally lower) doses of MDMA, such toxic effects are much weaker [620]. However, assessing the possible functional significance of these effects is elusive because of considerable heterogeneity of the chronic drug-abusing population. Recent findings indicate that a genetic polymorphism of the 5-HT transporter is associated with pathological scores on a clinical rating scale of depression in a group of chronic MDMA users [621]. Ecstasy abuse is also associated with a pattern of cognitive impairment, which however is subject to the caveats noted above [614].

There is little doubt about the potential devastating effects of chronic alcohol abuse on brain function. Alcohol dementia is a clearly-defined syndrome associated with structural brain changes [622; 623]. Among the main actions of alcohol are the enhancement of GABA-ergic transmission in combination with a reduction of glutamatergic (including NMDA

receptor) function [2], which are likely to promote sedation and impair learning and memory in regions such as the hippocampus. There is also conclusive evidence of foetal alcohol syndrome (FAS) produced by heavy drinking in pregnancy that leads to a pattern of physical malformations and mental retardation. Indeed, with an prevalence rate of about 0.2 per cent in all live births (6 per cent of alcoholic mothers) reported in the US [624], FAS is one of the leading causes of mental retardation. Recent experimental evidence suggests that exposure to alcohol in developing rats led to severe reductions of glutamate receptors of the AMPA subtype in the neocortex [625] (see also section 6.7). These adverse actions on the brain and intellect, as well as the social burden of domestic violence arising from the heightened aggression produced by abuse, and overall greater morbidity and mortality, place alcohol among the most behaviourally toxic of all psychoactive substances. However, not all alcohol consumption has adverse effects. There is consistent evidence of significant beneficial health effects of drinking alcohol (and associated substances such as the polyphenols of red wine) in small amounts which reduce the incidence of strokes and dementia [626].

By contrast with alcohol, the evidence for deleterious cognitive effects of cannabis intoxication is controversial. Any significant effects may depend on chronic use over many years in that small sub-population of users who become addicted [614]. However, accumulating evidence suggests that cannabis can act as a triggering factor for schizophrenia [627].

8. DRUG ADDICTION: A SOCIAL COGNITIVE NEUROSCIENCE PERSPECTIVE

Until recently, the gap between social cognition and molecular and cellular neuroscience has seemed unbridgeable given the complexities of linking social constructs such as theory of mind with simple causal neural networks [628]. However, the emergence of cognitive neuropsychology in the 1970s illustrated the potential of a productive synthesis of cognitive psychology and clinical neuroscience in addressing common questions of how the mind/brain works. Cognitive neuroscience will continue to prove important in the objective evaluation of cognitive effects of drugs and the intellectual sequelae of chronic drug use. A similar initiative in 'social cognitive neuroscience', embracing developments in 'affective neuroscience' and 'neuroeconomics' promises to be of considerable importance for understanding the nature of addiction in its social context.

Social cognitive neuroscience (SCN) is a systematic and theoretically driven approach designed to understand social and emotional phenomena in terms of the interaction between motivations and social factors that influence behaviour, information-processing mechanisms that underlie social-level phenomena, and the brain mechanisms that instantiate cognitive-level processes [628-631]. The concern with neural substrates underlying normal social cognitive mechanisms links social neuroscience to the basic neurosciences and has been facilitated by the increasing availability of methodologies for investigating neural function in non-brain damaged adults. SCN bridges the gap between social cognition and neuroscience by exploring how the brain influences social process as well as how social processes influence the brain [632]. Of particular interest is the issue of whether the processes that give rise to social cognition are a subset of more general cognitive operations, or whether instead there are unique processes governing social cognition [628; 629].

Although still in its infancy, the social cognitive neuroscience approach has already been successfully applied to a broad range of topics in the social sciences [628] and neuropsychiatric conditions which potentially include addiction [633]. It is proving possible to elucidate the neural and cognitive mechanisms underlying more complex social constructs such as volition [634]; attribution theory [628; 635; 636]; self regulation [637]; cognitive reappraisal [638]; attitudes [636]; mental representation of self [639; 640]; reward [641]; beliefs [642]; emotions [643; 644], deception [645]; empathy

[646]; theory of mind [647]; cognitive control [648]; intuition [649]; moral emotions [650] and complex social and economic judgements such as decision-making [651; 652].

8.1 Addiction as a disorder of social cognition

Viewed as a complex brain disorder, it is possible to consider the main behavioural characteristics of drug addiction in terms of at least four impairments of social cognition:

8.1.1 Impairment in the processing and representation of saliency or rewards. Many modern theories of drug use and dependence assign central prominence to the role of compulsive craving in drug use and relapse. Until recently it was believed that addiction was predominantly driven by reward processes mediated by limbic circuits [653]. However, results from recent neuroimaging studies implicate a highly interconnected network of brain areas including orbital and medial PFC, amygdala, striatum and dopaminergic mid-brain in reward processing (see Sections 3 & 4). Distinct reward-related functions can be attributed to different components of this network. The OFC is involved in coding stimulus reward value and in concert with the amygdala and ventral striatum is implicated in representing predicted future reward. These frontal areas are frequently activated in addicted subjects during intoxication, craving, and bingeing, but deactivated during withdrawal [654; 655]. The same regions are also involved in higher-order cognitive and motivational functions, such as the ability to track, update, and modulate the salience of a reinforcer as a function of context and expectation and the ability to control and inhibit prepotent responses. Cognitive theories have been influential by embedding craving within a network based on social learning theory [656; 657]. According to Goldstein and Volkow [658] these results imply that addiction involves brain areas involved in several cortically regulated cognitive and emotional processes including "the overvaluing of drug reinforcers, the undervaluing of alternative reinforcers, and deficits in inhibitory control for drug responses" .

8.1.2 Impairment of social reasoning and decision-making. The PFC has been implicated in guiding social cognition (decision-making and inhibitory control) by eliciting emotional states that serve to bias cognition, a role that is further supported by investigations of normal decision making and social reasoning studies [628]. The effects of damage to medial and orbital PFC are consistent with a role for these regions in guiding the strategic adoption of someone else's point of view [647] and impaired performance in reasoning about social exchange [659]. Compromised decision-making could contribute to the development of addiction and undermine attempts at abstinence. The behaviour of those addicted to drugs could be viewed as demonstrating faulty decision-making given their inability to discontinue self-destructive drug-seeking behaviours. A go/no-go response inhibition task in which working memory demands were varied [660; 661] demonstrates that the compromised abilities of cocaine users to exert control over strong prepotent urges were associated with reduced activity in both anterior cingulate and right prefrontal cortices. The results suggest a neuroanatomical basis for this dysexecutive component in addiction, supporting the importance of cognitive functions in prolonging abuse or predisposing users toward relapse. Abnormalities in the PFC are found consistently in most drug-addicted subjects using imaging studies [658; 662; 663]. Thus, one might expect that the disruptions of self-monitoring and decision-making processes observed in drug-addicted subjects [125; 664] might possibly arise from drug dependent disruption of these prefrontal functions. However, as described in Section 7, an alternative possibility is that the deficits are not a consequence of drug-taking, but that both arise from premorbid changes in the PFC. Furthermore, it is even possible that the drug-taking behaviour might arise from a propensity to self-medication.

8.1.3 Impairment of voluntary control. The issue of volition is central to social cognition since most consider the willed action as essential to social democracy and to social

constructs such as guilt, responsibility, accountability, law and sanctioning deviant behaviour. Drug addiction is typically portrayed as a compulsive drive to take drugs despite awareness of serious adverse consequences. The self-perceived 'loss of control' where the addict seems unable or unwilling to control their drug use is traditionally viewed as 'voluntary' despite studies showing long-lasting changes in the brain that could compromise crucial elements of the volitional system [665-667]. Campbell [668] has argued that addiction should be considered a disease of volition caused by a cognitive impairment involving an inability to recall the negative effects of the addictive behaviour.

