Reward system and addiction: what dopamine does and doesn't do

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Addictive drugs share with palatable food the property of increasing extracellular dopamine (DA), preferentially in the nucleus accumbens shell rather than in the core. However, by acting directly on the brain, drugs bypass the adaptive mechanisms (habituation) that constrain the responsiveness of accumbens shell DA to food reward, abnormally facilitating Pavlovian incentive learning and promoting the acquisition of abnormal DA-releasing properties by drug conditioned stimuli. Thus, whereas Pavlovian food conditioned stimuli release core but not shell DA, drug conditioned stimuli do the opposite, releasing shell but not core DA. This process, which results in the acquisition of excessive incentive–motivational properties by drug conditioned stimuli, initiates the drug addiction process. Neuroadaptive processes related to the chronic influence of drugs on subcortical DA might secondarily impair the function of prefronto-striatal loops, resulting in impairments in impulse control and decision making that form the basis for the compulsive feature of drug seeking and its relapsing character.

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Introduction

In November 2006, a PubMed search for 'dopamine and addiction' gave 1220 citations against 503 for 'ventral striatum and addiction', 416 for 'cortex and addiction', 336 for 'serotonin and addiction', 213 for 'glutamate and addiction', 208 for 'GABA and addiction' and 163 for 'amygdala and addiction'. This simple search indicates that studies in the addiction field have privileged dopamine (DA) over all other topics.

Knowledge of the involvement of DA in the action of addictive drugs came almost 20 years [1] after its discovery as the transmitter of the motor striatum in the late 1950s. Moreover, this involvement was originally utilized to support a role for DA in reward, rather than in drug addiction [1]. This evidence was initially obtained by lesioning of DA neurons and by pharmacological manipulation of DA transmission [2]. Although this experimental approach greatly contributed to the foundations of our present view of the function of DA, it also generated significant debate owing to the difficulty of excluding a contribution by non-specific motor effects to the behavioral impairments induced by experimental manipulation of DA transmission [2–4]. In the past 25 years, several methods have become available that enable the function of the DA system, and its correlation with behaviour, to be monitored.

DA function can be monitored by extracellular recording of the firing activity of DA neurons [5] and by estimating the extracellular concentrations of DA by microdialysis [6,7••], voltammetry [8] and brain imaging (i.e. positron emission tomography [PET]) [9,10••]. Each of these methods has different time frames: milliseconds for extracellular recordings, seconds for voltammetry, and minutes for microdialysis and PET. These different methods do not necessarily estimate the same aspect of the function of DA. It has been proposed that DA operates in different modalities depending upon the time-scale of its action [11,12••]. Thus, a phasic modality, operating in a time-frame of hundreds of milliseconds and related to release of DA by a burst of spikes onto low affinity DA receptors, has been distinguished from a tonic modality, operating in a circadian time-frame and related to the basal steady-state concentration of DA in the extracellular compartment arising from the dilution and diffusion of released DA. The phasic modality corresponds to DA transients estimated by voltammetry, the tonic modality to basal DA concentrations estimated by microdialysis [11]. This dicotomous categorization, however, is insufficient to describe the changes in the minute time-frame observed by microdialysis and PET in response to reward-related stimuli. Therefore, a more comprehensive model envisions the existence of multiple time-related modalities of DA transmission that depend upon the number of bursts fired by specific pools of DA neurons [13].

Here we examine the current views on the role of DA in drug reward and motivation; specific emphasis has been placed on the differential responsiveness of DA transmission at different terminal areas to drug and food reinforcers, as well as to drug- and food-conditioned stimuli, and on the role that these differences might play in the mechanism of drug addiction.

