DOPAMINE, LEARNING AND MOTIVATION

Roy A. Wise

The hypothesis that dopamine is important for reward has been proposed in a number of forms, each of which has been challenged. Normally, rewarding stimuli such as food, water, lateral hypothalamic brain stimulation and several drugs of abuse become ineffective as rewards in animals given performance-sparing doses of dopamine antagonists. Dopamine release in the nucleus accumbens has been linked to the efficacy of these unconditioned rewards, but dopamine release in a broader range of structures is implicated in the 'stamping-in' of memory that attaches motivational importance to otherwise neutral environmental stimuli.

NEUROLEPTIC
A drug that blocks the effects of dopamine by binding to and occluding the dopamine receptor.

REINFORCEMENT
The strengthening of stimulus–stimulus, stimulus–response or response–reward associations that results from the timely presentation of a reward. The term applies to both Pavlovian and instrumental conditioning, though it is most frequently used with the latter.

Behavioral Neuroscience Branch, Intramural Research Program, National Institute on Drug Abuse, National Institutes of Health, Bethesda, Maryland 20892, USA.
e-mail: rwise@intra.nida.nih.gov
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The neurotransmitter dopamine — particularly nigrostriatal dopamine (BOX 1) — has long been identified with motor function[1]. However, moderate doses of NEUROLEPTIC drugs (dopamine antagonists) attenuate the motivation to act before they compromise the ability to act. Such drugs do not immediately compromise the initiation of well-learned response habits[2–13] or even consummatory behaviour[14]. Rather, initiation of habitual responding declines progressively — sometimes over minutes[3,4] and sometimes over days[5,14] — in neuroleptic-treated animals[12,14]. Therefore, dopamine has come to be identified with motivational[15–17] as well as motor function.

Different versions of the hypothesis that dopamine is important for the normal effectiveness of rewarding stimuli have been challenged on various grounds. In this review, I first identify several versions of the hypothesis, indicating which have been falsified and which remain viable. I then differentiate between the largely conditioned motivation that precedes and guides an instrumental act, and the REINFORCEMENT of stimulus–REWARD and response–reward associations that follows the receipt of reward. This separation of what comes before and what comes after reward contact leads not only to a better appreciation of the role of dopamine in immediate motivation, but also to an appreciation of its role in the learning and memory consolidation functions that establish the motivational foundation of most goal-directed behaviour.

Multiple dopamine hypotheses

Dopamine was first identified with motivational function on the strength of Ungerstedt's[18] report that feeding and drinking deficits that are similar to those caused by lesions of the lateral hypothalamus can be induced by selective damage to the dopamine fibres that traverse this region. Damage to the nigrostriatal dopamine fibres causes feeding and drinking deficits[19,20], whereas selective damage to the mesolimbic dopamine fibres decreases the forward locomotion[21] that is common to most reward-seeking[22]. With the development of selective dopamine antagonists, it was found that compromise of dopamine function affects instrumental responding for food[5] even more effectively than it attenuates free feeding[14].

Neuroleptics were found to attenuate or block the rewarding effects of lateral hypothalamic electrical stimulation[3,4,11,23–25], intravenous amphetamine[2] or cocaine injections[26], and food[5] and water[6]. Although they could perform the required responses[12], neuroleptic-treated rats did not learn[27], nor, if previously trained, did they long continue[3,5,12,24,28], to press a lever or run along an alley[4] for such rewards. Selective depletion of forebrain dopamine had similar effects[29–33]. Such findings led to the dopamine hypotheses of reinforcement[34], reward[35] and hedonia[5].

The dopamine hypothesis of reinforcement. Reinforcement is the specialist term for the 'stamping-in' of stimulus associations and response habits[36] that follows

REWARD
In the noun form (a reward), an object or event that elicits approach and is worked for; its analogue is 'a reinforcer'. In the verb form (to reward) the term is synonymous with 'to reinforce'. As a verb it is used with respect to instrumental but not Pavlovian conditioning.

the receipt of reward. The hypothesis was originally advanced in relation to instrumental reinforcement, dealing with the learning and maintenance of habits that lead to rewards. As mentioned, animals do not learn to lever-press for such things as food, water or sexual contact if the training takes place while dopamine function is impaired[27]. Moreover, although well-trained animals perform normally for an initial period, they do not continue to do so if their dopamine systems are blocked[5,9,28,37] (FIG. 1). The progressive decline in responding under dopamine blockade, like the progressive decline under conditions of non-reinforcement, occurs more rapidly and more completely across trials (the resistance-to-extinction effect[5,12]), as if the expectancy of the animal, based on the memory of devalued reinforcement from previous days, becomes progressively weaker (FIG. 2).

The interpretation of within-session declines as evidence of devalued reinforcement[3–5,28] is widely accepted[38] but has been questioned[39–42]. Few alternatives have been offered, however, and several of the original skeptics have reversed their initial judgements[7,43,44]. The only serious alternative, that neuroleptics cause some form of progressive motoric, fatigue-like impairment, is called into question by the finding that a sensory change can reinstate the extinguished behaviour while the animal is still under the influence of the neuroleptic[3,24] (FIGS 1,3). Even more telling is evidence that derives from across-session changes (FIGS 2,4). First, when animals are tested many times under neuroleptic treatment, responding drops out more and more quickly from one neuroleptic session to the next[5]. This cannot be interpreted as an accumulating effect of the drug, because responding is normal on drug-free test days between the neuroleptic treatments. The only residual effect from the previous sessions that is offered to explain the progressively deteriorating performance on the second, third and fourth tests is the memory of devalued reinforcement from previous tests under the neuroleptic[5,12,38].

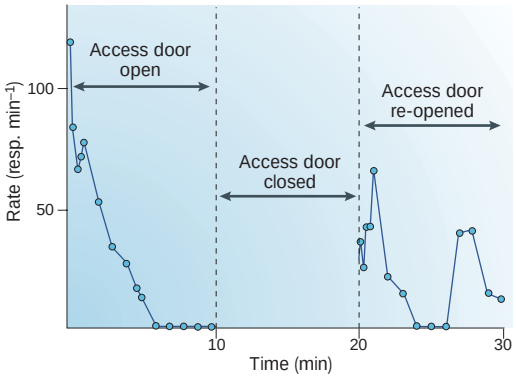

Figure 1 | **Effect of dopamine receptor blockade on lever-pressing for brain stimulation reward.** The normal response rate for this animal was about 100 responses per minute (resp. min^{-1}). With dopamine receptors blocked (1 mg kg^{-1} of pimozide, 4h before the start of testing) responding was initially normal but dropped to zero within a few minutes. Animals in this condition rarely approached the lever during the last 25 min of their 30-min test sessions. In this case, the door to the alcove containing the lever was quietly closed four minutes after response cessation. When the door was re-opened 10 min later, the animal temporarily resumed responding. Franklin and McCoy[24] more formally demonstrated stimulus control of responding after neuroleptic-induced extinction of responding. Modified, with permission, from REF. 3 © (1976) Elsevier Science.

The assumption that neuroleptics blunt the reward value of food is also required to explain the increased responding in extinction of animals that have been trained under intermittent neuroleptic treatment[7] (FIG. 5). The only other treatment that produces such increased responding in extinction is intermittent reinforcement. The unchallenged interpretation of the increased resistance to extinction of rats with intermittent dopamine blockade is that the intermittent dopamine blockade is functionally equivalent to intermittent omission of reinforcement[38].

The stamping-in of stimulus–reward associations through Pavlovian conditioning also fails when dopamine systems are blocked. Animals normally learn preferences for places in the environment where they have experienced reward; such preferences do not develop if the reward is experienced under dopamine blockade[44–48]. So, most normally reinforcing stimuli and events fail to reinforce either instrumental behaviour or associations between rewards and other stimuli when dopamine function is impaired. This is not to say that dopamine is important for all reinforcement or that dopamine is important only for reinforcement. Intracranial self-administration of phencyclidine and other NMDA (*N*-methyl-D-aspartate) antagonists, for example, is dopamine-independent (it acts in the same circuitry, but downstream from dopamine input)[49]. Moreover, dopamine does more than simply stamp in reward-related memories[1,50,51]. With these caveats, the dopamine hypothesis of reinforcement is well established. Whatever else dopamine might do, it is crucial in

Box 1 | The dopamine systems

Most dopamine-containing cells develop from a single embryological cell group that originates at the mesencephalic–diencephalic junction and projects to various forebrain targets. These long-axon dopamine cells figure strongly in motivational and motor theory. The cell group has been subdivided into several nominal systems. The best known is the nigrostriatal system, which originates in the zona compacta of the substantia nigra (SNc); it is identified most strongly with motor function. Fibres from this subdivision project primarily to the caudate–putamen in the rat (now commonly known as the dorsal striatum in rodents). More medial are the mesolimbic and mesocortical dopamine systems, which are thought to be more important for motivational function and arise from the dopamine cells that are associated with the ventral tegmental area (VTA).

The boundaries between these 'systems' are not well defined. The dopamine cells of the VTA and SNc form a continuous layer and project to adjacent and overlapping terminal fields[196]. The SNc projects primarily to the caudate putamen. The cells of the VTA project most strongly to the nucleus accumbens and olfactory tubercle, but also innervate the septum, amygdala and hippocampus. This subset of projections is known as the mesolimbic dopamine system. Cells in the medial VTA project to the medial prefrontal, cingulate and perirhinal cortex. This subset is known as the mesocortical dopamine system. There is considerable overlap between the VTA cells that project to these various targets. Because of the overlap between the mesocortical and mesolimbic dopamine neurons, the two systems are often collectively referred to as the mesocorticolimbic dopamine system.