Historically however, the construct of 'will' has been generally defined as the capacity to choose what action to perform or withhold [669] and in a recent review Zhu [670] distinguishes three stages of volition: the mental act of decision-making; the mental act of initiating voluntary action; and the mental activity of executive control. According to Zhu [670] the essential engagement of the ACC in all three types of volition suggests a pivotal role in sustaining the volitional function. Other imaging studies implicate PFC, SMA and lateral PFC [669; 671].

Dysfunction in these regions has been associated with neuropsychiatric disorders of action including hysterical weakness, alien hand and schizophrenia [671; 672] and have also been found in relation to issues of deception and malingering [645; 673]. Spence and Frith [634] suggest that dorsolateral PFC and the brain regions with which it is connected are essential to performing willed action, and that diseases or dysfunction of these circuits may be associated with a variety of disorders of volition, such as Parkinson's disease, 'utilization' behaviour, 'alien' and 'phantom' limbs, delusions of 'alien control', and the passivity phenomena of schizophrenia.

The issue of impaired volition raises possible ethical issues about the capacity of addicted persons to give "free and informed" consent to participate in studies that involve detecting neural abnormalities in addiction and treatments designed to reduce their addiction. Research involving persons who are cognitively or physically impaired in their decision making or volitional control would require special ethical consideration [674] because they may not be capable of providing informed consent. The view among addiction researchers has been that drug-dependent people are able to give free and informed consent to participate in research studies and clinical trials so long as they are not intoxicated or suffering acute withdrawal symptoms at the time that they give consent [675-677]. However Cohen [678] controversially argues that "the nature and pathology of untreated substance dependence make the condition inherently incompatible with a rational, internally uncoerced and informed consent on the part of those volunteering to receive addictive drugs in a non-therapeutic research setting".

8.1.4 Impairment of awareness of the serious adverse consequences. Drug-addicted individuals use drugs despite apparently knowing the long-term physical and psychological consequences. Rinn *et al.* [679] tested the hypothesis of this lack of apparent awareness by suggesting that it was a product of cognitive failure rather than an emotion-driven rejection of the truth. In their study they found persistent denial to be significantly correlated with greater impairment of executive function, verbal memory, visual inference, and mental speed. Self-awareness deficits are common after traumatic brain injury [680] and reflect a person's "inability to recognise deficits or problem circumstances caused by neurological injury" [681]. Such awareness disorders are believed to reflect a complex interaction between neurological, psychological and social factors depending on lesion location and cognitive dysfunction [680].

9. THE MIND/BRAIN INTERFACE: NEUROBEHAVIOURAL ECONOMICS OF ADDICTION

9.1 Basic principles of behavioural economics

Behavioural economics, a merging of traditional economic theory with psychological studies of choice [682; 683], offers different perspectives on addiction. Much of economics is based on utility theory [25; 684], which assumes that agents are rational and exhibit certain reasonable attributes of preference. For example, one assumption is transitivity of preference: if an agent prefers A to B and B to C, then it must prefer A to C or it would easily be exploited by more rational agents. Given these assumptions, there must exist a utility function that assigns unidimensional values to real-world multidimensional events or outcomes, such that the agent prefers outcomes with higher utility. Psychologically and neurally, a similar process must also happen [685] if only to decide access to motor output. Agents can then use their knowledge about the world, and about the consequences of their actions (which may be uncertain), to act so as to maximize their expected utility [686]. Rational behaviour need not require complex, explicit thought. Conversely, if people are logical, then we can infer their value system by observing their behaviour [687; 688].

A direct application of traditional economics to addiction is the calculation of elasticity of demand for goods, such as drugs. In a barter economy, and therefore in animal experiments, the 'price' of a commodity has no absolute meaning. We can speak of price only in terms of what other commodities an animal will give up to obtain the good, and that may depend on the specific commodities being traded [118; 687; 689]. In humans, elasticity has a more general meaning, since humans use a monetary economy. Money is a single commodity that is substitutable for almost all others (fungible), so we can calculate elasticity as the change in consumption as money price changes. Elasticity is defined as the proportional change in consumption divided by the proportional change in price. Elasticity is usually negative (we consume less as price goes up), so elasticities between −1 and 0 represent relatively 'inelastic' demand (consumption is not reduced much by price increases) and elasticities below −1 represent relatively 'elastic' demand (consumption is strongly affected by price).

9.2 Addiction in behavioural economic terms

An obvious way to think about addiction is that demand for drugs is inelastic compared to demand for other things. The more someone is addicted, the more inelastic their demand is — they will therefore sacrifice other commodities (work, money, social interaction) rather than sacrifice the drug. Alcohol demand in rats can be more inelastic than demand for food [690; 691]. Yet drug demand is not completely inelastic, and addiction is not an all-or-nothing phenomenon. Most users of heroin, cocaine, and alcohol do not use extremely large amounts, as the stereotype of an addict would suggest. Instead, most use infrequently, or 'chip' [692; 693]. Furthermore, over 75 per cent of those dependent on an illicit drug recover [694; 695]. In fact, the elasticity of demand for cigarettes is typically about −0.4 [696; 697] — that is, if the price goes up by 10%, consumption goes down by 4%. When the price goes up, some people quit altogether and others smoke less. As for most commodities, elasticity varies with price: smokers working for cigarette puffs in the laboratory are fairly inelastic when the price is low (ε = −0.56), but become more elastic when the price goes up (ε = −1.58) [698; 699]. Probably for this reason, elasticity is greater for poorer smokers, for whom cigarettes are proportionally more expensive [697]. In the UK, elasticity of demand for alcohol varies from −1.69 for wine through −0.86 for spirits to −0.76 for beer [700]. Participation price elasticities (the effect of price on the number of people using a drug) are about −0.90 to −0.80 for heroin and −0.55 to −0.36 for cocaine. Overall elasticities (the effect of price on the total amount consumed) are about −1.80 to −1.60 for heroin and −1.10 to −0.72 for cocaine [701]. Elasticity also varies with motivational state and other factors. Animals' demand for food is more inelastic when they are hungry and if there are no alternative ways of obtaining food

[702]. Similarly, demand for cigarettes is more inelastic when smokers have been abstinent [703]. From a policy perspective, it is also important to consider cross-price elasticity. If a policy reduces consumption of drug A, will the benefits be mitigated by increased consumption of drug B? In the case of alcohol and cigarettes, the two are either complements ($\varepsilon < 0$) or independent, so reducing consumption of one tends to reduce (or not affect) consumption of the other [697]. Similar analyses have been conducted for other drugs and non-drug reinforcers [704].

9.3 Irrationality and its consequences for addiction

Some economists have described addiction as rational [109], in that addicts take the future consequences of their behaviour into account and have stable preferences. In rational addiction theory, addiction arises because the quantities of the addictive good consumed at different time periods are complements, which can lead to unstable states. This accounts for binges of consumption. Assuming rationality allows us to predict behaviour much better than not assuming it unless we can predict the specific way in which people will be irrational [687]. A contribution of rational addiction theory [109; 110] was therefore to consider price as a major influence on the consumption of addictive drugs [705]. However, the premise that drug addicts choose rationally, maximizing their total happiness, has been criticized [119; 705; 706]. Certainly, humans do not always choose according to rational norms. They deviate from the optimum when making decisions [707-710] because human cognitive abilities are limited ('bounded rationality') and because people frequently make choices that are not in their long-term interest ('bounded willpower').

