Abstract

The argument advanced in this review is that drug addiction can be understood in terms of normal learning and memory systems of the brain which, through the actions of chronically self-administered drugs, are pathologically subverted, thereby leading to the establishment of compulsive drug-seeking habits, strengthened by the motivational impact of drug-associated stimuli and occurring at the expense of other sources of reinforcement. We review data from our studies that have utilized procedures which reveal the various influences of pavlovian stimuli on goal-directed behaviour, namely discriminated approach, pavlovian-to-instrumental transfer and conditioned reinforcement, in order to demonstrate their overlapping and also unique neural bases. These fundamental studies are also reviewed in the context of the neural and psychological mechanisms underlying drug-seeking behaviour that is under the control of drug-associated environmental stimuli. The ways in which such drug-seeking behaviour becomes compulsive and habitual, as well as the propensity for relapse to drug-seeking even after long periods of relapse, are discussed in terms of the aberrant learning set in train by the effects of self-administered drugs on plastic processes in limbic cortical–ventral striatal systems.

Theme: Neural basis of behaviour

Topic: Drugs of abuse: cocaine; Drugs of abuse: opioids and others

Keywords: Addiction; Reward; Conditioning; Cocaine; Heroin; Actions; Habit; Drug-seeking

1. Introduction

Drug addiction places a significant burden on society through its impact on health, social cohesion, crime and comorbidity with neuropsychiatric disorders. Major advances in genetics, molecular and cell biology have led to the identification and cloning of many of the primary targets of addictive drugs and revealed neuroadaptations that develop with chronic drug administration [62–64]. But understanding the precise relevance of these neuroadaptations to the clinical reality of drug addiction in humans remains a major challenge.

Many drugs of abuse, including amphetamine, cocaine, heroin, nicotine, cannabis and alcohol, while having very different primary molecular targets, all have the common action of increasing dopamine (DA) transmission in the nucleus accumbens (NAcb), perhaps especially in its shell subregion [5,22,77,112]. This commonality of action has led to the widely held view that the mesolimbic DA system has a general role in the reinforcing effects of drugs,
perhaps stemming from a more general role in mediating aspects of natural reward [21,121,122]. Molecular neuroadaptations induced by chronic administration of cocaine, heroin, nicotine and alcohol have been shown to occur downstream of DA receptors in the NAc and elsewhere [65], encouraging a view of drug addiction as gradual brain adaptations to chronic drug exposure, possibly triggered by a drive to homeostasis, i.e. the regulation of activity of brain systems affected by self-administered drugs within certain defined limits [49,50]. These neuroadaptations are the product of both decremental (tolerance/withdrawal) and incremental (sensitization) pharmacological effects.

Sensitization has acquired a recent prominence, especially as conceptualized in the Incentive Sensitization Theory, which attributes the development of addiction to the progressive establishment of compulsive ‘drug wanting’ through up-regulation of the mesolimbic DA system [7,88,89]. By contrast, avoidance of the dysphoria and anhedonia that follows withdrawal from many drugs underlies another, compelling view that sees addiction as resulting from opponent motivational processes [48,103,118]. Whilst there have been recent and impressive attempts to reconcile these viewpoints [49,50], it is likely that further precision is required in specifying the psychological processes determining human drug addiction [108] and in the interpretation of the molecular and neurochemical correlates of chronic drug administration.

The case for modelling addictive processes in animals has been strongly made [33,62,84]. Apart from their greater neurobiological accessibility, a key point is that animals can be studied from the drug naïve state through dependence, whereas clinical studies begin with an addicted individual who is usually seeking help to maintain abstinence. Among the processes to be further characterized and understood are those underlying: (i) vulnerability; (ii) the maintenance of drug-taking seeking behaviour, which might be viewed as a dynamic product of the gradual strengthening or ‘consolidation’ of behaviour arising from the reinforcing action of drugs, supplemented by a recurrent shaping of drug-related memories; (iii) the eventual progression of addiction to a form of habit-based learning through which voluntary control over drug use is lost [66,84]; (iv) the propensity for relapse of drug-seeking/taking, which often occurs after protracted abstinence.