Glossary
Anhedonia: inability to experience pleasure.
Habituation: reduction or cessation of response to a stimulus after repeated exposure. Habituation, in contrast to tolerance, is not reversed by increasing stimulus strength.
Hedonia: the interoceptive sensation of pleasure. 'State hedonia', related to a drug-induced 'high' or 'rush', is distinguished from 'sensory hedonia', which is related to hedonic stimuli arising from rewards (e.g. taste stimuli, sexual stimuli).
Incentive: a stimulus that promotes approach to the reward and facilitates the emission of responses instrumental to the presentation of the related reward. Incentives have acquired their properties as a result of predictive association (Pavlovian conditioning) with rewards. Incentives are provided with two properties: a directional property, promoting responses directed towards the reward they predict, and an activational property (incentive arousal), amplifying the incentive properties of other incentive stimuli present in the environment but not necessarily related to the reward to which the incentive has been conditioned.
Incentive-motivation: the process by which incentive stimuli are acquired (incentive learning) and act to promote responding.
Instrumental learning: learning of contingencies between stimuli and responses. Two types of instrumental learning are distinguished: learning of an act–outcome contingency and learning of an automatic response habit, resulting in outcome-dependent and -independent responding, respectively.
Liking: a self-reported measure of hedonia. By this definition, liking is an explicit measure. Some authors, however, utilize this term to refer to the implicit central substrate of pleasure/hedonia.
Motivation: the process by which organisms emit responses to stimuli in relation to their predicted consequences in terms of survival of the self and of the species.
Pavlovian learning: learning of stimulus–stimulus (reward) contingencies
Reinforcer: a stimulus that increases the probability of responses contingent upon its presentation (positive reinforcer) or its termination (negative reinforcer). In contrast with incentives, reinforcers elicit reponding on the basis of their contingency with responses (instrumental conditioning). Reinforcers can be unconditioned and conditioned.
Reward: a class of unconditioned motivational stimuli provided with hedonic properties that can act as positive reinforcers.
Reward-prediction error: dopamine neurons have been hypothesized to code for an error in the prediction of the occurrence of reward. Accordingly, unexpected occurrence of a reward would result in phasic activation, whereas failure of an expected reward to occur would result in depression of DA neurons.

Basic aspects of dopamine transmission relevant for behavior

DA acts via G-protein-coupled receptors in a typical neuromodulatory fashion [14]. DA release sites are placed immediately outside the synaptic cleft [13]. Once released, DA diffuses in the extracellular fluid, from which it is slowly cleared as a result of reuptake and metabolism [15]. DA does not directly affect the conductance of receptive membranes but modifies their response to afferent input [16]. These three aspects (extrasynaptic release, G-protein-coupled receptor signal transduction and a modulatory mechanism) contribute to a basic feature of DA transmission; that is, the long delay occurring between stimulus-bound activity (burst firing) and functional changes in the receptive elements. It has been estimated that, following electrical stimulation of DA neurons, a change in activity is recorded in striatal neurons after a delay of approximately 300 ms [17]. Although burst firing of DA neurons occurs in response to motivationally relevant stimuli [5], it is unlikely that these phasic DA signals influence, to any significant extent, the behavioral response (mediated by fast transmitting pathways) to the same stimulus that triggered them. Thus, a more realistic view of the role of DA in responding involves DA as a delayed amplifier of responding, affecting the behavioral impact of stimuli that follow the one that triggered its release. Recent fast-scan cyclic voltammetry studies support this contention. Thus, in rats responding for sucrose [18] or intravenous cocaine [19], the largest DA transient recorded in the nucleus accumbens (NAc) core peaked either at the start (sucrose) of the response or 1–2 s thereafter (cocaine). Therefore, rather than being 'in series' between stimuli and responses, DA should be envisioned in parallel with stimuli, modulating their ability to elicit a response [20].

In vivo monitoring of dopamine responsiveness to taste stimuli

Microdialysis studies in the rat have shown that appetitive taste stimuli release DA in the NAc shell and core, as well as in the prefrontal cortex (PFC) [21,22]. NAc shell DA responsiveness shows some differences to that of the NAc core and PFC, as it is dependent upon the hedonic valence (appetitive or aversive) [23] and relative novelty of taste stimuli [21,23,24]. Thus, NAc shell DA release is stimulated by unfamiliar appetitive tastes, but is unaffected or even decreased by aversive tastes [23]. NAc shell DA responsiveness habituates after a single exposure to palatable food in a taste-specific manner [21,23–26]. By contrast, taste stimuli release DA in the NAc core and in the PFC independently of their positive or negative hedonic valence, and do not show single-trial habituation (see Glossary) [21,23]. Mild food deprivation is sufficient to impair habituation of NAc shell DA responsiveness to palatable food [26]; this could account for the failure of DA neurons to undergo habituation in food-restricted monkeys [5]. Habituation of the DA response to intraoral sweet chocolate is not associated with reduction in hedonic taste reactions [23]. This indicates that habituation is unrelated to satiety-induced hedonic devaluation and, in turn, that hedonic taste reactions are independent of NAc shell DA. Accordingly, DA release in the NAc shell is not the cause, but the consequence, of food reward. The adaptive properties of the responsiveness of NAc shell DA to taste stimuli (one-trial habituation) are consistent with a role in associative learning [21]. Consistent with this suggestion, intra-NAc shell infusion of D1 receptor antagonists impairs acquisition of conditioned taste aversion, whereas systemic amphetamine facilitates this process by an action in the NAc shell [27,28]. Therefore, release of DA in the NAc shell following food intake might serve to associate the taste

properties of food with its post-ingestive consequences [27].