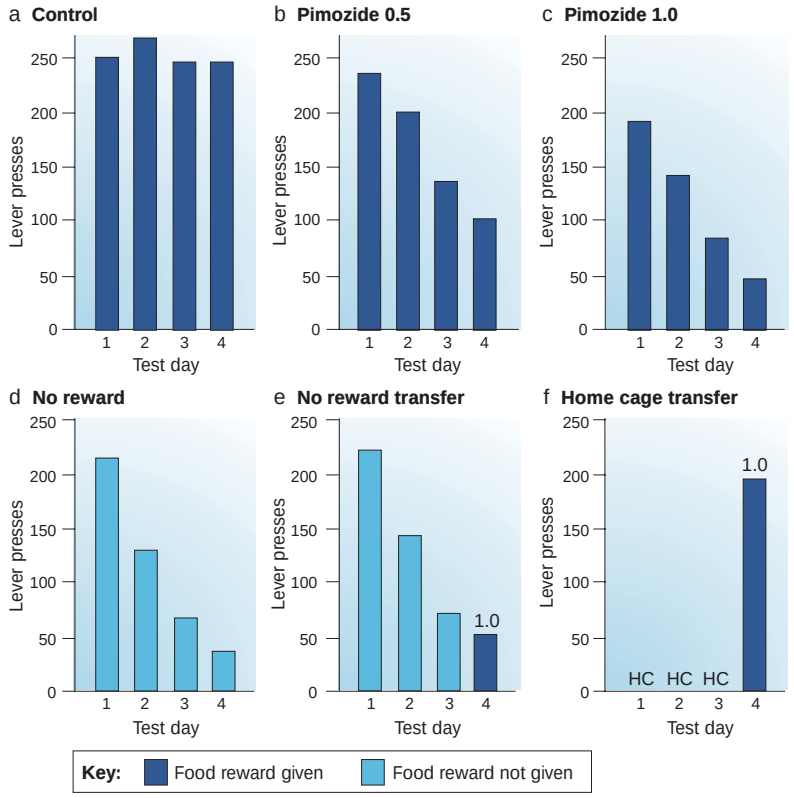

Figure 2 | **Effect of dopamine receptor blockade on lever-pressing for food reward.** **a** | Animals were trained for 2–3 weeks to lever-press for food under conditions of 20-h deprivation. **b**–**f** | The effects of dopamine blockade (**b**,**c**) or non-reward (**d**,**e**) were then assessed on four occasions, which were separated by two days each of retraining. On the first day of such testing, both non-rewarded and pimozide-treated animals (0.5 or 1.0 mg kg^{-1} 4 hours before the start of testing) persisted in responding at almost normal levels. Such responding in the non-reward condition demonstrated the strength of conditioned responding; such responding in the pimozide conditions shows that the drug did not severely attenuate performance capacity. On subsequent days, responding decreased progressively in both conditions. Weak responding on the fourth day of testing in the high-dose pimozide condition was not a consequence of drug accumulation, as animals given the first three pimozide injections without the opportunity to taste food in this condition (**f**, home cage (HC) transfer condition) responded as much after their fourth injection as did the animals that were given their first injection in the test box. Modified, with permission, from REF. 5 © (1978) American Association for the Advancement of Science.

most instances of positive reinforcement. Most normally rewarding stimuli fail to serve as effective reinforcers in dopamine-compromised animals[16,38].

The dopamine hypothesis of reward. Reinforcement is sometimes called a retroactive effect on learning because it occurs after the behaviour that is being reinforced (it affects the still-active memory trace of the behaviour, not the behaviour itself). In addition to their reinforcing effects, rewarding and reward-associated stimuli have proactive, DRIVE-like effects. Such stimuli cause motivational arousal[52] and increase the probability of response initiation when the primary reward has not yet been earned or directly sensed[53–55]. This is illustrated in the case of an animal pressing a lever for brain stimulation reward in the goal box of a runway. Post-response stimulation not only reinforces the trace of the initial lever-presses; it also energizes the animal before and during the next lever-press (before delivery of the next reward). Moreover, stimulation before the next trial decreases response latency and increases speed in the alleyway that leads to the lever[54]. Another example is the enhanced attractiveness of a second salted peanut after the tasting of a first. The common term 'reward' is often used to denote the undifferentiated effects of reinforcement and motivational arousal[36].

The energizing (motivating) effect of 'free' reward given before an instrumental act is known as PRIMING. The priming effect of a free reward tends to decay quickly. In the case of rewarding lateral hypothalamic electrical stimulation, the effect of pre-trial stimulation decays in seconds[54]. The reinforcing effect of stimulation given after a response also affects subsequent responding, but the effect is long lasting. The effect of a reward that is given after a response can affect the strength of the next response even if it occurs days or weeks later[54]. So although the priming effect is not stored in long-term memory, the reinforcing effect is[54]. Both the priming effect[56] and the reinforcing effect[3,4,11,24,25,57] of rewarding brain stimulation seem to be at least partially[57] dopamine-dependent. Dopamine and dopamine agonists can also prime food-, cocaine- and heroin-seeking behaviours[58–63]. As with the reinforcement hypothesis, the hypothesis that dopamine contributes to pre-reward motivational arousal is well supported.

However, dopamine does not make the only contribution to the priming of an animal that is about to perform a learned reward-seeking response. Immediate dopaminergic activation is not a necessary — only an amplifying[64] — condition for pre-reward motivation. That is, experienced animals tested under conditions of dopamine receptor blockade initiate and perform previously rewarded actions normally, often until after they have had considerable experience with the reward under the treatment condition[5,9,14,28].

The dopamine hypothesis of incentive motivation. Incentive motivation refers primarily to the priming or drive-like effects of an encounter with an otherwise neutral stimulus that has acquired motivational importance through prior association with a primary reward. How fast an animal runs in an alleyway depends in part on the degree of association between the start box and alley cues with a previous reward[65]. The runway itself comes to have a memory-dependent effect on the response. This external contribution to the motivation of the animal combines with internal drive states to determine the strength of goal-directed behaviour. The distal cues (sight or smell) of the reward itself gain learned incentive value through their association with reward contact. Until we have had contact with the fruit of the banana, the yellow skin is a neutral stimulus; after it has been associated with the taste and post-ingestive consequences of the fruit, it becomes an incentive-motivational stimulus. Incentive-motivational stimuli such as the yellow skin are, essentially, the learned predictors of reward.

Although it has been suggested that dopamine is essential for incentive motivation[36,66], the most important role of dopamine in incentive motivation is historical; it is the stamping-in of stimulus–reward associations that has

DRIVE
The energizing effects on behaviour of internal stimuli associated with tissue need or hormonal level, or of external stimuli associated with past rewards ('incentive motivational' stimuli).

PRIMING
The precipitation of a learned response habit by administration of an unearned sample of the reward.

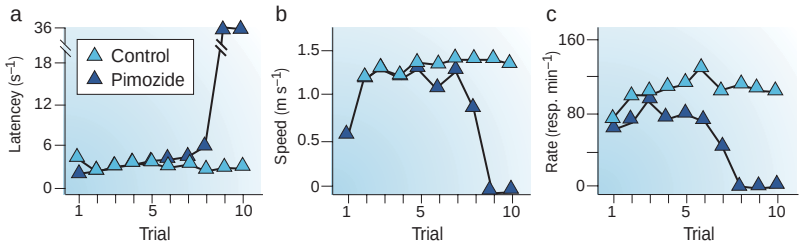

Figure 3 | **Effect of dopamine receptor blockade on lever-pressing for brain stimulation reward.** In this experiment, pimozide (0.5 mg kg^{-1}, 4 hours before testing) failed to affect latency to leave the start box (**a**), speed to traverse a 1.8-m runway (**b**), or the rate of lever-pressing for fifteen 500-ms trains of lateral hypothalamic stimulation (**c**). Within 10 trials, however, the animals stopped running and lever-pressing. Note that the animals did not stop running until the trial after they stopped lever-pressing, and the animals did not stop leaving the start-box quickly until the trial after they stopped running. So, pimozide impaired the ability of the stimulation to sustain responding rather than the ability of the animals to initiate responding. Indeed, after a 10-min time-out, the animals again initiated responding normally, and ran normally but responded minimally on the first of a new set of trials[4]. Modified, with permission, from REF. 4 © (1978) American Psychological Association.

established incentive-motivational value for previously neutral stimuli. When the dopamine system is blocked in an animal learning a task, normal rewards fail to confer incentive-motivational value on potentially predictive stimuli. When the dopamine system is blocked in animals that have already learned the task, established reward-predictors now become associated with devalued rewards and so do not retain their incentive-motivational efficacy. A rewarding stimulus must be effective as a reinforcer if it is to confer or maintain, by association, incentive value for otherwise neutral stimuli. If the dopamine system is blocked when an animal first encounters food reward in a new setting, the start box, alleyway, choice-point or manipulandum will not gain the conditioned ability to attract or accelerate the animal[27,44,46–48,67].

Once established, incentive-motivational stimuli are at least temporarily autonomous; they can instigate response habits, learned preferences and consummatory behaviour even when the animal is not in an appropriate internal (drive) state[67,68] and even when the dopamine system is blocked[3–6,9–11,13,14,24,69,70]. When the animal is tested for any length of time in these conditions, the ability of the incentive-motivational stimulus to elicit a response and to energize the animal is extinguished[3–6,11,14,24,28,68–70] because the stimulus is now being paired with an ineffective reinforcer. That is, the incentive value of the stimulus will be progressively unlearned or weakened as the stimulus comes to predict non-reward or devalued reward.

Although incentive-motivational stimuli can be normally or near-normally effective in initiating and motivating learned habits even with dopamine function blocked, such stimuli can cause brief phasic activation of the dopamine system[63,71,72] and such activation can amplify conditioned motivation[62,64]. This activation of the dopamine system by brief incentive-motivational cues (reward predictors) causes only minor dopamine overflow[63], relative to that seen when an animal is offered a meal[73] or an addictive drug[74–76].

The dopamine hypothesis of reward proposes that dopamine is important not only in the reinforcement that follows the earning of a reward, but also in the incentive motivation that precedes the earning of a reward. Incentive motivation can be strong even when the dopamine system is phasically blocked, and the traditional incentive-motivational stimuli seem to activate the dopamine system relatively weakly, so it would seem that the primary role of dopamine in incentive motivation is the establishment of conditioned incentive stimuli. However, dopamine not only helps to establish the incentive-motivational value of such stimuli during initial conditioning; it also helps to maintain that value through periodic reinforcement. So, administration of dopamine agonists before responding can potentiate the incentive motivational effects of conditioned stimuli and can retard the extinction that normally develops when conditioned stimuli are experienced repeatedly in the absence of earned reward. The hypothesis that dopamine is important for incentive motivation reflects most strongly the fact that incentive stimuli are effective in the present because of past association with dopamine release evoked by a primary reinforcer. This is an essential premise of the more general dopamine hypothesis of reward[36].