In our recent research, we have placed special emphasis on the fact that drug abusers have to forage for their drugs in a real world in which they are not freely available [28,84,116]. We have established a general model of drug-seeking and taking in which this behaviour is sensitive not only to the contingency between instrumental behaviour and drug administration, but also to the presence of drug-associated stimuli which have a powerful effect on performance [1,2]. In this procedure, rats respond for prolonged periods of time in order to obtain an infusion of cocaine or heroin and this drug-seeking behaviour is not affected by any pharmacological effects of the drug, since it occurs prior to drug infusion. However, it does depend upon the contingent presentation of cocaine- or heroin-associated cues, since if they are not presented, then drug-seeking is markedly reduced and only recovers when the cues are reintroduced [1,2]. This procedure not only provides an opportunity to study the neural basis of such cue-controlled drug-seeking, but also provides a means of assessing potential treatments that will diminish cue-controlled drug-seeking (and relapse). The basolateral amygdala (BLA) is a critical structure, since animals with lesions of the BLA cannot acquire a second-order schedule of cocaine-seeking [116]. Rats with lesions of the anterior cingulate cortex (Ant Cing) and also medial prefrontal cortex show persistent high levels of responding for cocaine, but which is no longer under the control of contingent presentation of the cocaine-associated cue [115]. Interestingly, the amygdala and Ant Cing have been consistently shown to be activated in functional imaging studies of cocaine and heroin addicts when they are exposed to drug cues that elicit craving [15,35,98].

But the second-order schedule, by modelling the complex contingencies of natural drug-seeking, engages a number of different learning and motivational processes. We have been concerned to understand the contribution of each of these processes to drug-seeking, as well as their neural basis. In order to do so, we have developed different behavioural procedures, each of which focuses more directly on a component process. We distinguish between pavlovian processes sensitive to the contingency between stimuli (S) and reinforcers or outcomes (O) and instrumental processes sensitive to the contingencies between actions or responses (R) and outcomes [24]. In order to study the instrumental processes in more detail, we developed a ‘seeking–taking’ chain schedule [68] in which an animal performs a drug-seeking response in the initial link of the chain which then gives access to a drug-taking response in the second link, performance of which delivers the drug. By varying the dose and time-out period between successive cycles of the chain, we demonstrated that cocaine-seeking is governed by an interaction between reinforcement, regulatory, and activation processes [68]. Moreover, after a limited experience with the drug, cocaine-seeking was shown to be a goal-directed action in that its performance was sensitive to devaluation of the drug-taking link [67]. This devaluation effect demonstrates that, under the conditions we have studied so far, cocaine-seeking is mediated by knowledge of the contingency between the seeking response and its outcome, in this case access to the drug-taking link. This $R-O$ process can be contrasted with the second, $S-R$ instrumental process in which seeking behaviour is a simple response habit triggered by environmental and drug-associated stimuli. In the case of drug-seeking, it has been argued [108], but has yet to be demonstrated experimentally, that drug-seeking is initiated under the control of the goal-directed $R-O$ process, but with the onset of addiction becomes a
compulsive habit under the control of the S–R process, even in parallel with an apparent reduction in those subjective effects of the drug which initially established self-administration [84]. This important issue warrants more detailed investigation and will require the development of novel approaches.

In contrast to these instrumental R–O and S–R processes, Robinson and Berridge, through their developing Incentive Sensitization Theory [88,89] emphasize the role of pavlovian S–O processes in drug seeking, which we suggest, can take three forms [27,28]. Firstly, drug-associated cues can elicit simple pavlovian approach responses, such as those manifest in so-called autoshaping procedures. Secondly, equally important is that drug-associated stimuli, like other appetitive conditioned stimuli (CS), exert a motivational influence on instrumental behaviour whether it is controlled by the R–O or S–R process. The critical procedure for demonstrating this motivational influence is the pavlovian-instrumental transfer (PIT) design in which the impact of a separately trained CS on instrumental responses is assessed. Thirdly, drug-associated CSs can act as conditioned reinforcers for instrumental drug-seeking. Some of our experiments on the neural basis of these pavlovian S–O processes that we hypothesize contribute powerfully to the development and persistence of addiction are summarized below (see also Refs. [27,28]).