In particular, humans and animals do not discount the future in a consistent way [111; 113]. It is rational to value future rewards somewhat less than immediate rewards (Figure 5a). Steep temporal discounting (temporal 'myopia' or short-sightedness) leads to short-termism and impulsive choice (Figure 5b). The shape of the temporal discounting function is also very important (Figure 5c). Simple economic models assume exponential temporal discounting, which leads to preferences that are temporally consistent (what is preferred at time x is also preferred at time y). But animals and people actually exhibit hyperbolic temporal discounting [113; 711-714]. This leads to preferences [111-113; 715] that depend on when a choice is made (preference reversal; Figure 5d). Therefore, many major behavioural economic theories of addiction [111-117] emphasize that addiction results from the maximization of short-term rather than long-term utility [118; 705], with preferences that are inconsistent over time thanks to hyperbolic discounting, and that drug addictions [689] are bad because short-term selection of drugs leads to lower long-term overall utility. Consumption of drugs reduces the value of future activities — the 'primrose path' to addiction (Figure 6). Knowing that one is predisposed to be temporally inconsistent allows the use of self-control strategies [111; 119; 716], such as precommitment to a particular course of action, which improve long-term utility.

Economic theories of addiction are also relevant when considering the extent to which drug use is voluntary. The diagnostic criteria for drug dependence [256] include a compulsion to take a drug, yet drug use can be voluntary. Drug use certainly has utility to the user; this may be in the form of euphoria, enhanced social experiences, or enhanced intellectual performance [2]. It is debatable whether even addicts take drugs involuntarily. Just because someone says they don't want to smoke and then later smokes doesn't mean they're smoking involuntarily — it might simply be that they're inconsistent [717; 718]. Furthermore, not everyone who smokes wants to give up. Appreciating these differences leads to a broader classification of addiction (Figure 7).

The fact that people do not act to maximize their total long-term expected reward can explain a number of otherwise counterintuitive results. For example, cigarette taxes can make smokers happier [719] because they serve as a valuable self-control device, helping them to avoid smoking. Such self-control strategies are not merely a human phenomenon [720-722]. Such short-termism can explain relapse [695]. Since one cigarette doesn't

cause cancer and one shot of heroin doesn't condemn you to a junkie lifestyle, a person can correctly reason that since it's 'just for one last time', the drug is the better choice. A series of 'one-last-times' is a relapse.

9.4 From behavioural economics to neuroeconomics

Research into the neural basis of decision-making and the way the brain processes economic variables is a large field. Some studies have sought neural correlates of utility [685] or hedonic evaluation [723] directly. Others have attempted to map the neural structures corresponding to psychological processes such as action–outcome contingency evaluation [215; 216], instrumental incentive value [724], stimulus–response habits [276; 725], and PIT [160; 174; 205; 209]. Lesions have also been used to establish the contribution of different brain structures and neuromodulators to choices between reinforcers differing in size, probability, delay, or the effort required to obtain them [157; 207; 726-738], while imaging studies have correlated human preferences with the activation of specific brain regions [240; 277; 739]. However, some basic psychological principles remain unknown. We have not discovered how the hyperbolic temporal discounting process operates neurally, or whether hyperbolic discounting is explicable as the overall effect of two different systems — for example, a cognitive, declarative system that exhibits minimal or exponential discounting, plus phenomena such as PIT or 'visceral factors' that make rewards more salient and promote their choice when they are immediately available [740-743]. Recently, such a two-factor model was used in the analysis of a functional magnetic resonance imaging (fMRI) study of choice involving rewards differing in magnitude and delays, with delays ranging from less than a day to six weeks [744]: lateral prefrontal and intraparietal cortical regions were activated independently of the delay, and were suggested to be part of a system that evaluates both immediate and delayed rewards according to a rational temporal discounting system, while limbic regions including the ventral striatum and medial OFC were preferentially activated by the relatively immediate rewards, and were suggested to be part of a system that promotes the choice of imminent rewards without consideration of delayed alternatives. These limbic regions were more likely to be activated than the 'delay-independent' areas by trials in which an earlier reward was chosen. A knowledge of the operation of these neural systems may offer opportunities for pharmacological treatment of addiction [745], but probably would not change the fact that the simplest and most powerful way to influence these neural systems is often through conventional economic tools [692].

10. FUTURE IMPLICATIONS: NEW DRUGS, THEIR IMPACT AND MANAGEMENT

10.1 Predicting further drugs of abuse

Abused drugs of the future are likely to arise from:

- refinement of the properties of known drugs
- synthesis of novel therapeutic compounds with abuse potential, such as euphorigenic or cognition-enhancing effects
- synthesis of drugs acting on newly defined molecular targets, especially within relevant areas of the brain such as the reinforcement ('reward') system and cortical areas devoted to cognitive or affective processes.

10.1.1 Refinement of the properties of known addictive or cognition-enhancing drugs

Powerful and effective addictive drugs are readily available. It is not understood whether the very non-selective actions of some drugs, such as cocaine and amphetamine, which affect the release or re-uptake of all the monoamines, enhance or limit their positive effects and therefore their abuse potential. It is frequently assumed that effects on the DA system are of paramount importance in their addictive potential and in mediating their positive effects. If this is the case,

highly selective DA re-uptake inhibitors (a 'super' cocaine) or releasers (a 'super' amphetamine) may have special abuse potential. By contrast, the very non-selective actions of these drugs may underlie their potent effects, in which case novel drugs will have broader, not more selective, actions. Direct agonists at specific receptors mediating the reinforcing effects of drugs by acting within the 'reward system', may also have abuse potential. Direct μ-opiate receptor agonists have exceptional efficacy, but DA receptor agonists are not generally abused, and this may represent a basic difference in the abuse potential of stimulants as opposed to CNS depressants such as opiates. However, DA receptor subtype-selective drugs, e.g. acting at the D3 receptor, may be abused because of their selective actions within key circuitries. Novel non-peptidergic agonists at opiate receptors may also have great abuse potential, particularly if they are devoid of effects at downstream systems mediating tolerance and physical withdrawal. Similarly, non-peptidergic drugs (or drugs from other classes able to penetrate the brain) acting on known peptide transmitter systems within key structures, such as the Acb, may also have abuse potential (e.g. drugs interacting with CCK, neurokinin as well as opioid peptide systems).

One of the key factors involved in addiction is the progressive development of neuroadaptations in the brain which may underlie withdrawal phenomena, impair functioning of specific areas of the brain (e.g. OFC and striatum) and induce persistent and maladaptive forms of learning. Limiting or preventing these neuroadaptations may enhance the abuse potential of known drugs. Thus the newly-introduced CB1 receptor antagonist (rimonobant) may ameliorate opiate withdrawal and also the cognitive impairments and intoxication caused by smoking cannabis. Thus, the acute, positive effects of heroin may be achieved without a severe withdrawal syndrome and cannabis may be smoked with less deleterious effects through use of drugs such as rimonabant. In general, drugs that might prevent long-term neuroadaptations to chronic drug intake could enhance the potential for acute use by reducing the chances of dependence. In particular, combining addictive drugs such as heroin or cocaine with others designed to prevent or reverse neuroadaptive changes in intracellular signalling cascades (Section 5, see also below) may be especially powerful — either as a way of minimizing harm and managing abuse or of countering the adaptations, through tolerance, that minimize the acute hedonic effects. This notion can be seen as a form of 'combination drug use' — rather as heroin and cocaine are already combined by some addicts to limit the adverse effects of one drug while enhancing those of the other (the aversive effects of cocaine and the sedating effects of heroin). There is great potential for combining drugs from different classes to enhance the positive subjective effects and the advent of new agents will amplify this potential.