Extracellular recording of dopamine neurons

Recordings from electrophysiologically identified DA neurons of the monkey substantia nigra show that they respond specifically to the unpredicted occurrence or non-occurrence of reward-conditioned stimuli [5]. These observations suggest that DA neurons respond to stimuli according to an error in the 'prediction of reward' occurrence. Because a reward-prediction error forms the basis of Pavlovian learning theories, it has been postulated that DA neurons provide an error signal for the learning of stimulus–reward associations [5]. Circumstantial evidence for this hypothesis derives from the ability of a reward-prediction error to act as a teaching signal in computational networks that learn complex behavioral tasks [5]. It should be noted, however, that DA neurons are but one of the many neuronal systems that respond in a reward-prediction error fashion [5]. Therefore, evidence that a computational model incorporating reward-prediction error results in successful learning does not prove that DA serves as a signal for learning. Indeed, given the possibility that DA neurons contain a fast excitatory co-transmitter [29,30•], it is unclear to what extent the response properties of DA neurons reflect the function of DA or that of its co-transmitter, or both [31,32].

Indeed, direct estimation of DA in the extracellular compartment from recordings in monkey DA neurons has resulted in several discrepancies. For example, although DA neuron recordings do not show differences in responsiveness to stimuli in relation to their predicted area of projection [5], *in vivo* microdialysis studies show quantitative and qualitative differences between terminal DA areas [20]. Thus, a conditioned stimulus to a palatable taste (US) releases DA in the PFC and NAc core but not in the shell. Moreover, in contrast to the 'reward-prediction error' hypothesis, presentation of a conditioned stimulus does not prevent, and might even potentiate, the DA response to the palatable taste in the PFC and NAc core [21]. Finally, reward omission during memory retrieval in a food search task is associated with a sustained increase of DA in the medial PFC [31]. These discrepancies, while challenging the 'reward-prediction error' hypothesis, support the contention that recordings of DA neuron activity do not provide a realistic estimate of the temporal and spatial dimensions of DA transmission *in vivo*.

Monitoring of extracellular dopamine after addictive drugs: focus on the accumbens shell

Microdialysis and PET studies show that addictive drugs increase extracellular DA preferentially in the ventral striatum (namely in the NAc) in rats, non-human primates and humans [20]. Furthermore, addictive drugs preferentially increase dialysate DA in the NAc shell, rather than the core, after response non-contingent [32–34] and response-contingent [35••–37••] administration in the rat. Caffeine, a non-addictive drug, fails to stimulate DA transmission in the NAc shell [38,39]. Local intracerebral self-administration studies also highlight the NAc shell (along with the adjacent medial olfactory tubercle) as the most sensitive site for DA-dependent reward [39]. Although some psychostimulants (e.g. cocaine and amphetamine) are known to increase DA in the PFC, addictive drugs do not generally affect DA in this area. Therefore, the NAc shell is the primary DA terminal area to be affected by acute exposure to addictive drugs in a naive subject. A similarly sensitive area is the bed nucleus of stria terminalis, which belongs to the extended amygdala and shares some anatomical similarities with the NAc shell [40].

Drug-reward versus food-reward: differential role of dopamine

Historically, evidence that drug (psychostimulant)-induced stimulation of DA transmission was rewarding proved highly influential in the formulation of a general anhedonia hypothesis that extended the role of DA to all rewards [1,2]. However, after years of debate, the anhedonia hypothesis appears no longer tenable. The main reason for this is that food reward is, to a large extent, independent of DA [4,41]. On this basis, activational and incentive-motivational theories have extended to all rewards the notion of the non-DA nature of food reward [4,41]. However, PET studies in humans show that self-reported 'liking' induced by cocaine, methylphenidate and amphetamine is related to an increase of striatal DA [42–44]. Failure to obtain convincing evidence for a role of DA in psychostimulant liking by interaction studies using amphetamine and DA receptor blockers might be a result of the inadequacies of neuroleptics as tools to investigate this issue [44]. Drug-induced hedonia can be modeled in rats by drug-conditioned saccharin taste avoidance [45••]. In this paradigm, predictive association of a saccharin taste with an addictive drug results in avoidance of saccharin on a subsequent test. This effect is explained as the result of the frustration of reward expectancy elicited by presentation of saccharin in place of the more rewarding addictive drug (reward-comparison hypothesis) [46]. Blockade of DA receptors prevents drug-conditioned saccharin avoidance by an action that is distinct from the disruption of associative learning and which is attributed to blockade of drug reward and hedonia [45••]. The differential DA dependence of food and psychostimulant reward might reflect the different nature of these rewards and of the hedonic effects they induce. Thus, food-related hedonia might belong to a kind of hedonia (i.e. sensory hedonia) elicited by stimuli (e.g. taste stimuli) instrumental for the initiation of consummatory fixed-action patterns. By contrast, psychostimulant hedonia might correspond to a 'state hedonia' elicited by reward-predictive stimuli and associated with reward expectancy [20]. This latter kind of