1.1. Appetitive pavlovian conditioning: autoshaping

Pavlovian conditioning is a fundamental learning mechanism that allows an animal to predict and adapt to future events based on previous experience. Autoshaping provides a simple and quantifiable measure of appetitive pavlovian conditioning relatively unconfounded by other forms of learning and allows investigation of the process by which environmental stimuli are associated with primary reward to gain motivational or emotional valence — measured in this task as discriminated approach to a reward-associated CS+, as opposed to a second stimulus never having been associated with reward (CS−) [10,43,109,110]. This approach behaviour has been interpreted as a pavlovian sign-tracking response [43] as it lacks the flexibility and goal-directed nature of instrumental actions [119]. We have demonstrated an extensive cortical–subcortical network involving the Ant Cing, nucleus accumbens (NAcb) core, central nucleus of the amygdala (CeN) and mesolimbic DA system underlying this fundamental form of appetitive behaviour (see Ref. [72]).

Autoshaping depends upon the integrity of the Ant Cing, but not posterior cingulate or medial prefrontal (including prelimbic and infralimbic) cortex [10]. We hypothesized that the Ant Cing may gain access to behavioural output through the striatum, leading to the prediction that lesions of the NAcb, the major recipient of projections from the Ant Cing, should also impair autoshaping as, indeed they did, whereas NAcb shell lesions were without effect, thereby revealing a dissociation in the involvement of NAcb subregions in appetitive pavlovian conditioning [74]. Lesions of the dorsal striatum, some areas of which also receive Ant Cing input, do not prevent animals from developing discriminative autoshaped approach responses [92], arguing for considerable neuroanatomical and functional specificity within the striatal targets of afferents from the Ant Cing.

In fact, the Ant Cing and NAcb core appear to operate as part of a corticostriatal circuit underlying specific aspects of pavlovian conditioning, since a disconnection lesion of the two structures (a unilateral cingulate cortical lesion and a NAcb core lesion on the contralateral side of the brain) also impaired autoshaping. The deficits following bilateral Ant Cing and bilateral NAcb core lesions differed, while the disconnection lesions resulted in a mixed pattern of deficits reflecting contributions from both Ant Cing and NAcb core, supporting the contention that the cortical and striatal nodes subserve different processes. This also suggests that such a corticostriatal circuit does not operate in isolation, but is influenced by other neural processes at different levels of the circuit, such as the major influence of dopamine (DA) specifically at the level of the striatum or the suggested spiralling, ventral-to-dorsal, influence of corticostriatal circuits on each other [39].

The amygdala is generally held to be a critical structure mediating various forms of appetitive and aversive conditioning, but our investigation of the involvement of the amygdala in autoshaping yielded perhaps surprising results. Thus, the CeN, but not the BLA, was shown to be the critical amygdala substrate since only CeN lesions impaired autoshaping by selectively reducing the number of CS+ approaches [75]. This is not to deny the important role played by the BLA in emotional learning, but we suggest that its involvement may be with more complex representations or more flexible outputs than the reflexive production of a pavlovian conditioned response [27,42]. There are now several strands of evidence indicating that selective lesions of the CeN consistently affect appetitive pavlovian conditioning in situations where BLA lesions are without effect [31,32,52,94].