The dopamine hypothesis of conditioned reinforcement. Reward-associated motivational stimuli do not only elicit and invigorate behaviour when given before a response; they can also serve as conditioned reinforcers when given contingent upon (after) a response. For example, thirsty rats will learn to work for the presentation of a light that has been previously paired with water. In such testing, injections of amphetamine into the nucleus accumbens, causing local dopamine release, enhance responding for the light[77], whereas dopamine-selective lesions of the nucleus accumbens reduce such responding[78]. Therefore, dopamine can modulate the expression of conditioned reinforcement as well as being essential for the establishment of conditioned reinforcers. It is the dopamine-dependent reinforcement history that establishes the conditioned reinforcer in the first place, and it is presumably the ability of the conditioned reinforcer, once established, to cause phasic dopamine release[61,62] that augments its momentary effectiveness.

The anhedonia hypothesis. Rewards are usually associated with a subjective feeling of pleasure or euphoria. The anhedonia hypothesis[5,12] posits that dopamine is important for this pleasure. Evidence from human studies on the possible role of dopamine in euphoria is limited and mixed. Brain imaging studies have indicated that stimulant-induced euphoria is loosely correlated with the degree of drug-induced dopamine release[79–81]. However, early reports that neuroleptics blunt the normal pleasures of life[82,83] have been questioned[84], and low doses of cocaine can control behaviour even when they are subjectively indistinguishable from placebo[85]. So, the correlation seems to be weak.

Against the assumption that pleasure is a necessary correlate of reinforcement is evidence that animals can be taught to work for painful stimulation[86] and that humans will sometimes compulsively self-inflict painful injury[87]. Also, pleasure and reward can be dissociated even in the case of drug euphoria: there is rapid within-session

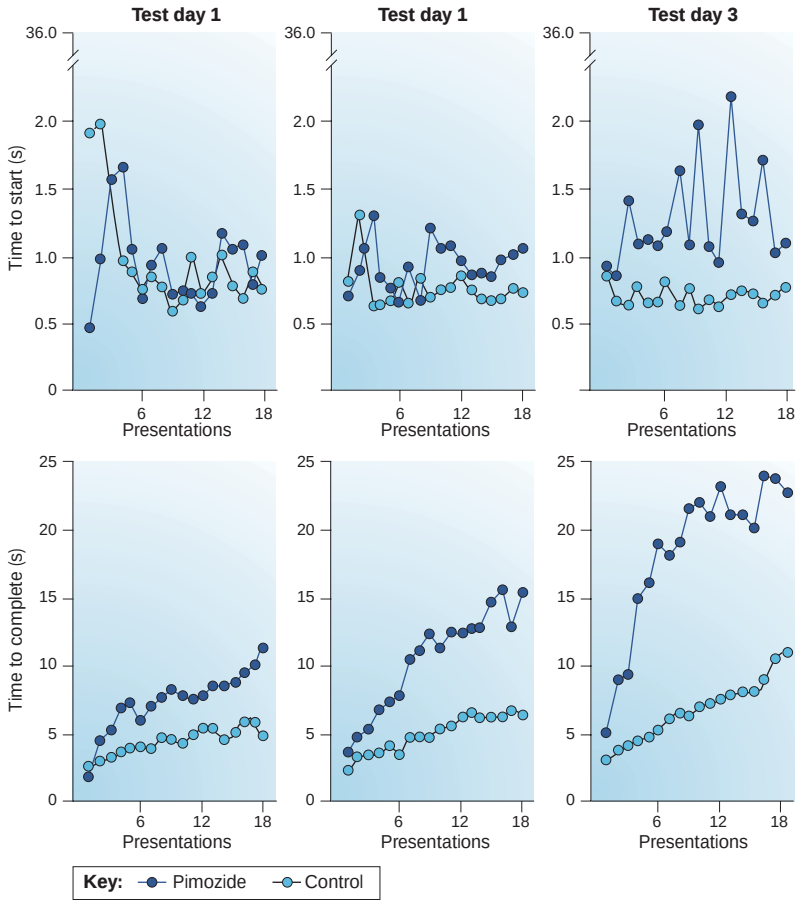

Figure 4 | **Effect of dopamine receptor blockade on free feeding.** Food-deprived (22 h) and pimozide-pretreated (0.5 mg kg^{-1}, 4 h before testing) animals were offered 18 dishes of 5 food pellets each at 36-s intervals. With each presentation, latency to make mouth contact with the first pellet and time to eat the five pellets once the first was contacted were separately timed. Testing was repeated three times, with two normal training days between tests. Latencies to mouth the first pellet were usually under 1 s for both pimozide-treated and vehicle-treated animals throughout the first two days of testing. Latencies began to slow toward the end of the second test and throughout the third test in the pimozide-treated group, despite normal latencies on the intervening neuroleptic-free training days. The time to finish the fifth pellet after tasting the first declined progressively in both groups, reflecting the satiating effects of the eaten pellets. These response times declined more rapidly, however, in the pimozide-treated animals. In these animals, the taste of food did not sustain normal responding after the first presentation on the first day. So, food failed to maintain responding in the pimozide-treated animals long before it lost the ability to elicit responding, and the more experience the animals had with food in the pimozide condition, the less effective food became in this regard. The pimozide-treated animals lost the motivation to pick up the food only long after the food lost the ability to maintain consumption. Modified, with permission, from REF. 14 © (1986) Elsevier Science.

tolerance to the subjective pleasure of rewarding drugs such as cocaine[88], morphine[89] and nicotine[90], but there is little or no within-session tolerance to the ability of these drugs to sustain repeated and regular self-administration[91]. The fact that the subject responds at a constant rate for a dose of drug that has progressively weaker subjective effects indicates that subjective pleasure might be merely the closest conscious correlate that humans can find for an event — reinforcement — that is subliminal[80,85].

A recent challenge to the anhedonia hypothesis comes from studies of the facial expression of rodents given sweet solutions directly into the mouth. Human infants and lower animals show arguably similar facial expressions when given intra-oral sweet solutions[92]. Berridge and colleagues have reported that the orofacial movements associated with liking sucrose are not altered by dopaminergic lesions[93] or neuroleptic drugs[94]. However, it is only the initial response to sucrose that is normal in neuroleptic-treated animals[95]. Although Pecina *et al.*[94] argued for a sensory-motor deficit, Leeb *et al.*[95] suggested that the progressive decline in liking signs reflects the extinction of conditioned liking, analogous to the extinction of instrumental behaviour that is seen in neuroleptic-treated animals. In other words, the reward value of sucrose was devalued under the neuroleptic, but experience with the taste of sucrose in this condition was necessary before a change in facial responses was seen.

In any case, the fact that normal facial responses to sucrose are seen in decorticate rats[96] and anencephalic human infants[97] indicates that these facial movements are more related to stereotyped fixed action patterns of ingestion[98] than to forebrain mechanisms of motivation and emotion. This would fit with the Robinson and Berridge caveats that wanting and liking can be 'pre-conscious' and that "People are not directly aware of their own likes and wants"[99]. On present evidence, it seems best to suggest that elevations in brain dopamine are only loosely correlated with subjective pleasure.

Motor hypotheses. The anhedonia hypothesis[5,12] was advanced on evidence that moderate doses of dopamine antagonists can block an animal's willingness to make instrumental responses without severely limiting its capacity to make those responses. The distinction between motor deficits (wants to but can not) and motivational deficits (can but does not want to) is troublesome; there is little agreement about a definition of motivational function that distinguishes it, operationally, from motor function[100]. It has been suggested that the dopamine system "Is a higher-order motor system, nothing more, nothing less"[40]. Unfortunately, the distinction between higher-order and lower-order motor systems is even more subjective than the distinction between motivational and motor systems.

The hypothesis that dopaminergic impairment causes only motor deficits is falsified by demonstrations of neuroleptic-treated animals that initiate or reinstate normal responding but fail to maintain it after substantial experience with the reward in the neuroleptic condition[3–5,9,11,14,24,28]. Indeed, neuroleptic-treated animals working for intravenous stimulants usually take more than the normal number of injections before being satisfied or giving up entirely[2,26,101]. Moreover, evidence that normal rewards are devalued when experienced under neuroleptic treatment can be seen when an animal is tested in subsequent neuroleptic-free conditions. When tested the day after experience with a given reward under neuroleptic treatment, animals initiate responding as if the remembered reward were devalued in the neuroleptic condition[9]. This can be true even when responses during the neuroleptic treatment are irrelevant, as in conditioned place preference experiments[44–48]. Perhaps most telling is the fact that intermittent training under a

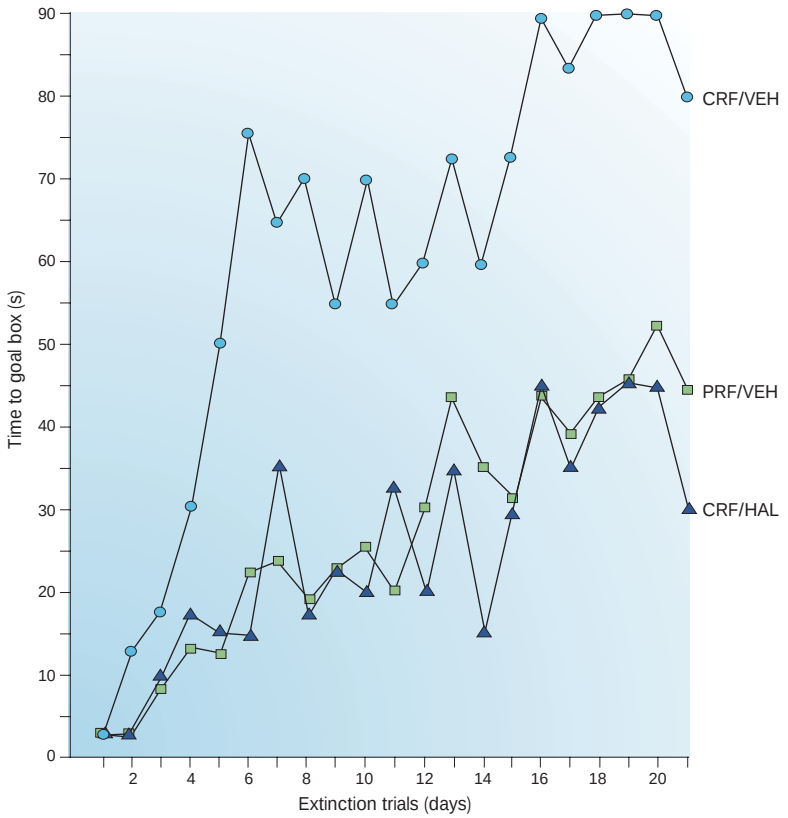

Figure 5 | **Effect of dopamine receptor blockade during training on the strength of subsequent performance.** Food-deprived rats traversed a runway for food once each day for 21 days. Runway performance was then monitored for another 21 days in which no food was given in the goal box. Rats that had received food every day in the training sessions (CRF) quickly slowed their performance during extinction testing. Rats that had been non-rewarded on one-third of their training trials (PRF) persisted much more. Rats that had received food on every training trial but were pretreated with the neuroleptic haloperidol on one-third of their trials (HAL) persisted like the animals that were non-rewarded on one-third of their trials. This group performed in drug-free extinction as if they had been only partially reinforced during training. The only explanation that has been offered to explain this counter-intuitive finding is that the haloperidol treatment rendered food, on those days, ineffective as a reward. VEH, vehicle Modified, with permission, from REF. 7 © (1986) Elsevier Science.

neuroleptic in the partial reinforcement extinction paradigm makes subsequent neuroleptic-free performance even more vigorous than normal[7,8] (FIG. 5).