hedonia is viewed as an integral component of the incentive arousal state.

Dopamine and incentive arousal

Mogenson and Yang [47] viewed the ventral striatum as an interface between motivation and action. Indeed, DA neurons respond to motivationally significant stimuli with a burst of spikes and a phasic release of DA in terminal areas [5,20]. However, as mentioned above, it is unlikely that DA is 'in series' between a stimulus and a response and that it mediates stimulus-response coupling. Rather, DA release by Pavlovian stimuli might modulate stimulus–response coupling, thus being in parallel with it. This view explains the results of experimental studies involving lesion or pharmacological manipulation of DA transmission in the NAc in a variety of paradigms that were dependent upon the action of Pavlovian stimuli. Thus, dopaminergic stimulation facilitates the rate-increasing effects of Pavlovian stimuli on instrumental responding (i.e. transfer from Pavlovian to instrumental) [48], stimulates responding with conditioned reinforcement [49], and facilitates reinstatement of extinguished instrumental responding by Pavlovian stimuli [50]. We have indicated the state associated with this function of DA as incentive arousal [20]. A role for DA in motivational arousal was postulated by Wise [2] in his revised anhedonia hypothesis but, in contrast to the present hypothesis, he assumed that DA was the substrate of all rewards. In turn, the current incentive arousal hypothesis of DA, at variance with other incentive–motivational hypotheses, envisages a DA-dependent incentive hedonia and 'liking' specifically induced by addictive drugs (see [44] for further discussion).

Dopamine release by drug and food conditioned stimuli

Past and current hypotheses of DA function in behavior attribute an important role to the ability of conditioned stimuli to release DA. Clear differences between drug and non-drug Pavlovian conditioned stimuli have been shown in microdialysis studies. Thus, Pavlovian stimuli conditioned to palatable food acquired incentive properties and released DA in the PFC and in the NAc core, but consistently failed to release DA in the NAc shell [21,23,24]. The same stimuli conditioned to morphine or nicotine also acquired strong incentive properties, but released DA in the NAc shell and PFC and not in the NAc core [51••]. These observations have recently been confirmed in rats implanted with intraoral cannuals (V Bassareo *et al.*, abstract 66, 11th International Conference on *in vivo* methods, Villasimius (Cagliari), May 2006). What is particularly striking about these observations is that drug conditioned stimuli, in contrast to food conditioned stimuli, mimic the DA-stimulant properties of novel unfamiliar highly palatable food and USs [21,23,24]. This feature might be the substrate of the powerful incentive-arousing and incentive-learning properties of drug conditioned stimuli.

Dopamine-dependent learning and drug addiction

DA has been implicated in virtually all stages of drug addiction, from induction to maintenance and then to relapse after a period of abstinence. Current theories of drug addiction attribute an important role to DA in mediating changes in synaptic efficiency resulting from repeated exposure to addictive drugs. Differences among theories relate to the mechanism by which these processes take place. Schematically, one can distinguish between associative learning and non-associative (neuroadaptive) theories. According to the incentive-learning theory, stimulation of NAc shell DA transmission by drugs is instrumental in learning the association between drugs and stimuli that predict their availability [52]. This hypothesis is generally consistent with the postulated role of DA in Pavlovian incentive learning [17] and, more specifically, with the adaptive properties of NAc shell DA to palatable food taste [21,23] and the ability of intra-NAc shell administration of D1 receptor antagonists to impair drug-conditioned acquisition of place preference [53••,54••]. The pathological feature of this learning arises from the fact that drug-induced stimulation of DA transmission in the NAc shell, in contrast to taste-induced stimulation, fails to undergo habituation [55]. Drug-induced stimulation of NAc shell DA transmission, in addition to strengthening the associative mechanism itself, might also mediate drug reward. As a result of the combined action of these two processes, repeated drug exposure would result in excessive strengthening of Pavlovian stimulus–drug associations that would be expressed in the acquisition of stimulant properties by drug-conditioned stimuli in the NAc shell [51••]. This property, specific to drug conditioned stimuli, might provide a mechanism for their resistance to 'extinction' and the long-lasting maintenance of incentive-motivational and incentive-learning properties [20]. Such a feature might be the basis for the impairment of impulsive choice and decision making typical of drug addiction. For example, an excessive incentive influence of reward-predictive stimuli has been suggested to account for the disturbances in decision making in a subgroup of drug addicts [56••].