What is not immediately clear is how the CeN interacts with the Ant Cing–NAcb core circuit, since, unlike the BLA, it does not project directly to the NAcb. However, the critical link may be provided by DA neurons in the VTA, since not only does a 6-hydroxydopamine-induced DA-depleting lesion of the NAcb profoundly impair autoshaping [73], but the CeN projects richly to the DA neurons of the VTA and substantia nigra [38,51]. Several observations support the contention that the CeN exerts a regulatory influence over midbrain DA neurons, e.g. DA lesions of the CeN or infusions of DA receptor antagonists into the amygdala have marked effects upon extracellular...
dopamine levels in the NAcB [12,44,54,57,100]. Further, disconnecting the CeN from the DA innervation of the dorsal striatum impairs conditioned orienting, another form of appetitive pavlovian response [41].

Taken together, these results reveal a distributed neural network underlying pavlovian approach behaviour that involves the Ant Cing, NAcB core, CeN and a modulatory influence of the mesolimbic DA system that is expressed within the NAcB. The precise functions of each node in this network remain to be established definitively. But we suggest that the Ant Cing–NAcB core system may mediate pavlovian associative processes and give direction to approach responses [28,76]. The CeN receives information about appetitive stimuli from a variety of sources (including the Ant Cing, high-order sensory cortices, BLA and thalamus), so enabling it to orchestrate not only autonomic and endocrine responses via its projections to the hypothalamus and brainstem, but also different forms of arousal processes dependent upon its projections to the chemically-defined systems of the reticular core of the brain [28,72]. Projections from the CeN to the DA neurons in the VTA, for example, may regulate the dopaminergic innervation of the NAcB and thereby behavioural activation that invigorates approach responses. This regulation of NAcB DA may also enhance the coupling of the anterior cingulate cortex–NAcB core circuit that provides direction to approach responses [28]. The consistent demonstration of activation in the Ant Cing and amygdala in functional imaging studies of cocaine and heroin addicts exposed to drug-associated stimuli [15,35,53] suggest that fundamental investigations of the neural substrates of appetitive conditioning such as those summarised here will further clarify the neural basis of cue-induced craving, drug-seeking behaviour and relapse.

1.2. Pavlovian-to-instrumental transfer

Appetitive pavlovian CSs not only elicit behavioural activation and approach responses, as summarized above, they are also able greatly to enhance instrumental behaviour [4,26,55,81]. To assess this influence, animals are first trained to associate presentations of a stimulus (CS) with delivery of primary reward (e.g. sucrose). During training, animals learn to approach the sucrose delivery location preferentially during the CS period (as in autoshaping). After this pavlovian conditioning, the animals are trained to lever press for the same sucrose reward in the absence of the CS. Finally, in the test phase, the ability of the CS to enhance lever pressing in extinction is assessed. The neural basis of this pavlovian-instrumental transfer (PIT) effect shares much in common with that underlying pavlovian discriminated approach behaviour. Thus, selective lesions of the CeN and NAcB core, but not the BLA nor NAcB shell abolished the enhancement of lever pressing during presentation of the CS [27,40,72]. Moreover, the mesolimbic DA system also influences PIT.

Thus, systemic administration of the dopamine D2 receptor antagonist pimozide abolished PIT, whereas this treatment had no effect on instrumental incentive learning [25]; amphetamine infused directly into the NAcB shell potentiated PIT [124], just as it potentiates responding with conditioned reinforcement (see below). This ability of pavlovian CSs to potentiate instrumental behaviour in a way that is influenced by increased DA transmission in the NAcB again indicates an important influence of conditioning on drug-seeking behaviour, since environmental stimuli are very readily associated with the effects of self-administered drugs such as cocaine and these drug cues are known strongly to influence drug-seeking [14,33].

1.3. Conditioned reinforcement

Stimuli that have been associated with a reinforcer will come to elicit the response produced by the reinforcer. This description of pavlovian conditioning expresses the learning as a mechanistic form of stimulus–response behaviour and does not necessarily assume that a more complex affective representation of the stimulus has been acquired. However, it is likely that in parallel to a mechanistic form of associative learning, an animal also develops a representation of the value of the predicted outcome. Stimuli that have acquired such value will act as conditioned reinforcers and support instrumental goal-directed actions. Thus, pavlovian conditioned stimuli not only elicit behavioural arousal and approach responses but, by acquiring some of the properties of a goal, gain motivational salience and thereby control over instrumental behaviour as conditioned reinforcers [29,56,82].