GABA-A receptor sub-type selective benzodiazepines (BZD) and related compounds are now being developed and have specific effects — e.g. alpha-1 subtype-selective compounds are hypnotic but not anxiolytic; alpha-5 subtype-selective compounds affect cognition, but are not hypnotic or anxiolytic. There is considerable interest in producing specific anxiolytic compounds that not only have no sedative or cognition-impairing effects, but also have no abuse potential — i.e. no euphorigenic effects and no dependence liability. Understanding the mechanisms of BZD dependence may result in the development of more effective anxiolytics, and define the targets for novel BZD ligands with non-anxiolytic abuse potential.

It seems likely that understanding genetic determinants of the responses to drugs will enhance therapeutics by allowing 'individualized' medicine. This may allow individuals to identify their own risks, possibly via counselling, for adverse effects of specific drugs and find drugs that are 'safer' to abuse. This may be achieved in conjunction with information derived from functional markers, such as cognitive test performance and brain neuroimaging. Genetic polymorphisms affecting the 5-

HT transporter can already be used to predict responses to SSRIs and also the likely susceptibility to depression following chronic Ecstasy abuse [621]. Understanding the polymorphisms in genes encoding proteins that regulate the efficiency of chemical neurotransmitter systems is a major goal for future tailored therapeutics, but will also carry the risk of more optimal selection of drugs for abuse by individuals to minimize harm or optimize positive effects.

10.1.2 Novel therapeutic compounds with abuse potential

Intense research activity is directed towards the development of conceptually novel antidepressant drugs. The majority of today's antidepressants are designed to treat depressed mood and sadness, rather than the dysphoria or anhedonia which also characterizes depression. Drugs that reverse these symptoms may therefore have hedonic effects and therefore considerable abuse potential. Indeed, there is a growing interest in pro-dopaminergic drugs to target anhedonia, such as bupropion, which has weak antidepressant effects but is also used to diminish cravings in smoking cessation. But a DA-selective re-uptake inhibitor may both alleviate the apathy and anhedonia of depression while carrying marked abuse potential (see above). Whether such drugs have this potential will depend upon their pharmacokinetic properties, since rapid onset short half-life stimulant drugs are those most readily abused and have greater addictive potential. Thus pro-dopaminergic drugs with more favourable (slower) pharmacokinetics may be effective therapeutically, but have limited abuse potential. CB receptor agonists developed for their analgesic and other properties may carry abuse potential. If they have appropriate pharmacodynamics, they may be safer than smoking cannabis but bring with them the risk of inducing psychosis in vulnerable individuals. Drugs primarily targeted at appetite reduction or weight loss (e.g. CB1 receptor antagonists, leptins) will increasingly become available and may be abused.

It is interesting to speculate whether our knowledge of the modulation of central neurotransmitters (cholinergic, serotonergic and dopaminergic) by dietary manipulation [746; 747] could become sufficiently sophisticated to allow significant subjective or cognitive effects in normal subjects. Similarly, novel drugs that enhance cognition are likely also to carry abuse potential, perhaps especially for short-term advantage under conditions of high demand such as examinations. Such drugs might affect glutamatergic transmission directly or indirectly via cholinergic or catecholaminergic neuromodulation, or by novel mechanisms of action (e.g. modafinil, CREB pathway memory consolidators). However, we do not anticipate major overlap between future recreational drugs and cognitive enhancers for the workplace because of their generally distinct neural domains of action.

10.1.3 Synthesis of novel psychoactive compounds having euphorigenic or cognition-enhancing effects

As indicated in this project's Pharmacology review **(cite Technology Foresight review:** by Morris et al., 2005) new drugs with abuse potential will always be synthesized either by the pharmaceutical industry or by illicit laboratories. Many of these drugs will be directed at known targets but it is likely that new targets will also be discovered — either new chemical transmitters or new receptors ('orphan receptors') that have no known endogenous ligand. The presence of these transmitter systems and novel receptors within the mesolimbic DA system, Acb or limbic cortical areas, such as the orbital pre-frontal cortex that define the neural systems underlying reward, hedonics and addiction, or those underlying cognitive processes, will be especially interesting targets for new psychoactive compounds for therapeutic or recreational use.

10.2 Future management of psychoactive substances: impact of neuroscience and neurobehavioural economics

Addiction is not an all-or-nothing problem, and it will not be sensible to search for a single cure. In the face of predictions of elevated drug use, policymakers should seek methods to reduce consumption and minimize the harm from drug-taking. Focusing only on prevalence (the number of people using a drug) may be inappropriate. A strategy of total harm reduction should also consider ways to reduce the average quantity used and the amount of harm per use.

Many neuroscientific addiction theories focus on the way in which drugs change the brain. As Kelley and Berridge [178] recently noted, drugs may activate the same circuits as natural rewards, perhaps in a more potent manner; they may create new states, such as the motivational state of withdrawal; and they may differentially affect the balance of processes that normally contribute to responding for natural rewards, such as habits, goal-directed actions, and cue-induced motivation. There may be other effects too. Food makes you full and exercise makes you tired, but not all drugs will satiate you to the same extent [695]. Acute intoxication impairs decision-making, so the decision to have the sixth pint of beer may not be made in the same way as the decision to have the first. Chronic use of some drugs may alter the brain so as to impair the ability to make good choices (e.g. [125]). Some forms of brain damage may make you more likely to choose impulsively, maximizing short-term rather than long-term gain [207]. Future treatment strategies will focus on these effects, attempting to reduce drug consumption and reduce the frequency of relapse.

Neuroscientific advances may contribute to the diagnostic process and the matching of treatments to addicts. Techniques ranging from genetics to functional neuroimaging may become useful as a way of predicting which treatments will work best for an individual patient, and in assessing the likely efficacy of that treatment at preventing relapse before the patient is discharged. Both would be important advances.

However, neuroscientific strategies are just one avenue of attack. Once addictive behaviours are recognized to be sensitive to drug price and to the relative value of drugs and other activities, it is clear that many options currently available may be further refined. When treating individual addicts, it is important to realise that neuroscientific strategies will potentially be increasingly interpreted in economic terms, allowing their comparison with other macroeconomic strategies. Pharmacological techniques can already reduce the value of specific drugs. For example, methadone treats opiate withdrawal symptoms and reduces the 'high' produced by concurrently-administered heroin, thus reducing the value of heroin. Heroin prescriptions [748] reduce the value of contaminated, street heroin. Nicotine patches treat nicotine withdrawal, reducing the value of nicotine. Disulfiram alters ethanol metabolism temporarily so that ethanol consumption induces

illness and so reduces the value of alcohol. Vaccination against cocaine is being tried at the moment [749]. This reduces the 'high' and therefore the value of cocaine. All of these can be seen as self-control tactics, and depend on the choices made by the addict. Because the addict would prefer a drug-free lifestyle in the long term, he deliberately adopts a strategy (e.g. taking disulfiram) that reduces the future value of the drug. It is also possible to target the brain's motivational systems directly. Thus, chemicals that reduce drug-seeking in animals (e.g. D3 receptor agents [252]) may be another line of therapy.

Better knowledge of the risks of drug-taking could also help reduce the perceived value of drugs [695], and effective advertising of risk should take advantage of human reasoning biases [750], perhaps by using vivid images of the potential unpleasant outcomes of drug use [751]. Taken to the opposite extreme, overestimation of the risks of drug-taking may also help some people avoid addiction. A personal theory that cocaine use inevitably leads to full-blown destructive addiction might not be true [692-695], but this belief is a self-control device that may prevent some people taking any cocaine [111]. Misinformation is clearly not a useful public health strategy, since the credibility of advisers depends upon providing accurate information, but clear and vivid statements of genuine risks are of value.