A motor hypothesis that ignores such evidence is the 'anergia' hypothesis[102], which posits that dopamine blockade or lesions cause "Decreased willingness to exert effort"[103]. However, the classification of decreased willingness as a motor deficit is difficult to reconcile with the primary distinction between motor and motivational function: the distinction between the ability to exert effort and the willingness to do so. An animal without the ability to exert effort might have a motor problem; an animal without the willingness to do so has, by definition, a motivational problem. Indeed, the anergia hypothesis has recently been re-classified by its authors as a motivational hypothesis[104]. It is best viewed as an incentive motivational hypothesis, as it deals with apathy in the face of normally motivational stimuli; in its original version it specified that "Neuroleptics attenuate the activating or arousing effect of positively reinforcing stimuli"[103]. It is clear that dopamine-blocked animals are less likely to work under low-density than high-density reinforcement schedules[105], but one should not expect a given reward to sustain hard work as readily as it sustains easy work. In any case, the arguments of the advocates of the anergia hypothesis[42,103] do not bear directly on the reinforcement hypothesis or reward hypothesis *per se*; rather, they are arguments against the anhedonia[42] hypothesis or a nucleus accumbens hypothesis[105].

The nucleus accumbens hypothesis. The widely held association of reward function with dopamine in the nucleus accumbens originated from lesion studies; dopamine-selective lesions of the nucleus accumbens attenuated the rewarding effects of cocaine[30] and amphetamine[106], but noradrenergic and other lesions did not[30]. Although such studies implicate the nucleus accumbens in reward function, they should not be taken as evidence that the nucleus accumbens is the only dopamine terminal field involved. Nigrostriatal lesions cause motivational deficits in feeding and drinking, but lesions that are restricted to the mesolimbic dopamine system do not[19]. Feeding is affected by manipulations in the nucleus accumbens[107], but also by more dorsolateral striatal manipulations[108]. Morphine[109] and methionine enkephalin[110,111] are self-administered directly into the nucleus accumbens, as are amphetamine[112,113], phencyclidine[49], nomifensine[114] and, with some difficulty, cocaine[114]. However, drug microinjections are also rewarding at other sites, and despite the fact that such injections can spread or migrate to distant sites of action[115], most studies have not controlled for such spread. Morphine is self-administered into the ventral tegmental area[116] as well as the nucleus accumbens, and phencyclidine[117] and cocaine[118] are also self-administered into the medial prefrontal cortex. Cocaine is even more avidly self-administered into the olfactory tubercle[119]. So, only the nucleus accumbens hypothesis — rather than the more general dopamine hypotheses — is vulnerable to evidence that nucleus accumbens depletions fail to block the effects of a given reward. Even the nucleus accumbens hypothesis would be difficult to falsify with lesion evidence, given the difficulty in ensuring that a given lesion damages nucleus accumbens completely while causing no damage to fibres of passage or to adjacent structures.

The dopamine hypothesis of addiction. Dopamine is thought to have an important role in the habit-forming actions of several addictive drugs[34,35,120,121]. The early versions of this hypothesis suggested that dopamine might be crucial for all drug reward[120,121], but phencyclidine[117], morphine[122] and nicotine[123], at least, seem to have dopamine-independent as well as dopamine-dependent rewarding effects. It is also questionable whether the rewarding effects of benzodiazepines, barbiturates or caffeine are dopamine-dependent[124]. So, the cautious view is that dopamine is crucial for the rewarding effects of the psychomotor stimulants and is important but perhaps not crucial for the rewarding effects of the opiates, nicotine, cannabis and ethanol[124].

The dopamine transporter hypothesis of cocaine addiction. Because cocaine is a dopamine uptake inhibitor[125], because cocaine's rewarding effects are dopamine-dependent in normal animals[26,48,101], and because the rewarding effects of cocaine-like drugs are better correlated with their affinities for the dopamine transporter (DAT) than with their affinities for other binding sites[126], it has been assumed that cocaine addiction results from the binding of cocaine to DAT and to the resultant inhibition of dopamine reuptake[26,30]. Although it remains clear that dopamine actions are essential for cocaine reward in normal animals[26,48,101], the unqualified version of the dopamine transporter hypothesis has been falsified by the finding that dopamine is rewarding even in DAT-deleted mutant mice[127,128]. The action of cocaine at DAT might be sufficient for cocaine to be rewarding, but it is not necessary. In the mutant mice, the blockade of other monoamine transporters by cocaine is apparently important. Cocaine blocks the noradrenaline and serotonin transporters (NET and SERT, respectively) as well as DAT, and each of these can clear local extracellular dopamine. For example, dopamine uptake in the prefrontal cortex, a cocaine reward site[118], is mediated primarily by NET, as DAT is sparse in this region and the abundant NET has a strong affinity for dopamine[129]. Dopamine levels are abnormally high in the nucleus accumbens of DAT-knockout animals, but even in these animals they can be elevated further by cocaine[130]; this is presumably mediated by the effects of cocaine on one of the other monoamine transporters. Moreover, dopamine levels in the olfactory tubercle, rather than nucleus accumbens, might be crucial[119], and it is not known which transporter normally clears dopamine from the olfactory tubercle. In any case, cocaine is no longer rewarding in mice with both DAT and SERT knocked out[131]. So, cocaine actions at NET, SERT or both contribute to cocaine reinforcement in DAT-knockout animals. In normal animals, actions of cocaine at NET and SERT seem to contribute little to the reinforcing actions of the drug[30,132,133].

Wanting versus liking. Berridge and Robinson[99,134,135] have used the terms 'liking' and 'wanting' to distinguish two seemingly independent dimensions of reward function. On the surface, the distinction seems to correspond to that between reinforcement on the one hand and drive plus incentive motivation on the other. This would identify wanting as the state of mind of an animal before receiving a reward, and liking with the state of mind of an animal after receiving that reward. However, Berridge and Robinson argue that wanting and liking are states of mind that can both be present before receipt of reward and that can, therefore, concurrently influence reward seeking. They rely on the taste reactivity test as their measure of liking (applicable only to food) and on drug sensitization as identifying the mechanism of wanting[136]. Berridge and Robinson argue that although dopamine is not important in the liking of reward (see anhedonia, above), it is important for the wanting of reward[134], or, in other words, for hunger or appetite.

Berridge and Robinson's suggestion that dopamine must be important for the wanting of rewards derives from their failure to observe effects of dopaminergic impairment[93,94] on the stereotyped fixed action pattern[98] that is their index of liking. They argue that deficits in reward seeking must, if they do not reflect decreased liking, reflect decreased wanting of reward. This argument seems to be falsified by the finding that neuroleptic-treated rats usually continue to approach rewards and reward predictors until they have had considerable experience with the reward while under the influence of the neuroleptic[3–5,9,12,14,28]. If wanting — and only wanting — were devalued under neuroleptics, responding in early trials should not be normal and should not depend on the animal's past history with the reward under neuroleptic treatment. The fact that responding decreases progressively and only after an initial experience with the reward in the neuroleptic condition[9,14] argues strongly for the position that the prior neuroleptic-induced decrease in liking of a reward explains any subsequent decreased wanting of that reward. Rats seem to need to learn that a given reward is not likeable (reinforcing) when experienced under neuroleptics. Until they have the requisite experience for such learning, they continue to demonstrate both wanting and motor competence[9,12,14,95].

Although phasic dopamine release is not a necessary condition for the apparent wanting that is triggered by a reward-associated environment, such activation can be sufficient to enhance cue-induced wanting[60,62,64]. This modulating effect notwithstanding, it is the dopamine-dependent reinforcement history of the animal that determines the apparent wanting that is implied by approach and instrumental behaviours.

Reward or reward prediction? One new line of study links midbrain dopamine neurons to error signals that are involved in learning algorithms[137,138]. Midbrain dopamine neurons are activated by proximal (touch, taste) contact with unexpected rewards[71,139,140]. When such events become predictable, the cells begin to respond to the more distal (visual or auditory) stimuli that precede and predict availability of the reward; the cells then stop responding to subsequent contact with the reward[139,140]. This finding has been interpreted to suggest that brain dopamine is more responsive to predictors of reward than to the receipt of reward[125]. This is an oversimplification, as cells that no longer burst in response to the proximal reward stimuli are still responsive to the omission of the reward; when the expected proximal contact does not occur, the dopamine cells are inhibited[71,139]. So, although dopamine release is triggered by the earliest reliable predictor of reward, midbrain dopamine neurons still remain sensitive to the receipt or lack of reward. The fact that the cells are most responsive to proximal contact with reward in the early phases of training is consistent with the fact that it is in the early phases of training that habits are most strongly influenced by the receipt of reward. Indeed, this is consistent with the finding that dopamine cells continue to respond to the taste or touch of food for between thirty and a few hundred

trials before switching to respond to an auditory or visual predictor of reward (W. Schultz, personal communication) as the behaviour becomes more automatic.

After tens or hundreds of trials, drug-predictive stimuli become conditioned reinforcers in their own right[141]. Once such stimuli have become conditioned reinforcers, animals will learn new responses with these as the only reward[142]. Even the tastes of most food rewards are conditioned reinforcers[143]. Taste is a predictor of the post-ingestive consequences of food that stamp in memories for food associations and make otherwise neutral tastes rewarding[126–128,144–146]. So, reward-predicting conditioned stimuli can serve two roles: guiding and modulating the behaviour that follows them, and stamping-in memories for associations that preceded them. Which role they play is largely determined by when in the instrumental sequence they are presented[147].