We have studied this using a procedure that isolates the conditioned reinforcement process. It has two phases: firstly, as in the autoshaping procedure, a neutral stimulus is paired with primary reward (e.g. water in thirsty subjects, sucrose in hungry subjects or intravenous cocaine) and the development of pavlovian conditioning is assessed by measuring discriminated approach to the CS+. In the second phase, which is carried out in extinction, thereby removing any influence of primary reinforcement, two novel levers enter the testing chamber; responding on one of them results in presentation of the light CS+. Responding on the second lever has no programmed consequence. The acquired motivational properties of the CS to serve as a conditioned reinforcer are therefore assessed by its ability to reinforce the acquisition of this novel and arbitrary response. An important aspect of this process is that the control over behaviour by a conditioned reinforcer is powerfully amplified by psychomotor stimulants and this effect has been shown to depend critically upon the DA innervation of the NAcB [83,105,106], specifically on its shell, rather than its core, compartment [74]. However, even in the face of extensive DA depletion from the NAcB, or general DA receptor blockade, rats still acquire a new response with conditioned reinforcement.
That is, the mesolimbic DA system does not mediate conditioned reinforcement, but only its potentiation by stimulant drugs.

Thus, information about conditioned reinforcers must be derived from another source, presumably one transferring such information to the NAc where its impact can be gain-amplified by increases in DA transmission [29,83]. Limbic cortical structures are the primary sources of information processed within the NAc, most notably the BLA, hippocampal formation (via the subiculum), prelimbic and anterior cingulate cortices [18,37,45,46,61] and we have studied their possible contributions to conditioned reinforcement.

Whilst the prelimbic cortex does not seem to contribute to conditioned reinforcement, lesions of the amygdala and subiculum had marked and different effects on responding for a conditioned reinforcer [9,11]. Lesions of the ventral subiculum did not impair pavlovian or instrumental conditioning, as measured by either stage of the procedure, but instead blocked the ability of intra-NAc amphetamine to potentiate instrumental responding for the conditioned reinforcer [9]. The glutamatergic projections from the ventral subiculum to the striatum may therefore modulate the potentiative effects of DA at the level of the striatum. Lesions of the BLA impaired the ability of the conditioned reinforcer to support the acquisition of a new response: lesioned subjects failed to respond selectively on the lever producing the conditioned reinforcer, though intra-NAc amphetamine still potentiated responding [9,11]. BLA-lesioned rats were not significantly impaired at magazine approach during the pavlovian stage of the experiment [11], consistent with the lack of effect of BLA lesions on autoshaping (see above). Further, BLA lesions did not impair instrumental responding per se [9] or responding on habit-based instrumental tasks [8]. Impairments following BLA lesions therefore appear to depend on whether the behaviour requires a conditioned representation of the reinforcer to perform the task [29,30,34]. In contrast, lesions of the CeN did not impair responding with conditioned reinforcement [91], but they did abolish the potentiative effects of intra-NAc amphetamine (much like the effects of ventral subiculum lesions) [91].

In summary, then, the BLA, CeN and ventral subiculum are all involved in conditioned reinforcement and its potentiation by the mesolimbic DA system, but their roles are clearly dissociable: (1) the BLA subserves a process by which affective representations of stimuli are used to guide instrumental goal-directed behaviour, and the integrity of this process is fundamental to the conditioned reinforcement effect itself; (2) both the CeN and ventral subiculum are essential for the potentiation of conditioned reinforcement by intra-NAc administration of stimulant drugs, but are not necessary for informational aspects of the conditioned reinforcement process. Whilst the ventral subiculum may provide the contextual background upon which the potentiation of conditioned reinforcement depends, the CeN may mediate a motivational influence on responding via the DAergic innervation of the NAc, through its projections to ascending DA systems originating in the midbrain. One last additional piece of data extends our current picture of the neural network that underlies conditioned reinforcement and its dopaminergic amplification. This concerns the role of the Ant Cing, implicated in the mnemonic retrieval of stimulus–reinforcer information in the autoshaping task. Lesions of the Ant Cing cortex did not impair temporally discriminated approach to the magazine or instrumental responding for conditioned reinforcement (Cardinal, Robbins and Everitt, unpublished); nor were the potentiative effects of intra-NAc amphetamine affected by these lesions. Thus whilst the Ant Cing is required for pavlovian approach to a CS+ in the autoshaping procedure, it does not appear to be involved in conditioned reinforcement.