Finally, the addict pays for drugs with money and therefore forfeits other alternative commodities, and may also forfeit commodities that cannot be bought with money, such as social support. Therefore, other strategies can be used to treat addiction [689]. For example, making it easier for an addict to obtain substitutes for drugs may in the future be as effective as making it harder for the addict to obtain drugs [689; 752; 753]. Rewarding abstinence directly with money or other tangible rewards also promotes abstinence [695; 754]. Addicts may also learn to use self-control techniques such as pre-commitment to improve their sensitivity to the long term [111].

Neuroscientific research aims to understand the neural mechanisms behind addiction. In the long run, this research is likely to identify a series of molecular mechanisms that operate to promote drug-taking in the addicted brain. Some will prove to be therapeutic targets, for example to reduce drug craving, and may be useful in the treatment of established addiction. Some potential therapies may be specific to the effects of drugs of abuse, but others will not be — for example, reducing strong cravings for all reinforcers, not just abused drugs. The potential to erase drug-related memories selectively [425] might be of substantial benefit if it can be translated to clinical practice. Other molecular markers may indicate individual vulnerability to addiction, indicating to potential users which drugs might be relatively safe to use and which would be likely to lead to strong addictions. Furthermore, techniques may become available to predict which treatments will be best suited to an individual addict by analysing the patient's genetic makeup or neural responses. Thus the most important policy decision to be made regarding the neuroscience of addiction will be how much to spend on research that may lead to treatments, and how much to spend on the treatment of addicts who seek help. However, we predict that the overall level of consumption of addictive drugs, and therefore the harm to society that such drugs cause, will be determined instead by macroeconomic decisions about drug regulation.

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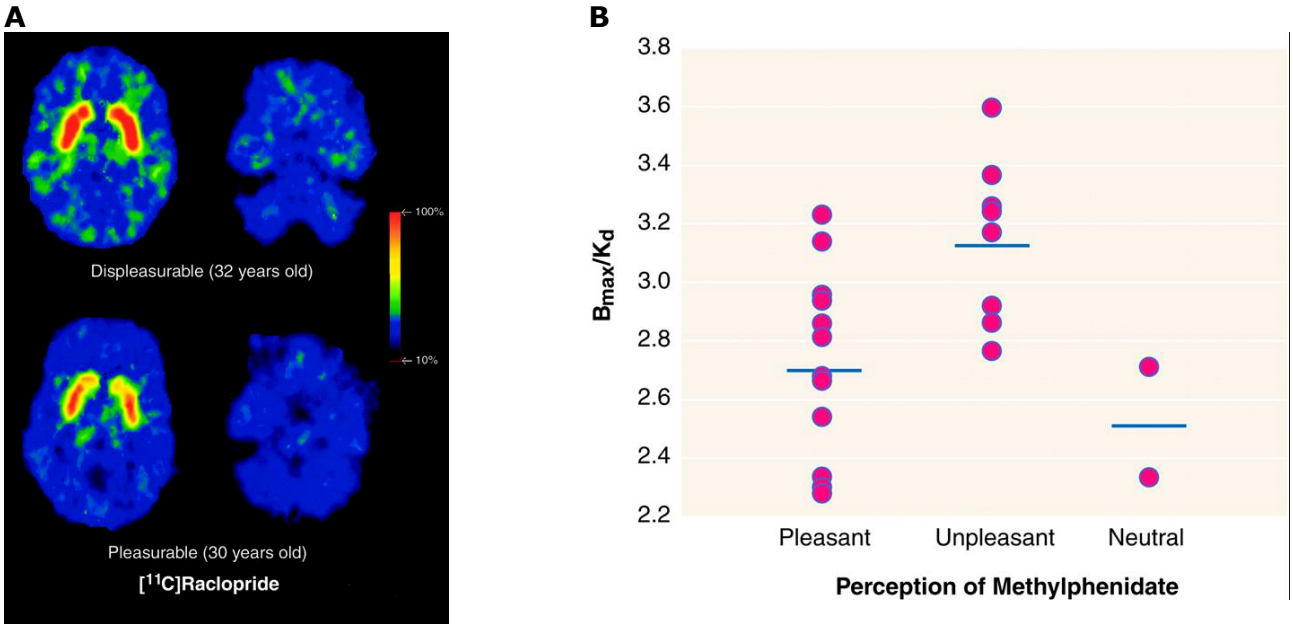

Figure 1

(A) Distribution volume images of [^{11}C]raclopride at the levels of the striatum (left) and cerebellum (right) in a healthy male subject who reported the effects of methylphenidate as pleasant and in a healthy male subject who reported them as unpleasant. 100% = 25 ml/mg; 10% = 0.4 ml/mg. **(B)** D2 receptor levels (B_{max}/K_d) in 23 healthy male subjects who reported the effects of methylphenidate as pleasant, unpleasant, or neutral. B_{max}/K_d values were lower in subjects who reported the effects of methylphenidate as pleasant than in those who reported them as unpleasant. The horizontal lines represent the means for the B_{max}/K_d estimates for the different groups. (From [755].)