It has been argued that, after prolonged responding for drug (e.g. in the addicted state), a shift of responding occurs from an action-outcome into a habit modality based on stimulus-response (rather than stimulus-reward) associations and dependent upon dorsal striatal function [57••]. On this basis, a role for neostriatal DA in the formation of a pathological drug habit has been hypothesized [57••].

Dopamine-dependent sensitization and drug addiction

Robinson and Berridge [58], largely on the basis of studies with psychostimulants, have proposed an incentive-sensitization theory of drug addiction. This theory posits that

repeated drug exposure induces a state of sensitization of mesocorticolimbic DA neurons; as a result of this adaptive non-associative change, drug-related stimuli would become more effective at stimulating DA transmission in mesocorticolimbic areas and in triggering craving, regarded as an abnormal incentive state (abnormal wanting). A basic difference between the incentive-sensitization and the incentive-learning hypotheses is that, whereas the first views addiction as a disorder of the expression of the incentive properties of stimuli, the second envisions it as a disturbance of the acquisition of those properties.

The main problem with the incentive-sensitization hypothesis derives from the fact that there is no evidence for sensitization to the euphorigenic and motor stimulant properties of cocaine in human addicts [59] Indeed, in human cocaine users, sensitization to the euphoric effects of the drug is typically not seen [60]. In contrast, in short- and long-term cocaine post-addicts, there is evidence for reduced, rather than increased, stimulant properties on behavior and DA transmission [43]. Sensitization is classically observed to the psychotic effects of cocaine and other psychostimulants, but this property appears to be negatively correlated with measures of dependence and craving in cocaine addicts [61]. It has been recently reported that strong behavioral and biochemical sensitization to cocaine and heroin is induced by passive drug exposure, and that response-contingency (i.e. intravenous self-administration) of the drug prevents the induction of biochemical sensitization and, at least in part, behavioral sensitization [37••]. These observations, while explaining the absence of behavioral sensitization in human addicts as being caused by the response-contingent nature of human drug exposure, challenge the view that behavioral and biochemical sensitization play a major role in human addiction.

Dopamine, relapse and vulnerability to drug addiction

A reduction of tonic DA transmission in striatal areas has been implicated in the motivational disturbances (anhedonia) of abstinence in dependent subjects, as well as in the individual vulnerability to drug addiction [62•]. Withdrawal from cocaine, nicotine and ethanol in dependent subjects results in a reduction of the excitability of the reward system, as indicated by an increase in the threshold for brain stimulation reward [63]. These changes are thought to maintain drug self-administration by counteracting the negative effects of abstinence [62•,63]. PET studies in abstinent cocaine addicts have shown decreased D2 receptor availability and extracellular DA in the striatum, which correlated with reductions of neural activity in the orbitofrontal and cingulate cortex [43]. Non-addicted subjects show an inverse relationship between basal striatal D2 receptor availability and self-reported liking in response to methylphenidate [43]. Collectively, these observations suggest that reduced basal striatal D2 receptor transmission increases the rewarding impact of drugs in non-addicted subjects, making them more vulnerable to addiction, as well as in abstinent addicts, increasing the likelihood of relapse [43]. According to this hypothesis, DA-dependent changes in the ventral striatal and/or medial PFC circuits result in disturbed impulse control and impulsive choice, and set the stage for addiction [43].