Dopamine and memory consolidation

Most goal-directed motivation — even the seeking of food or water when hungry or thirsty[148] — is learned. It is largely through selective reinforcement of initially random movements that the behaviour of the neonate comes to be both directed at and motivated by appropriate stimuli in the environment[149,150]. For the most part, our motivations are motivations to return to the rewards we have experienced in the past, and to the cues that mark the way to such rewards. It is primarily through its role in the selective reinforcement of associations between rewards and otherwise neutral stimuli that dopamine is important for such motivation. Once stimulus–reward associations have been formed, they can remain potent for some time even after the reward has been devalued by the absence of appropriate drive states such as hunger or thirst[67,68,151], or because the dopamine system of the animal is blocked[3–5,9,28]. Once a habit has been established, it remains largely autonomous until the conditioned significance of incentive motivational stimuli has been extinguished or devalued through experience. Extinction of the conditioned significance of such stimuli can result from repeated unrewarded trials[5], repeated trials in the absence of an appropriate drive state[67,68], or repeated trials under the influence of neuroleptics.

The ability of phasic dopamine release to augment the motivation that is induced by drives and conditioned stimuli is thought to involve dopamine's actions in the nucleus accumbens[62]. However, dopamine appears to be important for learning and memory in most terminal fields of the nigrostriatal, mesolimbic and mesocortical dopamine systems. Indeed, at the cellular level there is evidence that dopamine is involved in learning and memory in all the main dopamine terminal fields except the nucleus accumbens.

Dopamine and memory at the cellular level. Early attempts to link reinforcement to a cellular mechanism considered it in relation to the consolidation of long-term memory[152–154]. From this perspective, the reinforcement process is seen as acting on the after-effects of a learning experience, increasing the probability that the residual activity corresponding to a short-term memory trace will be effective in laying down a long-term memory trace. In its most basic form, reinforcement is seen as potentiating, 'stamping-in' or 'consolidating' memory traces.

In *Aplysia californica*, learning at the neuronal level has been demonstrated when a sensory neuron excites a motor neuron and that excitation occurs in the presence of the neuromodulatory transmitter serotonin[155]. Serotonin does not itself open or close the ion channels of the motor neuron, but, through intracellular messenger cascades, makes the motor neuron more responsive to subsequent excitatory input. Therefore, it strengthens (reinforces, stamps in or consolidates) the synaptic connection between the sensory and motor neurons.

In mammals, two models of such learning have been studied in detail: long-term potentiation (LTP) and long-term depression (LTD). LTP and LTD have been demonstrated in a number of brain regions, each linked to an effect of dopamine receptor activation. In the hippocampus, dopamine seems to have a reinforcing role analogous to that of serotonin in *A. californica*[155]. LTP and LTD are each seen at excitatory synapses on hippocampal pyramidal cells. Hippocampal LTP is blocked by dopamine D1 receptor antagonists[156–159] and facilitated by D1 receptor agonists[160]. Hippocampal LTD is potentiated by D1 agonists or D2 antagonists, and is blocked by D1 antagonists or D2 agonists[161]. LTP and LTD are also dopamine-dependent in the dorsal STRIATUM[162,163], amygdala[164] and frontal cortex[165–167]. Interestingly, although LTP[168,169] and LTD[169] have each been demonstrated at excitatory synapses in the nucleus accumbens, dopamine does not seem to be important for such plasticity in this brain region[168,169].

On the other hand, dopamine is involved in LTP[170,171] and LTD in the ventral tegmental area. LTP is seen in excitatory synapses on dopamine-containing neurons of the SUBSTANTIA NIGRA[170] and ventral tegmental area[171] but not in GABA (γ-aminobutyric acid)-containing neurons of the ventral tegmental area[171]. LTD is also seen at excitatory synapses on dopamine-containing neurons in the ventral tegmental area; this LTD is blocked by dopamine at D2 receptors[172]. Treatments with the dopamine releasers amphetamine, morphine, nicotine and ethanol also cause LTP-like sensitization[173] in the ventral tegmental area, as does the dopamine-activating stress of a forced swim test[173].

So, reinforcing properties of D1 or D2 activation have been demonstrated in a number of cortical and limbic sites that surprisingly exclude the nucleus accumbens, which is the site most frequently identified with reward function in behavioural studies.

Dopamine and memory at the behavioural level. An important role for dopamine in memory consolidation is also suggested by behavioural studies in which dopamine or a dopamine agonist is given after a learning trial involving some other form of reinforcement. The ability of post-trial sucrose to enhance memory consolidation has been mentioned above[146]. Similar effects on memory consolidation can result from post-trial injections of amphetamine or a D2 agonist into the appropriate part

SUBSTANTIA NIGRA
Originally named for the pigmented dopamine cells of zona compacta of the substantia nigra (SNc) and ventral tegmental area, the term now designates only the lateral portion of the dopamine cells: those that project to the caudate–putamen. The term has also been extended to include the group of non-pigmented (γ-aminobutyric acid-mediated) substantia nigra pars reticulata (SNr) cells that lies ventral to the SNc and that provides feedback to it.

STRIATUM
In the rat the multiple bundles of the internal capsule give the caudate–putamen and the nucleus accumbens a striated appearance in sagittal section. For this reason they have come to be known as the dorsal and ventral striatum, respectively. The olfactory tubercle, beneath nucleus accumbens, has been recognized as an extension of the ventral striatum.

of the striatum. For example, injections into the postero-ventral caudate nucleus potentiate conditioned emotional responses to a visual (but not an olfactory) conditioned stimulus, whereas injections into the ventro-lateral caudate potentiate conditioned emotional responses to an olfactory (but not a visual) conditioned stimulus[174]. Post-trial injections of amphetamine into the hippocampus potentiate the consolidation of a spatial but not a visual task, whereas injections into the caudate nucleus potentiate consolidation of the visual but not the spatial task[175]. Similarly, post-trial intra-hippocampal (but not intra-caudate) amphetamine, D1 agonists or D2 agonists improve retention of a win–stay strategy, whereas post-trial intra-caudate (but not intra-hippocampal) injections of these agents potentiate consolidation of the memory of a win–shift strategy. Post-trial injections of a selective D3 agonist differentially affect memory consolidation in conditioned approach or conditioned instrumental responding, depending on whether the injections are into the central or basolateral nucleus of the amygdala[176]. So, dopamine seems to have a distributed role in post-trial memory consolidation or reinforcement, stamping-in memory traces associated with different types of task or learning in different terminal fields.

Beyond nucleus accumbens. The mesolimbic dopamine system and its terminal field in the nucleus accumbens have long had a privileged place in motivational theory. In large part this is because activation of this system is associated with the locomotion that is central to the foraging for, energizing and approaching of the various needs of an animal in its environment[15,22]. Recent studies, however, underscore the need to consider other dopamine terminal fields as probable components of brain reward mechanisms. Drug reward sites and brain stimulation reward sites[177] have been identified in the frontal cortex, olfactory tubercle and ventral tegmental area as well as in the nucleus accumbens, and the memory-enhancing effects of post-trial dopamine actions are found in terminal fields other than the nucleus accumbens. A conservative position would be that dopamine acts in the nucleus accumbens, dorsal striatum, amygdala, frontal cortex and perhaps other sites to reward immediate behaviour and to establish conditioned motivational cues that will guide and motivate future behaviour.

Recent findings suggest that information regarding conditioned motivational stimuli converges through glutamatergic afferents on the same medium spiny neurons that receive mesolimbic dopamine input. The glutamatergic input to these neurons terminates on the heads and the dopaminergic input on the shafts of dendritic spines of the nucleus accumbens output neurons[178]. The origins of glutamate input to the nucleus accumbens include a range of dopamine-innervated cortical and limbic structures, including the amygdala, orbital frontal cortex, cingulate cortex, prefrontal cortex and hippocampus. These structures have been implicated in various aspects of reward and addiction, and some are known to undergo dopamine-dependent LTP or LTD.

Of these areas, the best known as a reward site in its own right is the medial prefrontal cortex (mPFC), where direct electrical[179] or chemical[49,118] stimulation can be rewarding. Rewarding electrical stimulation in this region causes glutamate and dopamine release in the nucleus accumbens; the glutamate release is thought to be directly from mPFC pyramidal cells and the dopamine release is thought to be indirect, through the ventral tegmental area[179]. Rewarding mPFC cocaine injections also cause dopamine release in the nucleus accumbens, by an unknown mechanism[180]. The mPFC is broadly associated with working memory and attentional functions[181], and has been implicated in cocaine- and stress-induced reinstatement of cocaine-seeking in response-extinguished animals[182–185].

The amygdala has been strongly implicated in the control of instrumental behaviour by reward-associated cues[186–188]. The basolateral amygdala seems to be more involved in conditioned reinforcement[187] and the central amygdaloid nucleus seems to be more involved in incentive-motivation[188]. The basolateral amygdala seems to interact with the orbitofrontal cortex in conditioned reinforcement[189–191].

The main sites of post-trial reinforcing effects of dopamine agonists and of dopamine-dependent LTP and LTD are the hippocampus and the dorsal striatum. Electrical stimulation of each is moderately rewarding[192,193], although there is minimal evidence to indicate that drugs are directly rewarding in either structure[194,195]. Each structure is strongly implicated in functions that should be important to reward-seeking behaviours. The hippocampus has been implicated in contextual learning, and disruptive post-trial stimulation in this structure impairs such learning. It would be interesting to know whether dopamine agonists given after the trial enhance consolidation of such learning.

The role of the dorsal striatum in reward function remains unclear. Although the nucleus accumbens has pride of place in reward theory, Phillips *et al.* reported self-administration of amphetamine into the dorsal striatum of a single monkey[194]. The facts that the dorsal and ventral striatum are innervated by a single dopamine system (BOX 1) and have largely parallel cytoarchitectures indicates that they should serve similar functions, with regional differences in the modalities of afferent information or the specific organs or body regions under efferent control. But we have no theory of striatal function — only a theory of striatal architecture[196,197] — that suggests graded transitions between the dorsal and ventral striatum. It is interesting to speculate that the release of dopamine in the ventral striatum, triggered by reward-associated conditioned stimuli, acts primarily to energize the next response, whereas dopamine release in the dorsal striatum[198], triggered less and less[72] by the receipt of expected reinforcers, acts primarily to stamp in the procedural memory traces that are essential for establishing and maintaining procedural habit structures. Strong stamping-in would be required for the establishment of such structures, but would be less and less necessary to maintain them.