FIGURES AND FIGURE LEGENDS

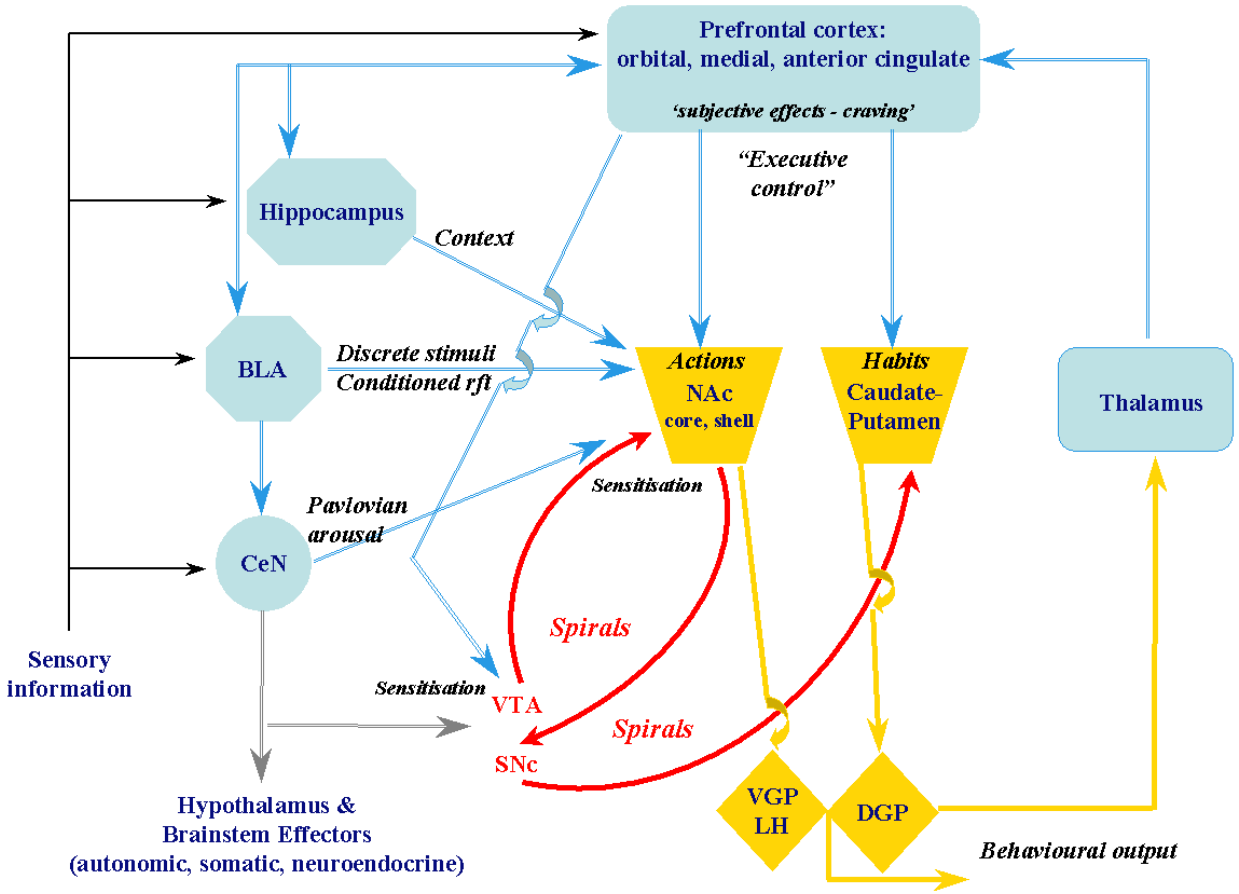

Figure 2

Schematic representation of limbic circuitry including cortex, ventral striatum, and pallidum, that tentatively localizes functions involved in addiction discussed in the text including: (i) processing of discrete and contextual drug-associated conditioned stimuli — basolateral amygdala and hippocampal formation, respectively with a special role of the basolateral amygdala in mediating conditioned reinforcement and the central amygdala in Pavlovian (or conditioned) arousal; (ii) goal-directed actions ('action–outcome' associations) — involving the interaction of prefrontal cortex with other structures, perhaps including the nucleus accumbens; (iii) 'habits' (stimulus–response learning) — dorsal striatum. Both (ii) and (iii) involve interactions between cortical projections to striatal domains, modulated by DA. (iv) 'Executive control' — prefrontal cortical areas; (v) subjective processes, such as craving, activate areas such as orbital and anterior cingulate cortex, as well as temporal lobe structures including the amygdala, in functional imaging studies; (vi) 'behavioural output' is intended to subsume ventral and dorsal striatopallidal outflow via both brainstem structures and re-entrant thalamo-cortical loop circuitry; (vii) 'spirals' refers to the serial, spiralling interactions between the striatum and midbrain DA neurons that are organized in a ventral-to-dorsal progression [281]; (viii) sensitization refers to the enhancement of drug and conditioned responses that is a consequence of earlier drug exposure and is at the heart of theories of addiction and relapse. The neural basis of stress-induced relapse, which involves the bed nucleus of the stria terminalis, central amygdala and their noradrenergic innervation is not illustrated. Blue arrows: glutamatergic pathways; orange arrows: GABAergic pathways; red arrows: dopaminergic pathways. The transmitter used by central amygdala neurons is less certain, but is probably glutamate and also a neuropeptide(s). Abbreviations: BLA: basolateral amygdala; CeN: central nucleus of the amygdala; VTA: ventral tegmental area; SNc: substantia nigra pars compacta; DGP, dorsal globus pallidus; LH, lateral hypothalamus; NAc, nucleus accumbens; rft, reinforcement, VGP, ventral globus pallidus. This diagram is modified from [49] and [99].

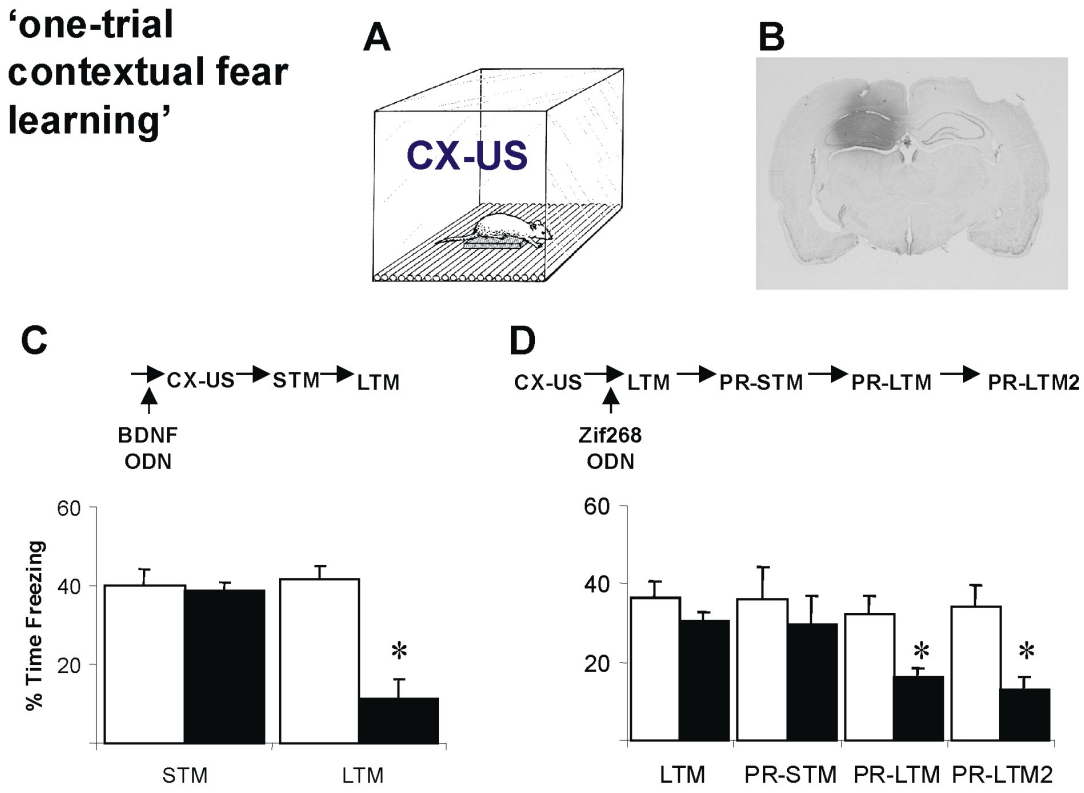

Figure 3

The consolidation and reconsolidation of contextual fear memories are mediated by independent cellular processes. Rats are fear conditioned to a novel context **(A)**, and infused into the dorsal hippocampus with antisense oligodeoxynucleotides (ODN) 90 minutes before conditioning or memory reactivation **(B)**. Subsequently, tests for long-term memory show that BDNF is required specifically for consolidation **(C)**, whereas Zif268 is necessary only for reconsolidation **(D)**. Based on data reported in [424].