2. Synthesis

From the above summary it can be seen that drug addiction might be understood as the aberrant engagement of these pavlovian and instrumental learning processes. The amygdala, hippocampus, cingulate and medial prefrontal cortex are clearly involved in these associative processes and have been quite extensively studied. But it is increasingly clear that the striatum may also be involved in some forms of learning. For example, the NAc core and its DA innervation have been shown to be involved in the acquisition of pavlovian approach [47,76] and in instrumental learning [101], whereas a role for the dorsal striatum (DS) in habit learning was originally suggested by Mishkin [60]. DA has been widely suggested to affect learning by its actions within the striatum [6,13,117] and both DA and glutamate receptors have been implicated in normal learning processes in striatal and limbic structures [3,6]. Although NAc DA may be especially responsive to many drugs of abuse when given acutely to naive subjects, the fact that DA transmission is increased in both the NAc and DS when drugs are self-administered over extended periods of time may contribute especially powerfully to aberrant learning involving both structures.

Dopaminergic neurons of the substantia nigra/ventral tegmental area (SNC/VTA) respond to unpredicted rewards and with training, this response transfers to stimuli predictive of rewards [95,96]. Thus, by signalling reward prediction errors, DA may act as a teaching signal for striatal learning [96]. There is also evidence for dopaminergic consolidation of S–R (habit) learning [70,71]. Since DA-dependent processes of the DS are involved in the development of S–R habits [60,69,80,87], whilst DA-dependent NAc processes are involved in incentive motivation/reward [21,85,86], a qualitative difference may exist between these two striatal domains, albeit using...
similar molecular and cellular mechanisms at the neuronal level.

Compulsive drug use is characterized by behaviour that is inflexible, since it persists despite considerable cost to the addict, may become dissociated from subjective measures of drug value [88], is elicited by specific environmental stimuli [14], and yet, at least initially, involves complex, goal-directed behaviours for procuring and self-administering a drug. One hypothesis is that limbic cortical–ventral striatopallidal circuits that underlie goal-directed drug-seeking actions, mediated by the R-O process, eventually consolidate habitual S-R drug-seeking through engagement of corticostriatal loops operating through the dorsal striatum. This progression from action to habit may have its neural basis within the recently described ‘spiral’ loop circuitry of the striatum, by which each striatal domain regulates its own DA innervation and that of its adjacent domain in a ventral-to-dorsal progression [39]. Thus, the NAc shell regulates its own DA innervation via projections to the VTA, and also that of the core. The core in turn regulates its own DA innervation via projections to the VTA, and also that of the next, more dorsal tier of the DS via projections to the SNc and so on [39]. Chronically self-administered drugs, through their ability to increase striatal DA, may consolidate this ventral-to-dorsal striatal progression of control over drug-seeking as a habitual form of responding.

The transition between control by the R-O process to S-R habits may also depend upon the executive control provided by descending influences on striatal mechanisms from the prefrontal cortex (PFC) [99]. Indeed, recent evidence suggests that chronic drug administration leads to pathological changes in PFC neuronal architecture in rats [90], characteristic post mortem neurochemical pathology in the orbital prefrontal cortex (oPFC) of amphetamine abusers [120] and major changes in the functional activation of the oPFC in cocaine addicts [111], each of which could have rebound effects on drug-seeking/taking behaviour as well as on cognitive decision making [93]. We have also shown that excitotoxic lesions of the mPFC disinhibit drug-, but not food-seeking behaviour [115]. However, much more needs to be understood about the ways in which different sectors of the PFC interact with their striatal domains in the context of drug addiction [79].