Conclusions

It is established that dopamine in the brain is important in goal-directed behaviour. Most normal rewards are rendered ineffective in animals that have had their dopamine systems blocked. Brain dopamine is important for establishing the conditioned tendency to re-approach environmental stimuli that have been associated with most primary rewards, and for maintaining habit strength once a task has been learned. The post-trial stamping-in of memory traces is essential for the control of behaviour by a conditioned stimulus, and such control seems to involve, to a great extent, glutamatergic input to the ventral striatum from various limbic and cortical structures. The conditioned control of glutamatergic input from these structures probably involves such post-trial stamping-in, as the glutamatergic cells are in the regions that receive dopamine input and, in some cases at least, receive synaptic input from dopamine terminals[178]. That such structures are subject to dopamine-dependent LTP and LTD encourages the hypothesis that these mechanisms are involved in behavioural conditioning. Whatever the mechanism, brain dopamine seems to stamp in response–reward and stimulus–reward associations that are essential for the control of motivated behaviour by past experience.

1. Barbeau, A. Drugs affecting movement disorders. *Ann. Rev. Pharmacol.* **14**, 91–113 (1974).
2. Yokel, R. A. & Wise, R. A. Increased lever pressing for amphetamine after pimozide in rats: implications for a dopamine theory of reward. *Science* **187**, 547–549 (1975).
3. Fouriezos, G. & Wise, R. A. Pimozide-induced extinction of intracranial self-stimulation: response patterns rule out motor or performance deficits. *Brain Res.* **103**, 377–380 (1976).
4. Fouriezos, G., Hansson, P. & Wise, R. A. Neuroleptic-induced attenuation of brain stimulation reward in rats. *J. Comp. Physiol. Psychol.* **92**, 661–671 (1978).
5. Wise, R. A., Spindler, J., deWit, H. & Gerber, G. J. Neuroleptic-induced 'anhedonia' in rats: pimozide blocks reward quality of food. *Science* **201**, 262–264 (1978).
6. Gerber, G. J., Sing, J. & Wise, R. A. Pimozide attenuates lever pressing for water reinforcement in rats. *Pharmacol. Biochem. Behav.* **14**, 201–205 (1981).
7. Ettenberg, A. & Camp, C. H. Haloperidol induces a partial reinforcement extinction effect in rats: implications for a dopamine involvement in food reward. *Pharmacol. Biochem. Behav.* **25**, 813–821 (1986).
8. Ettenberg, A. & Camp, C. H. A partial reinforcement extinction effect in water-reinforced rats intermittently treated with haloperidol. *Pharmacol. Biochem. Behav.* **25**, 1231–1235 (1986).
9. McFarland, K. & Ettenberg, A. Haloperidol differentially affects reinforcement and motivational processes in rats running an alley for intravenous heroin. *Psychopharmacology* **122**, 346–350 (1995).
A particularly clear demonstration of how neuroleptics impair reinforcement before they impair motivation.
10. McFarland, K. & Ettenberg, A. Haloperidol does not affect motivational processes in an operant runway model of food-seeking behavior. *Behav. Neurosci.* **112**, 630–635 (1998).
11. Franklin, K. B. J. Catecholamines and self-stimulation: reward and performance effects dissociated. *Pharmacol. Biochem. Behav.* **9**, 813–820 (1978).
12. Wise, R. A. Neuroleptics and operant behavior: the anhedonia hypothesis. *Behav. Brain Sci.* **5**, 39–87 (1982).
13. McFarland, K. & Ettenberg, A. Haloperidol does not attenuate conditioned place preferences or locomotor activation produced by food- or heroin-predictive discriminative cues. *Pharmacol. Biochem. Behav.* **62**, 631–641 (1999).
14. Wise, R. A. & Raptis, L. Effects of naloxone and pimozide on initiation and maintenance measures of free feeding. *Brain Res.* **368**, 62–68 (1986).
A particularly clear demonstration that neuroleptics attenuate the ability of food to maintain eating long before they attenuate the animal's motivation to feed.
15. Mogenson, G. J., Jones, D. L. & Yim, C. Y. From motivation to action: functional interface between the limbic system and the motor system. *Progr. Neurobiol.* **14**, 69–97 (1980).
This classic paper, more than any other, identified nucleus accumbens dopamine with motivational function.
16. Wise, R. A. & Rompré, P.-P. Brain dopamine and reward. *Ann. Rev. Psychol.* **40**, 191–225 (1989).
17. Di Chiara, G. Nucleus accumbens shell and core dopamine: differential role in behavior and addiction. *Behav. Brain Res.* **137**, 75–114 (2002).
18. Ungerstedt, U. Adipsia and aphagia after 6-hydroxydopamine induced degeneration of the nigro-striatal dopamine system. *Acta Physiol. Scand.* (Suppl.) **367**, 95–122 (1971).
19. Smith, G. P., Strohmayer, A. J. & Reis, D. J. Effect of lateral hypothalamic injections of 6-hydroxydopamine on food and water intake in rats. *Nature New Biol.* **235**, 27–29 (1972).
20. Ervin, G. N., Fink, J. S., Young, R. C. & Smith, G. P. Different behavioral responses to L-DOPA after anterolateral or posterolateral hypothalamic injections of 6-hydroxydopamine. *Brain Res.* **132**, 507–520 (1977).
21. Smith, G. P. The arousal function of central catecholamine neurons. *Ann. NY Acad. Sci.* **270**, 45–56 (1976).
22. Schneirla, T. C. in *Nebraska Symposium on Motivation* (ed. Jones, M. R.) 1–42 (Univ. Nebraska Press, Lincoln, 1959).
23. Liebman, J. M. & Butcher, L. L. Comparative involvement of dopamine and noradrenaline in rate-free self-stimulation in substantia nigra, lateral hypothalamus, and mesencephalic central gray. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **284**, 167–194 (1974).
24. Franklin, K. B. J. & McCoy, S. N. Pimozide-induced extinction in rats: stimulus control of responding rules out motor deficit. *Pharmacol. Biochem. Behav.* **11**, 71–75 (1979).
A nice demonstration of sensory control of responding under neuroleptic treatment. This study refutes the notion that neuroleptic-induced response deficits are the result of motor impairment or vulnerability to fatigue.
25. Gallistel, C. R., Boytim, M., Gomita, Y. & Klebanoff, L. Does pimozide block the reinforcing effect of brain stimulation? *Pharmacol. Biochem. Behav.* **17**, 769–781 (1982).
26. de Wit, H. & Wise, R. A. Blockade of cocaine reinforcement in rats with the dopamine receptor blocker pimozide, but not with the noradrenergic blockers phentolamine or phenoxybenzamine. *Can. J. Psychol.* **31**, 195–203 (1977).
27. Wise, R. A. & Schwartz, H. V. Pimozide attenuates acquisition of lever pressing for food in rats. *Pharmacol. Biochem. Behav.* **15**, 655–656 (1981).
28. Dickinson, A., Smith, J. & Mirenowicz, J. Dissociation of Pavlovian and instrumental incentive learning under dopamine antagonists. *Behav. Neurosci.* **114**, 468–483 (2000).
29. Lippa, A. S., Antelman, S. M., Fisher, A. E. & Canfield, D. R. Neurochemical mediation of reward: a significant role for dopamine. *Pharmacol. Biochem. Behav.* **1**, 23–28 (1973).
30. Roberts, D. C. S., Corcoran, M. E. & Fibiger, H. C. On the role of ascending catecholaminergic systems in intravenous self-administration of cocaine. *Pharmacol. Biochem. Behav.* **6**, 615–620 (1977).
31. Koob, G. F., Fray, P. J. & Iversen, S. D. Self-stimulation at the lateral hypothalamus and locus coeruleus after specific unilateral lesions of the dopamine system. *Brain Res.* **146**, 123–140 (1978).
32. Roberts, D. C. S., Koob, G. F., Klonoff, P. & Fibiger, H. C. Extinction and recovery of cocaine self-administration following 6-OHDA lesions of the nucleus accumbens. *Pharmacol. Biochem. Behav.* **12**, 781–787 (1980).
33. Roberts, D. C. S. & Koob, G. Disruption of cocaine self-administration following 6-hydroxydopamine lesions of the ventral tegmental area in rats. *Pharmacol. Biochem. Behav.* **17**, 901–904 (1982).
34. Fibiger, H. C. Drugs and reinforcement mechanisms: a critical review of the catecholamine theory. *Ann. Rev. Pharmacol. Toxicol.* **18**, 37–56 (1978).
35. Wise, R. A. Catecholamine theories of reward: a critical review. *Brain Res.* **152**, 215–247 (1978).
36. Wise, R. A. in *The Neuropharmacological Basis of Reward* (eds Liebman, J. M. & Cooper, S. J.) 377–424 (Oxford Univ. Press, Oxford, 1989).
37. Wise, R. A., Spindler, J. & Legault, L. Major attenuation of food reward with performance-sparing doses of pimozide in the rat. *Can. J. Psychol.* **32**, 77–85 (1978).
38. Smith, G. P. in *Progress in Psychobiology and Physiological Psychology* (eds Morrison, A. & Fluharty, S.) 83–144 (Academic, New York, 1995).
39. Mason, S. T., Beninger, R. J., Fibiger, H. C. & Phillips, A. G. Pimozide-induced suppression of responding: evidence against a block of food reward. *Pharmacol. Biochem. Behav.* **12**, 917–923 (1980).
40. Koob, G. F. The dopamine anhedonia hypothesis: a pharmacological phrenology. *Behav. Brain Sci.* **5**, 63–64 (1982).
41. Ettenberg, A., Koob, G. F. & Bloom, F. E. Response artifact in the measurement of neuroleptic-induced anhedonia. *Science* **213**, 357–359 (1981).
42. Salamone, J. D., Cousins, M. S. & Snyder, B. J. Behavioral functions of nucleus accumbens dopamine: empirical and conceptual problems with the anhedonia hypothesis. *Neurosci. Biobehav. Rev.* **21**, 341–359 (1997).
43. Beninger, R. J. The role of dopamine in locomotor activity and learning. *Brain Res. Rev.* **6**, 173–196.
44. Spyraki, C., Fibiger, H. C. & Phillips, A. G. Attenuation by haloperidol of place preference conditioning using food reinforcement. *Psychopharmacology* **77**, 379–382 (1982).
45. Bozarth, M. A. & Wise, R. A. Heroin reward is dependent on a dopaminergic substrate. *Life Sci.* **29**, 1881–1886 (1981).
46. Spyraki, C., Fibiger, H. C. & Phillips, A. G. Dopaminergic substrates of amphetamine-induced place preference conditioning. *Brain Res.* **253**, 185–193 (1982).
47. Spyraki, C., Fibiger, H. C. & Phillips, A. G. Attenuation of heroin reward in rats by disruption of the mesolimbic dopamine system. *Psychopharmacology* **79**, 278–283 (1983).
48. Spyraki, C., Nomikos, G. G. & Varonos, D. D. Intravenous cocaine-induced place preference: attenuation by haloperidol. *Behav. Brain. Res.* **26**, 57–62 (1987).
49. Carlezon, W. A. Jr & Wise, R. A. Rewarding actions of phencyclidine and related drugs in nucleus accumbens shell and frontal cortex. *J. Neurosci.* **16**, 3112–3122 (1996).
50. Brown, L. L. Sensory and cognitive functions of the basal ganglia. *Curr. Opin. Neurobiol.* **7**, 157–163 (1997).
51. Jenner, P. The MPTP-treated primate as a model of motor complications in PD: primate model of motor complications. *Neurology* **61**, (Suppl. 3) S4–11 (2003).
52. Bindra, D. Neuropsychological interpretation of the effects of drive and incentive-motivation on general activity and instrumental behavior. *Psychol. Rev.* **75**, 1–22 (1968).
53. Wetzel, M. C. Self-stimulation aftereffects and runway performance in the rat. *J. Comp. Physiol. Psychol.* **56**, 673–678 (1963).
54. Gallistel, C. R., Stellar, J. R. & Bubis, E. Parametric analysis of brain stimulation reward in the rat: I. The transient process and the memory-containing process. *J. Comp. Physiol. Psychol.* **87**, 848–859 (1974).
This classic paper distinguishes clearly between the priming and reinforcing functions of brain stimulation reward. The first decays in seconds, whereas the second is effective for weeks.
55. Pickens, R. & Harris, W. C. Self-administration of D-amphetamine by rats. *Psychopharmacologia* **12**, 158–163 (1968).
56. Esposito, R. U., Faulkner, W. & Kornetsky, C. Specific modulation of brain stimulation reward by haloperidol. *Pharmacol. Biochem. Behav.* **10**, 937–940 (1979).
Although it is couched in terms of reinforcement, this study measures the priming effects of free brain stimulation on the latency to lever-press for more.
57. Wasserman, E. M., Gomita, Y. & Gallistel, C. R. Pimozide blocks reinforcement but not priming from MFB stimulation in the rat. *Pharmacol. Biochem. Behav.* **17**, 783–787 (1982).