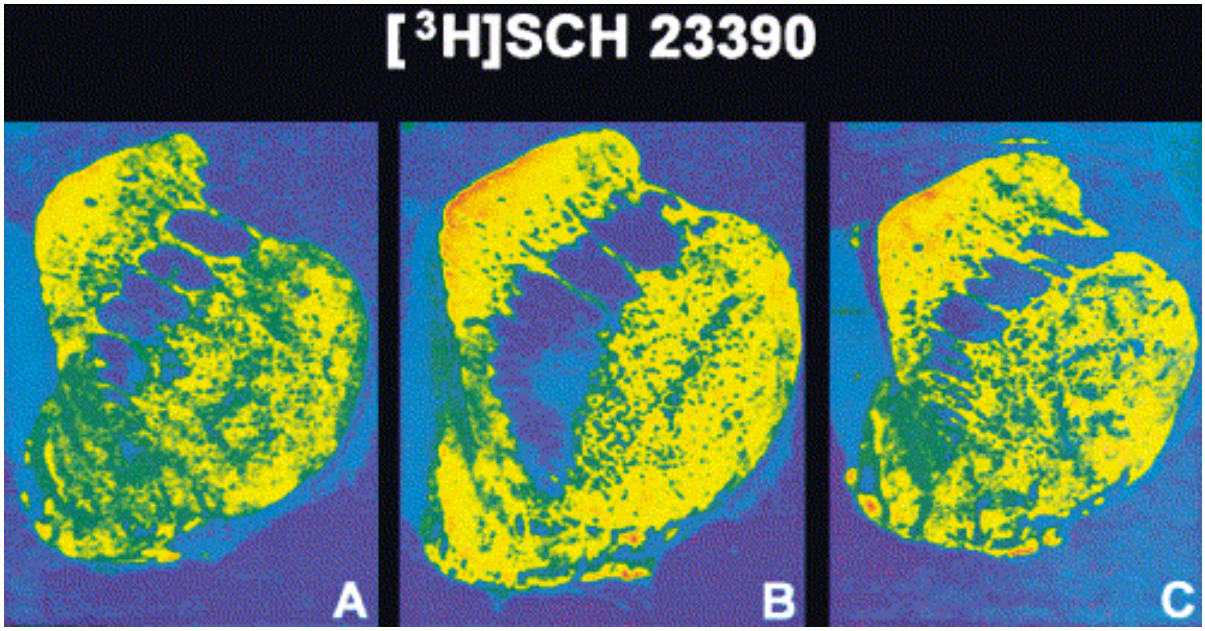

Figure 4

Representative color-coded autoradiograms depicting specific D1 binding using [^{3}H]SCH-23390 at the level of the posterior ventral precommissural striatum of a control rhesus monkey (panel A) and from a representative monkey in the chronic 0.03 mg/kg cocaine per injection (panel B) and 0.3 mg/kg cocaine per injection (panel C) groups. The autoradiogram is scaled in fmol/mg wet-weight tissue. (From [279].)

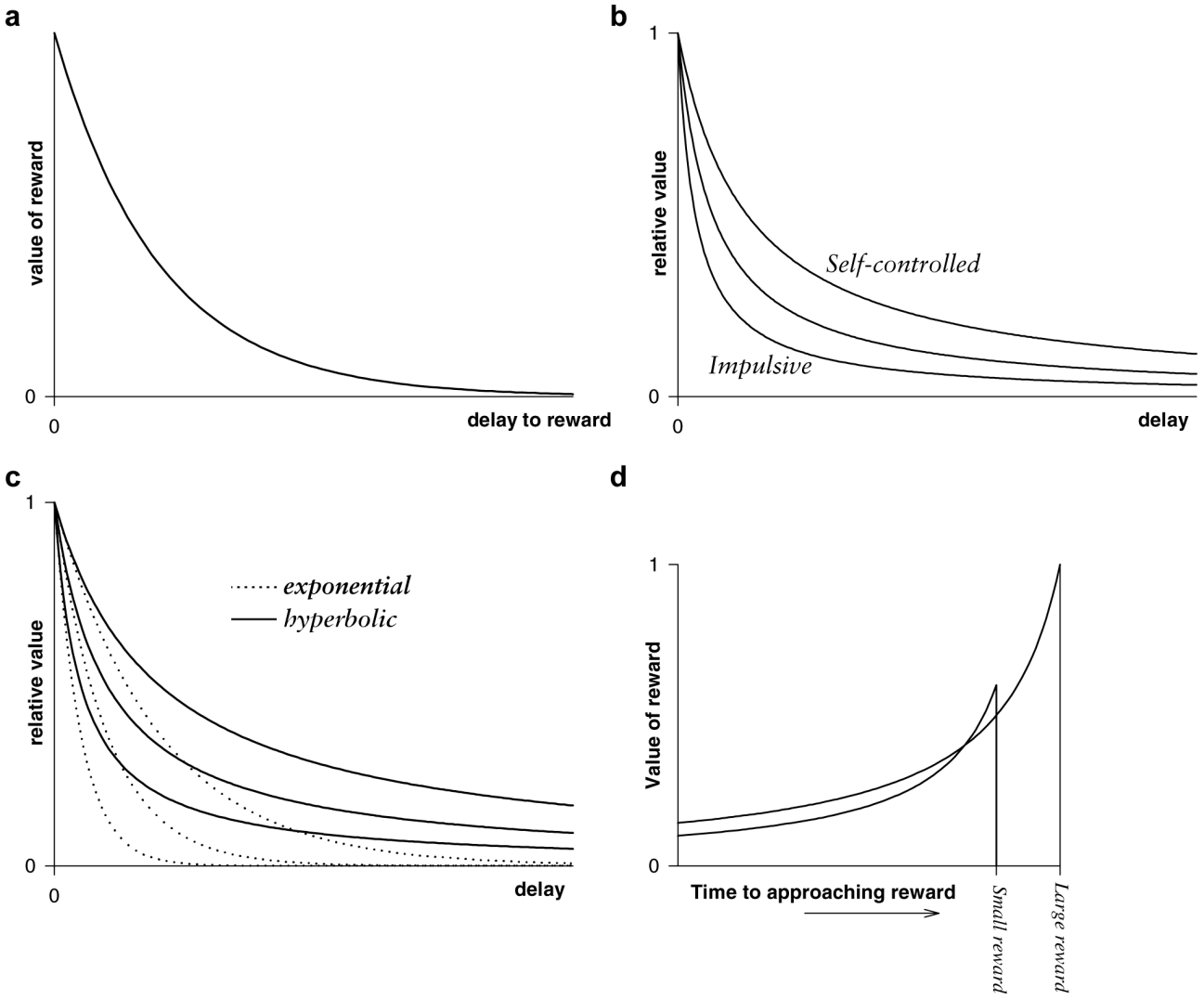

Figure 5

Temporal discounting. **(a)** The value of a reward declines the more it is delayed. **(b)** Some individuals do not value future rewards very much (they discount steeply) and are impulsive. Others value future rewards more, and are self-controlled. **(c)** Animals and people tend to discount the future in a hyperbolic, not exponential, way. **(d)** This leads to preference reversal. If a subject chooses between a big reward and a small reward when both are a long way in the future, he'll choose the big one. But as time passes and he gets closer in time to both, there may come a point at which preference reverses, he values the small reward more highly, and he chooses the smaller reward — he acts impulsively.