Relapse can be modeled in rats by reinstatement of extinguished drug self-administration behavior following exposure to drugs (priming), drug-conditioned cues and stressful stimuli [64••]. Consistent with a preferential stimulation of NAc shell DA by systemic cocaine and with a critical role of NAc shell DA receptors are the observations that intra-NAc shell, but not core, infusion of a D1 receptor antagonist prevents cocaine-primed reinstatement and that cocaine-seeking is reinstated by stimulation of D1 and D2 receptors in the NAc shell, but not in the core, by locally infused DA receptor agonists [65••]. Reinstatement induced by drug cues after extinction training is dependent upon an intact DA transmission in the basolateral amygdala [66•] and is associated with an increase of extracellular DA in this area, in addition to the NAc [67]. By contrast, reinstatement contingent upon a drug-associated cue after simple abstinence from cocaine (i.e. without extinction training) appears to depend upon an intact dorso-lateral caudate-putamen [68], and is associated with DA release in this area [69]. Given the role that neostriatal DA plays in habit learning, these observations are thought to support a role for response habit modality in relapse [56••].

Conclusions

Addictive drugs of different classes preferentially stimulate DA transmission in the NAc shell and extended amygdala complex, thus inducing a state of incentive arousal. This DA-dependent state has hedonic properties (e.g. state-hedonia, euphoria) and is accordingly self-referred to as 'liking', but should not be distinguished from DA-independent sensory stimulus-bound hedonia elicited by conventional non-drug rewards (e.g. taste, sex). Incentive arousal exerts profound effects on behavior, increasing motivation for instrumental action and facilitating Pavlovian-incentive learning (i.e. learning of contingencies between stimuli and rewards). Conventional rewards, in addition to eliciting DA-independent sensory hedonia, also elicit state-hedonia as part of an incentive arousal state induced by their ability to release of DA in the NAc shell. This property, however, rapidly undergoes habituation on repeated exposure to the reward. Drug rewards, by acting directly on the brain, bypass and usurp the adaptive mechanisms (i.e. habituation) that constrain the responsiveness of NAc shell DA. As a result of this, incentive arousal and related behavioral consequences can be maintained (unless a different

adaptive mechanism — tolerance — takes place) throughout weeks of drug self-administration. The ability to usurp physiological adaptive mechanisms of NAc shell reponsiveness results in abnormal strengthening of drug–stimulus associations. An example of such abnormal learning is the ability, peculiar to drug-conditioned stimuli compared with stimuli conditioned to food rewards, to stimulate DA transmission in the NAc shell. These mechanisms do not operate exclusively at the beginning of the addiction process but might be critical for reinstating instrumental responding and for re-boosting drug–stimulus associations in relapse, secondary to drug re-exposure (priming). With continuing drug exposure, an additional process is thought to take place; that is, a reduction in the baseline activity of DA transmission that would act as a powerful motivation for maintenance and relapse of drug consumption. Neuroadaptive processes related to the chronic influence of drug exposure on subcortical DA transmission might secondarily impair the function of prefrontal striatal loops, thus resulting in impairments of impulse control and decision making that form the basis for the compulsive feature of drug seeking.

Future directions of this field might be (i) the further application of PET instruments with heightened resolution to human brain imaging studies of DA transmission in decision-making tasks and craving paradigms, (ii) the monitoring of DA and glutamate by microdialysis and enzyme-coated probes during various stages of drug dependence in animals and (iii) the application of lentivirus-carried siRNAs for silencing the expression of DA receptors in animal models of drug dependence.

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This review expands the hypothesis previously suggested by Chuhma *et al*. [29] and by Lavin *et al*. [12••]

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This is the first of a series of studies (together with [36••,37••]) monitoring the response of extracellular DA to response-contingent drug exposure by repeated microdialysis sampling through daily insertion of microdialysis probes into chronic guide cannulae. In this way, the DA response in the NAc shell and core could be monitored from acquisition to maintenance and extinction of drug self-administration. In this study, nicotine increased dialysate DA preferentially in the NAc shell, rather than in the core, from the very first self-administration session, and this feature was maintained as long as the drug was available (i.e. for up to six weeks). Responding under extinction was not associated with release of DA in the NAc.

36. •• Lecca D, Cacciapaglia F, Valentini V, Di Chiara G: **Monitoring extracellular dopamine in the rat nucleus accumbens shell and core during acquisition and maintenance of intravenous WIN 55, 212-2 self-administration**. *Psychopharmacology (Berl)* 2006, **188**:63-74.

See annotation [35••].

37. •• Lecca D, Cacciapaglia F, Valentini V, Acquas E, Di Chiara G: **Differential neurochemical and behavioral adaptation to cocaine after response contingent and noncontingent exposure in the rat**. *Psychopharmacology (Berl)* 2006, [Epub ahead of print].