Another important potential consequence of the aberrant learning engendered by chronic drug self-administration is the strong and persistent propensity to relapse, especially in the presence of drug-associated stimuli in the addict’s environment. Even following protracted abstinence from drug-taking, relapse can be seen as a logical consequence of the conditioning processes that underlie compulsive drug-seeking, since this habit can be reactivated and motivated by drug-related cues. In humans, this may involve retrieval from memory of vivid drug-related experiences, manifested as craving, that lead to further drug-seeking and taking [15,35]. In animals, this has been modelled as cue-induced reinstatement of drug-seeking after extinction [19,20,36,58,104,114]. The neural correlates of such cue exposure include conditioned changes in DA release in the NAc as well as the altered expression of genes and intracellular markers within the NAc, amygdala and Ant Cing [97,107,113]. Lesions of the amygdala, as well as intra-amygdala or intra-NAc infusions of glutamatergic (especially AMPA) or dopaminergic receptor antagonists can prevent the reinstatement of extinguished cocaine-seeking behaviour induced by exposure to drug-associated stimuli [16,17,36,59] or diminish cocaine-seeking under a second-order schedule of cocaine reinforcement [23].

It may prove possible, therefore, to prevent relapse in human addicts by systemically administering drugs that diminish the motivational properties of drug-associated cues, thereby preventing lapses into drug-taking. We have shown that a partial agonist at D3 DA receptors can greatly diminish cocaine-seeking behaviour [78], but it remains unclear whether this effect is mediated by blockade of D3 receptors within the NAc, the amygdala or autoreceptors on the mesolimbic DA neurons themselves. One advantage of drugs acting at the D3 receptor is that its distribution in the brain is restricted to these few sites [78,102] and so unwanted side effects of such drugs are minimal. It has not been established whether systemically administered antagonists at AMPA or NMDA glutamate receptors can be used to prevent cued relapse without general effects on behaviour. A better understanding of the neural mechanisms though which pavlovian and instrumental learning processes may be engaged aberrantly to underlie drug addictive behaviour holds great promise for the development of novel treatments in the future.

Acknowledgements

The research summarised here is supported by an MRC Programme Grant (G9537855) to BJE, TWR and AD and was carried out within the MRC Co-operative in Brain, Behaviour and Neuropsychiatry. We gratefully acknowledge the major contributions of Helen Alderson, Mercedes Arroyo, Rudolf Cardinal, Patricia Di Ciano, Jeremy Hall, Rutsuko Ito, Athina Markou, Cellia Olmstead, John Parkinson, Maria Pilla, Patricia Robledo and Rachel Whitelaw to this work.

References

effects of conditioned cues and continuous access to cocaine, Psychopharmacology 140 (1998) 331–344.

\(\text{D}-\)aspartate receptor-dependent plasticity within a distributed corti-


[4] B. Balleine, Asymmetrical interactions between thirst and hunger in 

[5] V. Bassareo, G. Di Chiara, Differential influence of associative and 
nonassociative learning mechanisms on the responsiveness of pre-
frontal and accumbal dopamine transmission to food stimuli in rats 


reward: hedonic impact, reward learning, or incentive salience?, 

of the basolateral amygdala on conditional discrimination learning 
with primary and conditioned reinforcement, Behav. Brain Res. 100 (1999) 123–133.

excitotoxic lesions of the basolateral amygdala, ventral subiculum 
and medial prefrontal cortex on responding with conditioned re-
forcement and locomotor activity potentiated by intra-accumbens 

[10] T.J. Bussey, B.J. Everitt, T.W. Robbins, Dissociative effects of 
cingulate and medial frontal cortex lesions on stimulus–reward 
learning using a novel Pavlovian autoshaping procedure for the 

in stimulus–reward associations: interaction with the ventral 
striatum, Neuroscience 30 (1989) 77–86.