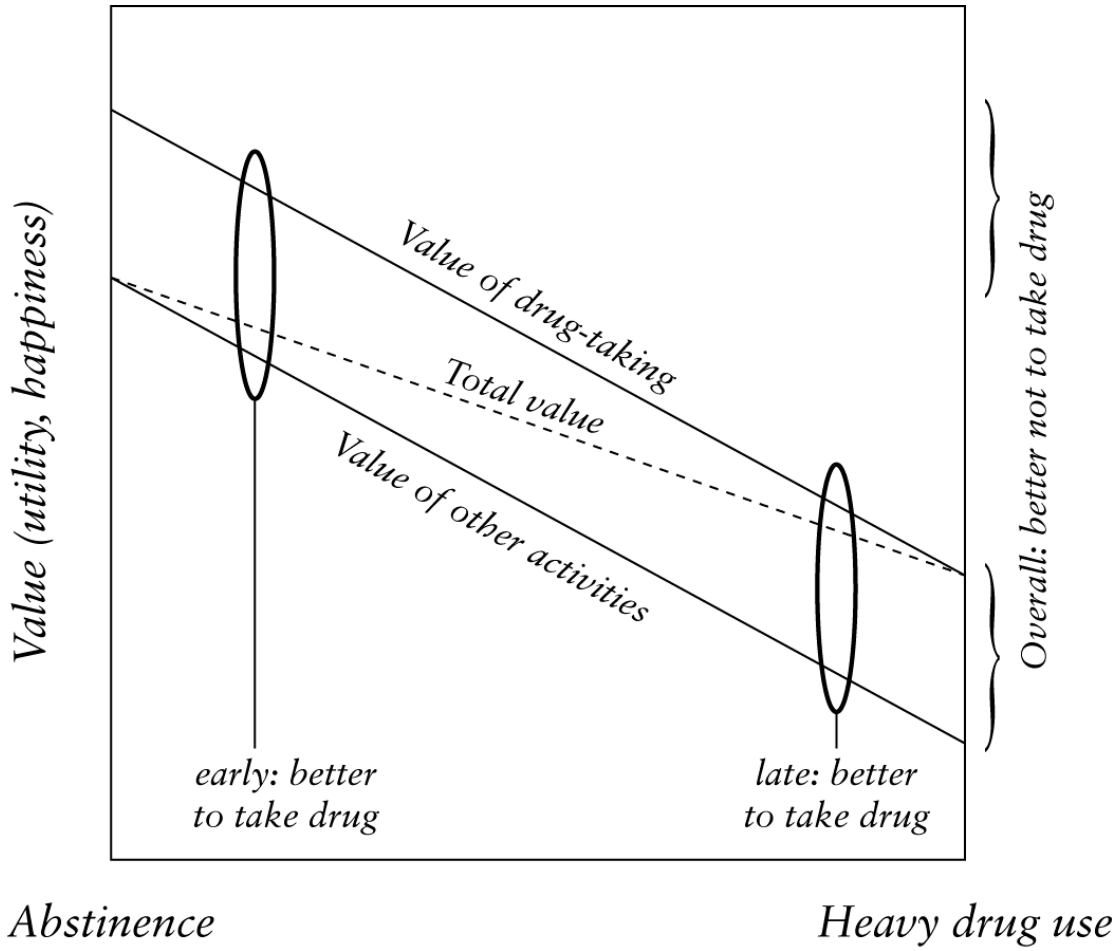

Figure 6

Good now, bad in the long run — the 'primrose path' to addiction [114; 116; 118; 689]. At any point, drug-taking has a higher value than other activities, so you take the drug. But drug-taking lowers both the value of future drug-taking (e.g. alcohol consumption causes tolerance, meaning that future alcohol isn't worth as much) and the value of other activities (e.g. the more alcohol you consume, the less you socialize and the worse you are at socializing; the more heroin you take, the worse you are at your job). So as you drink more, your total happiness goes down — you'd be better off not being an alcoholic. But even when you are an alcoholic, drinking now is worth more than not drinking now — for you are sensitive to local, not global, utility. As Rachlin [756] puts it: 'The alcoholic does not choose to be an alcoholic. Instead he chooses to drink now, and now, and now, and now. The pattern of alcoholism emerges in his behaviour… without ever having been chosen.'

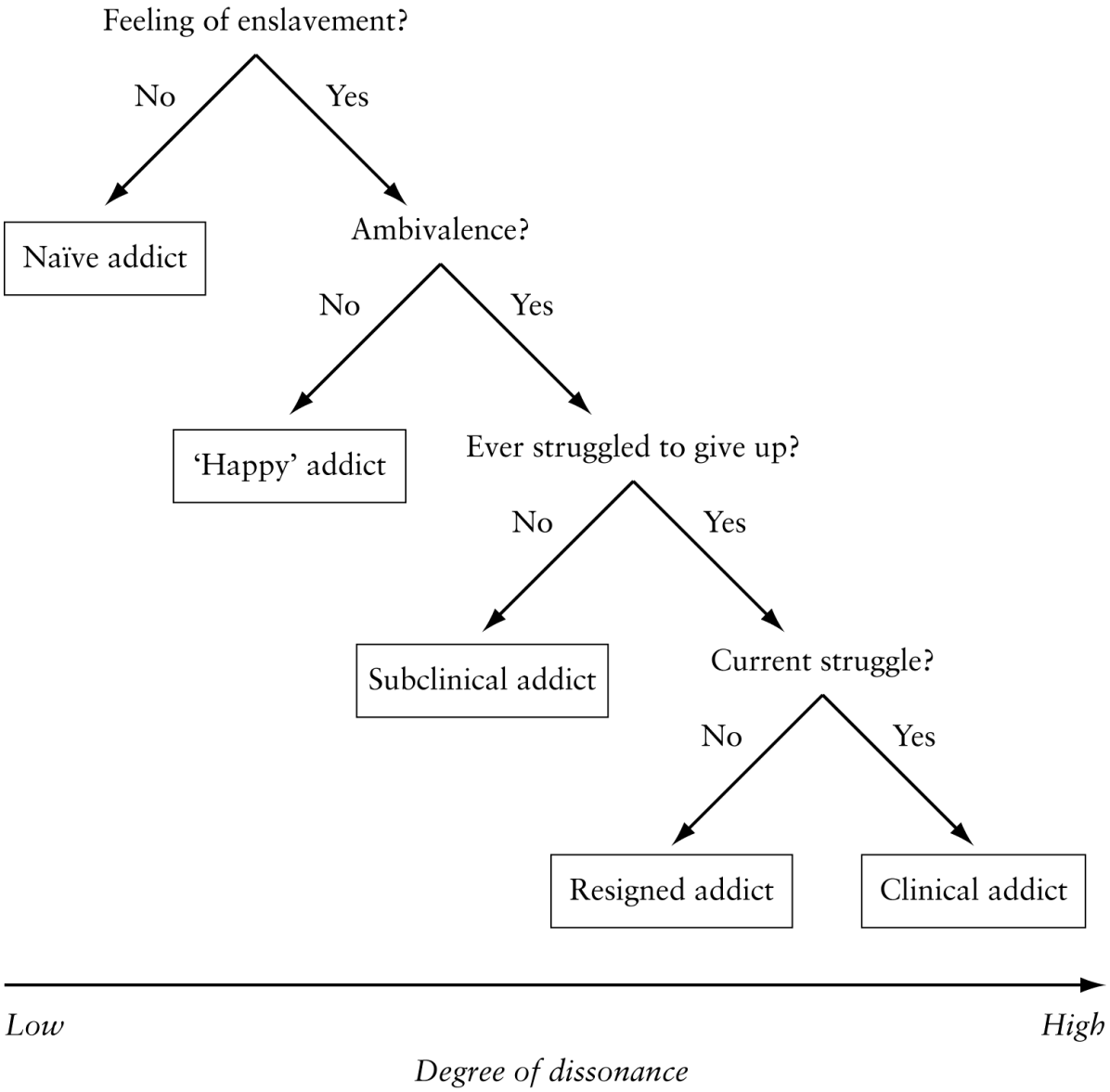

Figure 7

Skog's [717] view of addiction. A person may be unaware that it is difficult for him or her to live without a drug. Such a person is enslaved, but unaware; Skog calls them 'naïve' addicts. He offers the example of a heavy drinker in Paris in World War II, who had never realised that he was dependent on alcohol until rationing came along and he was limited to one litre of wine per week. Then there are those who know that life would be harder without, but are happy with this situation: 'happy' addicts, such as the 1950s smoker who thought that smoking was good for you (or at least, not bad). Those who are aware smoking is bad for you but feel no particular motivation to cut back are called 'subclinical' addicts by Skog. Finally, there are those who have tried and failed but are not trying at the moment, and those in an active struggle to quit.

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