This work investigated for the first time the neurochemical and behavioral effects of response-contingent versus response-non-contingent drug administration in rats bilaterally implanted with chronic intracerebral guide cannulae and trained to self-administer cocaine in daily 1-hr sessions for three weeks. Nose poking in the active hole by master rats resulted in intravenous injection of cocaine (0.25 mg/kg) to master rats and to rats yoked to them. In master rats, dialysate DA increased preferentially in the NAc shell during cocaine self-administration throughout the three weeks of cocaine exposure. In yoked rats, DA initially increased preferentially in the shell but to a lesser extent than in master rats. With continued exposure to cocaine, the shell/core ratio of DA changes decreased progressively and, on the third week, was reversed so that DA was increased more in the core than in the shell. Yoked rats showed a progressive and faster increase in stereotyped behaviors than did master rats. Therefore, response-non-contingent cocaine administration is particularly prone, compared with response-contingent administration, to induce behavioral and biochemical sensitization.

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41. Berridge KC, Robinson TE: **What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience?** *Brain Res Brain Res Rev* 1998, **28**:309-369.

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44. Di Chiara G: **From rats to humans and return: testing addiction hypotheses by combined PET imaging and self-reported measures of psychostimulant effects. Commentary on Volkow *et al.* 'Role of dopamine in drug reinforcement and addiction in humans:results from imaging studies'**. *Behav Pharmacol* 2002, **13**:371-377.

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This study shows that saccharin avoidance conditioned by nicotine and morphine is impaired by DA receptor blockade. It is suggested that avoidance is the result of comparison between the rewarding properties of saccharin and the DA-dependent drug reward. This study suggests the existence of two kinds of hedonia, a DA-independent sensory stimulus hedonia (e.g. taste-hedonia) and a DA-dependent state-hedonia associated to incentive arousal, and proposes saccharin avoidance as a model for the study of state hedonia.

46. Grigson PS: **Drugs of abuse and reward comparison: a brief review**. *Appetite* 2000, **35**:89-91.

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50. Crombag HS, Grimm JW, Shaham Y: **Effect of dopamine receptor antagonists on renewal of cocaine seeking by reexposure to drug-associated contextual cues**. *Neuropsychopharmacology* 2002, **27**:1006-1015.

51. •• Bassareo V, De Luca MA, Di Chiara G: **Differential impact of pavlovian drug conditioned stimuli on *in vivo* dopamine transmission in the rat accumbens shell and core and in the prefrontal cortex**. *Psychopharmacology (Berl)* 2006, in press.

This study investigates, by microdialysis, the response of extracellular DA in three different terminal areas — the NAc shell and core and medial PFC — to a salient complex olfactory-visual contextual stimulus (a perforated box filled up with a snack food) conditioned to systemic morphine or nicotine. Similar effects were observed with each drug. After three drug–stimulus associations, box presentation elicited strong incentive responses towards the box and increased DA in the shell and PFC, but not in the core, in conditioned, but not in unconditioned and pseudoconditioned, groups. Pre-exposure to the drug conditioned stimuli potentiated drug-induced increase of DA in the shell but not in the core. These observations show that drug conditioned stimuli differentially affect accumbens DA when compared with food conditioned stimuli. Thus, as reported by [21,24] and by [23], food conditioned stimuli stimulate DA efflux in the NAc core and PFC, but not in the NAc shell.

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Using an original single-trial place preference paradigm, this study, along with [54••], shows that intra-shell infusion of D1 receptor antagonists impairs acquisition but not expression of drug-conditioned place preference. It is suggested that drugs, by activating DA transmission in the shell, induce an incentive arousal state that elicits hedonia and facilitates incentive learning.

54. •• Fenu S, Spina L, Rivas E, Di Chiara G: **Morphine-conditioned single-trial place preference: role of nucleus accumbens shell dopamine receptors in acquisition, but not expression**. *Psychopharmacology (Berl)* 2006, **187**:143-153.

See annotation [53••].

55. Bassareo V, De Luca MA, Aresu M, Aste A, AriuT, Di Chiara G: **Differential adaptive properties of accumbens shell dopamine responses to ethanol as a drug and as a motivational stimulus**. *Eur J Neurosci* 2003, **17**:1465-1472.

56. •• Bechara A: **Decision making, impulse control and loss of willpower to resist drugs: a neurocognitive perspective**. *Nat Neurosci* 2005, **8**:1458-1463.