This study shows that the priming effect of stimulation undergoes an extinction-like decline under neuroleptic treatment, indicating that even the rapidly decaying priming effect is partially conditioned.

58. Shaham, Y., Adamson, L. K., Grocki, S. & Corrigall, W. A. Reinstatement and spontaneous recovery of nicotine seeking in rats. *Psychopharmacology* **130**, 396–403 (1997).
59. de Wit, H. & Stewart, J. Reinstatement of cocaine-reinforced responding in the rat. *Psychopharmacology* **75**, 134–143 (1981).
60. Wise, R. A., Murray, A. & Bozarth, M. A. Bromocriptine self-administration and bromocriptine-reinstatement of cocaine-trained and heroin-trained lever-pressing in rats. *Psychopharmacology* **100**, 355–360 (1990).
61. Phillips, P. E., Stuber, G. D., Heien, M. L., Wightman, R. M. & Carelli, R. M. Subsecond dopamine release promotes cocaine seeking. *Nature* **422**, 614–618 (2003).
62. Cornish, J. L. & Kalivas, P. W. Glutamate transmission in the nucleus accumbens mediates relapse in cocaine addiction. *J. Neurosci.* **20**, RC89 (2000).
63. Roitman, M. F., Stuber, G. D., Phillips, P. E., Wightman, R. M. & Carelli, R. M. Dopamine operates as a subsecond modulator of food seeking. *J. Neurosci.* **24**, 1265–1271 (2004).
64. Wyvell, C. L. & Berridge, K. C. Intra-accumbens amphetamine increases the conditioned incentive salience of sucrose reward: enhancement of reward 'wanting' without enhanced 'liking' or response reinforcement. *J. Neurosci.* **20**, 8122–8130 (2000).
65. Crespi, L. P. Quantitative variation of incentive and performance in the white rat. *Am. J. Psychol.* **55**, 467–517 (1942).
66. Stewart, J., de Wit, H. & Eikelboom, R. Role of unconditioned and conditioned drug effects in the self-administration of opiates and stimulants. *Psychol. Rev.* **91**, 251–268 (1984).
67. Mendelson, J. The role of hunger in the T-maze learning for food by rats. *J. Comp. Physiol. Psychol.* **62**, 341–349 (1966).
68. Morgan, M. J. Resistance to satiation. *Anim. Behav.* **22**, 449–466 (1974).

References 67 and 68 show that response initiation depends more on the animal's habit strength based on recent reinforcement history than on the current hunger level of the animal. The parallel between the role of hunger and the role of dopamine in response initiation in well-trained animals is central to the suggestions of the current review.

69. Wise, R. A. & Colle, L. M. Pimozide attenuates free feeding: best scores analysis reveals a motivational deficit. *Psychopharmacology* **84**, 446–451 (1984).
70. Koechling, U., Colle, L. M. & Wise, R. A. Effects of SCH 23390 on latency and speed measures of deprivation-induced feeding. *Psychobiology* **16**, 207–212 (1988).
71. Ljungberg, T., Apicella, P. & Schultz, W. Responses of monkey dopamine neurons during learning of behavioral reactions. *J. Neurophysiol.* **67**, 145–163 (1992).
72. Schultz, W., Apicella, P. & Ljungberg, T. Responses of monkey dopamine neurons to reward and conditioned stimuli during successive steps of learning a delayed response task. *J. Neurosci.* **13**, 900–913 (1993).
73. Hernandez, L. & Hoebel, B. G. Food reward and cocaine increase extracellular dopamine in the nucleus accumbens as measured by microdialysis. *Life Sci.* **42**, 1705–1712 (1988).
74. Wise, R. A., Leone, P., Rivest, R. & Leeb, K. Elevations of nucleus accumbens dopamine and DOPAC levels during intravenous heroin self-administration. *Synapse* **21**, 140–148 (1995).
75. Wise, R. A. *et al.* Fluctuations in nucleus accumbens dopamine concentration during intravenous cocaine self-administration in rats. *Psychopharmacology* **120**, 10–20 (1995).
76. Ranaldi, R., Pocock, D., Zereik, R. & Wise, R. A. Dopamine fluctuations in the nucleus accumbens during maintenance, extinction, and reinstatement of intravenous D-amphetamine self-administration. *J. Neurosci.* **19**, 4102–4109 (1999).
77. Taylor, J. R. & Robbins, T. W. Enhanced behavioural control by conditioned reinforcers produced by intracerebral injections of D-amphetamine in the rat. *Psychopharmacology* **84**, 405–412 (1984).
78. Taylor, J. R. & Robbins, T. W. 6-hydroxydopamine lesions of the nucleus accumbens, but not of the caudate nucleus, attenuate enhanced responding with conditioned reinforcement produced by intra-accumbens amphetamine. *Psychopharmacology* **90**, 310–317 (1986).
79. Laruelle, M. *et al.* SPECT imaging of striatal dopamine release after amphetamine challenge. *J. Nuc. Med.* **36**, 1182–1190 (1995).
80. Volkow, N. D. *et al.* Reinforcing effects of psychostimulants in humans are associated with increases in brain dopamine and occupancy of D(2) receptors. *J. Pharmacol. Exp. Ther.* **291**, 409–415 (1999).
81. Drevets, W. C. *et al.* Amphetamine-induced dopamine release in human ventral striatum correlates with euphoria. *Biol. Psychiatry* **49**, 81–96 (2001).
82. Jönsson, L., Änggard, E. & Gunne, L. Blockade of intravenous amphetamine euphoria in man. *Clin. Pharmacol. Ther.* **12**, 889–896 (1971).
83. Gunne, L. M., Änggard, E. & Jönsson, L. E. Clinical trials with amphetamine-blocking drugs. *Psychiatr. Neurol. Neurochir.* **75**, 225–226 (1972).
84. Brauer, L. H. & de Wit, H. High dose pimozide does not block amphetamine-induced euphoria in normal volunteers. *Pharmacol. Biochem. Behav.* **56**, 265–272 (1997).
85. Martinez, D. *et al.* Cocaine dependence and D2 receptor availability in functional subdivisions of the striatum: relationship with cocaine-seeking behavior. *Neuropsychopharmacology* (in the press).
86. Kelleher, R. T. & Morse, W. H. Schedules using noxious stimuli. 3. Responding maintained with response produced electric shocks. *J. Exper. Anal. Behav.* **11**, 819–838 (1968).
87. Horrocks, J. & House, A. Self-poisoning and self-injury in adults. *Clin. Med.* **2**, 509–512 (2002).
88. Foltin, R. W. & Fischman, M. W. Smoked and intravenous cocaine in humans: acute tolerance, cardiovascular and subjective effects. *J. Pharmacol. Exp. Ther.* **257**, 247–261 (1991).
89. Lamb, R. J. *et al.* The reinforcing and subjective effects of morphine in post-addicts: a dose-response study. *J. Pharmacol. Exp. Ther.* **259**, 1165–1173 (1991).
90. Russell, M. A. Subjective and behavioural effects of nicotine in humans: some sources of individual variation. *Prog. Brain Res.* **79**, 289–302 (1989).
91. Johanson, C. E. in *Contemporary Research in Behavioral Pharmacology* (eds Blackman, D. E. & Sanger, D. J.) 325–390 (Plenum, New York, 1978).
92. Berridge, K. C. Measuring hedonic impact in animals and infants: microstructure of affective taste reactivity patterns. *Neurosci. Biobehav. Rev.* **24**, 173–198 (2000).
93. Berridge, K. D., Venier, I. L. & Robinson, T. E. Taste reactivity analysis of 6-hydroxydopamine-induced aphagia: implications for arousal and anhedonia hypotheses of dopamine function. *Behav. Neurosci.* **103**, 36–45 (1989).
94. Pecina, S., Berridge, K. C. & Parker, L. A. Pimozide does not shift palatability: separation of anhedonia from sensorimotor suppression by taste reactivity. *Pharmacol. Biochem. Behav.* **58**, 801–811 (1997).
95. Leeb, K., Parker, L. A. & Eikelboom, R. Effects of pimozide on the hedonic properties of sucrose: analysis by the taste reactivity test. *Pharmacol. Biochem. Behav.* **39**, 895–901 (1991).
96. Grill, H. J. & Norgren, R. The taste reactivity test. II. Mimetic responses to gustatory stimuli in chronic thalamic and chronic decerebrate rats. *Brain Res.* **143**, 281–297 (1978).
97. Steiner, J. E. The gustofacial response: observation on normal and anencephalic newborn infants. *Symp. Oral Sens. Percept.* **4**, 254–278 (1973).
98. Berridge, K. C., Flynn, F. W., Schulkin, J. & Grill, H. J. Sodium depletion enhances salt palatability in rats. *Behav. Neurosci.* **98**, 652–660 (1984).
99. Berridge, K. C. & Robinson, T. E. The mind of an addicted brain: neural sensitization of wanting and liking. *Curr. Direct. Psychol. Sci.* **4**, 71–76 (1995).
100. Wise, R. A. Sensorimotor modulation and the variable action pattern (VAP): toward a noncircular definition of drive and motivation. *Psychobiology* **15**, 7–20 (1987).
101. Ettenberg, A., Pettit, H. O., Bloom, F. E. & Koob, G. F. Heroin and cocaine intravenous self-administration in rats: mediation by separate neural systems. *Psychopharmacology* **78**, 204–209 (1982).
102. Salamone, J. D., Cousins, M. S. & Bucher, S. Anhedonia or anergia? Effects of haloperidol and nucleus accumbens dopamine depletion on instrumental response selection in a T-maze cost/benefit procedure. *Behav. Brain Res.* **65**, 221–229 (1994).
103. Neill, D. B. & Justice, J. B. J. in *The Neurobiology of the Nucleus Accumbens* (eds Chronister, R. B. & DeFrance, J. F.) 515–528 (Haer Institute, New Brunswick, 1981).
104. Salamone, J. D. & Correa, M. Motivational views of reinforcement: implications for understanding the behavioral functions of nucleus accumbens dopamine. *Behav. Brain Res.* **137**, 3–25 (2002).
105. Aberman, J. E. & Salamone, J. D. Nucleus accumbens dopamine depletions make rats more sensitive to high ratio requirements but do not impair primary food reinforcement. *Neuroscience* **92**, 545–552 (1999).
106. Lyness, W. H., Friedle, N. M. & Moore, K. E. Destruction of dopaminergic nerve terminals in nucleus accumbens: effect on D-amphetamine self-administration. *Pharmacol. Biochem. Behav.* **11**, 553–556 (1979).
107. Hanlon, E. C., Baldo, B. A., Sadeghian, K. & Kelley, A. E. Increases in food intake or food-seeking behavior induced by GABAergic, opioid, or dopaminergic stimulation of the nucleus accumbens: is it hunger? *Psychopharmacology* **172**, 241–247 (2004).
108. Bakshi, V. P. & Kelley, A. E. Striatal regulation of morphine-induced hyperphagia: an anatomical mapping study. *Psychopharmacology* **111**, 207–214 (1993).
109. Olds, M. E. Reinforcing effects of morphine in the nucleus accumbens. *Brain Res.* **237**, 429–440 (1982).
110. Olds, M. E. & Williams, K. N. Self-administration of D-ala^2-met-enkephalinamide at hypothalamic self-stimulation sites. *Brain Res.* **194**, 155–170 (1980).
111. Goeders, N. E., Lane, J. D. & Smith, J. E. Self-administration of methionine enkephalin into the nucleus accumbens. *Pharmacol. Biochem. Behav.* **20**, 451–455 (1984).
112. Hoebel, B. G. *et al.* Self-injection of amphetamine directly into the brain. *Psychopharmacology* **81**, 158–163 (1983).
113. Phillips, G. D., Robbins, T. W. & Everitt, B. J. Bilateral intra-accumbens self-administration of D-amphetamine: antagonism with intra-accumbens SCH-23390 and sulpiride. *Psychopharmacology* **114**, 477–485 (1994).
114. Carlezon, W. A. Jr, Devine, D. P. & Wise, R. A. Habit-forming actions of nomifensine in nucleus accumbens. *Psychopharmacology (Berl.)* **122**, 194–197 (1995).
115. Johnson, A. K. & Epstein, A. N. The cerebral ventricles as the avenue for the dipsogenic action of intracranial angiotensin. *Brain Res.* **86**, 399–418 (1975).