dopamine D-1 antagonist SCH 23390 microinjected into the accumb-
s, amygdala or striatum on cocaine self-administration in the 

term synaptic depression in the striatum: physiological and pharma-

Classically conditioned factors in drug dependence, in: W. reward-relevant limbic nuclei in an animal model of relapse, 

O’Brien, Classically conditioned factors in drug dependence, in: W. reward-relevant limbic nuclei in an animal model of relapse, 

activation during cue-induced craving for cocaine and for natural 

glutamate transmission in the relapse to cocaine-seeking behavior, 

[18] J.L. Cornish, P.W. Kalivas, Glutamate transmission in the nucleus 


[21] H. de Wit, J. Stewart, Reinstatement of cocaine-reinforced respond-

[22] G. Di Chiara, The role of dopamine in drug abuse viewed from the 

[23] G. Di Chiara, A. Imperato, Drugs abused by humans preferentially 
increase synaptic dopamine concentrations in the mesolimbic system 


and instrumental incentive learning under dopamine antagonists, 

[26] W.K. Estes, Discriminative conditioning. I. A discriminative prop-
erty of conditioned anticipation, J. Exp. Psychol. 32 (1943) 150–155.

[27] B.J. Everitt, R.N. Cardinal, J. Hall, J.A. Parkinson, T.W. Robbins, 
Differential involvement of amygdala subsystems in appetitive 
conditioning and drug addiction, in: J.P. Aggleton (Ed.), The 
Amygdala: A Functional Analysis, Oxford University Press, Oxford, 

T.W. Robbins, Associative processes in addiction and reward — The 
role of amygdala–ventral striatal subsystems, Ann. NY Acad. Sci. 

[29] B.J. Everitt, T.W. Robbins, Amygdala–ventral striatal interactions 
and reward-related processes, in: J.P. Aggleton (Ed.), The 


nucleus and appetitive Pavlovian conditioning: lesions impair one 


[33] F.H. Gawin, Cocaine addiction: psychology and neurophysiology, 

[34] J.C. Gewirtz, M. Davis, Second-order fear conditioning prevented 

Contoreggi, R.L. Phillips, A.S. Kimes, A. Margolin, Activation of 

reward-relevant limbic nuclei in an animal model of relapse, 

[37] H.J. Groenewegen, C.I. Wright, A.V.J. Beijer, The nucleus accum-
bens: gateway for limbic structures to reach the motor system?, 

[38] S.N. Haber, J.L. Fudge, The central nucleus of the amygdala 

[39] S.N. Haber, J.L. Fudge, N.R. McFarland, Striatonigral pathways in 
primates form an ascending spiral from the shell to the dorsolateral 

[40] J. Hall, J.A. Parkinson, T.M. Connor, A. Dickinson, B.J. Everitt, 
Involvement of amygdalo-striatal sub-systems in pavlovian to 

[41] J.S. Han, R.W. McMahan, P. Holland, M. Gallagher, The role of an 

[42] T. Hatfield, J.S. Han, M. Conley, M. Gallagher, P. Holland, 
Neurotoxic lesions of basolateral, but not central, amygdala interfere 
with Pavlovian second-order conditioning and reinforcer devolution 

[43] E. Hearst, H.M. Jenkins, in: Sign Tracking: The Stimulus–Re-
inforcer Relation and Directed Action, Monograph of the Psychono-
mic Society, 1974.


A. McGregor, D.C.S. Roberts, Dopaminergic antagonism within the nucleus accumbens or the amygdala produces differential effects on intravenous cocaine self-administration under fixed and progressive ratio schedules of reinforcement, Brain Res. 624 (1993) 245–252.


M.C. Oomsteed, M. Lafond, B.J. Everitt, A. Dickinson, Seeking by rats is a goal directed action, Behav. Neurosci., in press.