On the basis of neuropsychological and brain imaging studies, the author suggests that addiction is the product of an imbalance between two separate, but interacting, neural systems that control decision making: an impulsive amygdala system for signaling pain or pleasure of immediate prospects, and a reflective PFC system for signaling pain or pleasure of future prospects. After an individual learns social rules, the reflective system controls the impulsive system via several mechanisms. However, this control is not absolute; hyperactivity within the impulsive system can override the reflective system. It is proposed that drugs can trigger 'bottom-up' involuntary signals originating from the amygdala that modulate, bias or even hijack the goal-driven cognitive resources that are needed for the normal operation of the reflective system and for exercising the willpower to resist drugs.

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

The authors view drug addiction as a process involving a transition from different modalities of responding that depend upon interactions between Pavlovian and instrumental learning processes. They hypothesize that the change from voluntary drug use to more habitual and compulsive drug use represents a transition from prefrontal cortical control to striatal control over drug-seeking and drug-taking behaviour, as well as a progression in dopaminergic innervation from ventral to more dorsal domains of the striatum. These neural transitions might themselves depend upon the neuroplasticity in both cortical and striatal structures that is induced by chronic self-administration of drugs.

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61. Reid MS, Ciplet D, O'Leary S, Branchey M, Buydens-Branchey L, Angrist B: **Sensitization to the psychosis-inducing effects of cocaine compared with measures of cocaine craving and cue reactivity**. *Am J Addict* 2004, **13**:305-315.

62. • Melis M, Spiga S, Diana M: **The dopamine hypothesis of drug addiction: hypodopaminergic state**. *Int Rev Neurobiol* 2005, **63**:101-154.

This review provides a view of dependence in terms of neuroadaptive changes of the DA system to chronic drug exposure, resulting in the induction of processes opposite to the DA-stimulant properties of addictive drugs. As a result of this process, drug withdrawal results in depression of DA transmission and firing of DA neurons that exceeds the duration of the physical signs of abstinence, and is attributed the role of promoting drug seeking. This hypothesis is a natural development of the theory by Koob *et al*. [63]. Indeed, given the evidence for a role of DA in intracranial self-stimulation, the observation made by Koob *et al*. [63] that abstinence from chronic drug exposure raises the threshold for intracranial self-stimulation is well explained as a consequence of the reduction in DA transmission induced by chronic drug exposure. Curiously, however, Koob *et al*. [63] are apparently reluctant to make this connection.

63. Koob GF, Sanna PP, Bloom FE: **Neuroscience of addiction**. *Neuron* 1998, **21**:467-476.

64. •• Bossert JM, Ghitza UE, Lu L, Epstein DS, Shaham Y: **Neurobiology of relapse to heroin and cocaine seeking: an update and clinical implications**. *Eur J Pharmacol* 2005, **526**:36-50.

The authors provide a review of recent data on the neurobiology of relapse. An important point they make is the discrepancy between results obtained by total DA inactivation and those obtained by lesion or local manipulation of DA transmission by infusion of specific DA receptor agonists and antagonists.

65. •• Schmidt HD, Anderson SM, Famous KR, Kumaresan V, Pierce RC: **Anatomy and pharmacology of cocaine priming-induced reinstatement of drug seeking**. *Eur J Pharmacol* 2005, **526**:65-76.

The authors review the controversial issue of the role of specific DA terminal areas in reinstatement induced by cocaine priming, and provide important evidence for a role for NAc shell DA in cocaine priming.

66. • See R: **Neural substrates of cocaine-cue associations that trigger relapse**. *Eur J Pharmacol* 2005, **526**:140-146.

This paper reviews studies from the authors' laboratory and from others on the role of the basolateral amygdala in learning cue-drug associations relevant for relapse. Reversible pharmacological inactivation of the basolateral complex of the amygdala just prior to acquisition of cocaine-cue associations blocks the ability of cocaine-paired stimuli to elicit conditioned-cued reinstatement. This learning process is mediated in part by muscarinic acetylcholine and dopaminergic inputs, as intra-amygdala infusion of selective receptor antagonists at the time of acquisition affects reinstatement. Disruption of neural activity within the basolateral complex of the amygdala at the time of consolidation (just after cocaine–cue pairings) also disrupts reinstatement. These results reveal the importance of the amygdala in the acquisition, consolidation and expression of drug-stimulus learning that drives relapse to drug-seeking behavior.

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69. Ito R, Dalley JW, Robbins TW, Everitt BJ: **Dopamine release in the dorsal striatum during cocaine-seeking behavior under the control of a drug-associated cue**. *J Neurosci* 2002, **22**:6247-6253.