The potential for migration of centrally administered drugs to and through the ventricular system is nicely illustrated in this classic paper.

116. Bozarth, M. A. & Wise, R. A. Intracranial self-administration of morphine into the ventral tegmental area in rats. *Life Sci.* **28**, 551–555 (1981).
117. Carlezon, W. A. Jr & Wise, R. A. Microinjections of phencyclidine (PCP) and related drugs into nucleus accumbens shell potentiate lateral hypothalamic brain stimulation reward. *Psychopharmacology* **128**, 413–420 (1996).
118. Goeders, N. E. & Smith, J. E. Cortical dopaminergic involvement in cocaine reinforcement. *Science* **221**, 773–775 (1983).
119. Ikemoto, S. Involvement of the olfactory tubercle in cocaine reward: intracranial self-administration studies. *J. Neurosci.* **23**, 9305–9511 (2003).
120. Wise, R. A. & Bozarth, M. A. A psychomotor stimulant theory of addiction. *Psychol. Rev.* **94**, 469–492 (1987).
121. Di Chiara, G. & Imperato, A. Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. *Proc. Natl Acad. Sci. USA* **85**, 5274–5278 (1988).
122. Bechara, A., Harrington, F., Nader, K. & van der Kooy, D. Neurobiology of motivation: double dissociation of two motivational mechanisms mediating opiate reward in drug-naive versus drug-dependent rats. *Behav. Neurosci.* **106**, 798–807 (1992).
123. Laviolette, S. R. & van der Kooy, D. Blockade of mesolimbic dopamine transmission dramatically increases sensitivity to the rewarding effects of nicotine in the ventral tegmental area. *Mol. Psychiatry* **8**, 50–59 (2003).
124. Wise, R. A. The neurobiology of craving: implications for the understanding and treatment of addiction. *J. Abnorm. Psychol.* **97**, 118–132 (1988).
125. Heikkila, R. E., Orlansky, H. & Cohen, G. Studies on the distinction between uptake inhibition and release of (^{3}H)dopamine in rat brain tissue slices. *Biochem. Pharmacol.* **24**, 847–852 (1975).
126. Ritz, M. C., Lamb, R. J., Goldberg, S. R. & Kuhar, M. J. Cocaine receptors on dopamine transporters are related to self-administration of cocaine. *Science* **237**, 1219–1223 (1987).
127. Rocha, B. A. *et al.* Cocaine self-administration in dopamine-transporter knockout mice. *Nature Neurosci.* **1**, 132–137 (1998).
128. Sora, I. *et al.* Cocaine reward models: conditioned place preference can be established in dopamine- and in serotonin-transporter knockout mice. *Proc. Natl Acad. Sci. USA* **95**, 699–704 (1998).
129. Morón, J. A., Brockington, A., Wise, R. A., Rocha, B. A. & Hope, B. T. Dopamine uptake through the norepinephrine transporter in brain regions with low levels of the dopamine transporter: evidence from knock-out mouse lines. *J. Neurosci.* **22**, 389–395 (2002).
130. Carboni, E. *et al.* Cocaine and amphetamine increase extracellular dopamine in the nucleus accumbens of mice lacking the dopamine transporter gene. *J. Neurosci.* **21**, 1–4 (2001).
131. Sora, I. *et al.* Molecular mechanisms of cocaine reward: combined dopamine and serotonin transporter knockouts eliminate cocaine place preference. *Proc. Natl Acad. Sci. USA* **98**, 5300–5305 (2001).

132. Loh, E. A. & Roberts, D. C. S. Break-points on a progressive ratio schedule reinforced by intravenous cocaine increase following depletion of forebrain serotonin. *Psychopharmacology* **101**, 262–266 (1990).
133. Lyness, W. H., Friedle, N. M. & Moore, K. E. Increased self-administration of D-amphetamine after destruction of 5-hydroxytryptaminergic nerves. *Pharmacol. Biochem. Behav.* **12**, 937–941 (1981).
134. Berridge, K. C. & Robinson, T. E. What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? *Brain Res. Rev.* **28**, 309–369 (1998).
135. Berridge, K. C. & Robinson, T. E. Parsing reward. *Trends Neurosci.* **26**, 507–513 (2003).
136. Robinson, T. E. & Berridge, K. C. The neural basis of drug craving: an incentive-sensitization theory of addiction. *Brain Res. Reviews* **18**, 247–292 (1993).
137. Schultz, W. & Dickinson, A. Neuronal coding of prediction errors. *Ann. Rev. Neurosci.* **23**, 473–500 (2000).
138. Contreras-Vidal, J. L. & Schultz, W. A predictive reinforcement model of dopamine neurons for learning approach behavior. *J. Comput. Neurosci.* **6**, 191–214 (1999).
139. Romo, R. & Schultz, W. Dopamine neurons of the monkey midbrain: contingencies of responses to active touch during self-initiated arm movements. *J. Neurophysiol.* **63**, 592–606 (1990).
140. Schultz, W., Apicella, P., Scarnati, E. & Ljungberg, T. Neuronal activity in monkey ventral striatum related to the expectation of reward. *J. Neurosci.* **12**, 4595–4610 (1992).
141. Wise, R. A. Brain reward circuitry: insights from unsensed incentives. *Neuron* **36**, 229–240 (2002).
142. Robbins, T. W. The acquisition of responding with conditioned reinforcement: effects of pipradrol, methylphenidate, D-amphetamine and nomifensine. *Psychopharmacology* **58**, 78–87 (1978).
143. Rozin, P. & Kalat, J. W. Specific hungers and poison avoidance as adaptive specializations of learning. *Psychol. Rev.* **78**, 459–486 (1971).
144. Le Magnen, J. Effets des administrations post-prandiales de glucose sur l'etablissement des appétits. *C. R. Seances Soc. Biol. Fil.* **158**, 212–215 (1959).
145. Myers, K. P. & Sclafani, A. Conditioned enhancement of flavor evaluation reinforced by intragastric glucose. II. Taste reactivity analysis. *Physiol. Behav.* **74**, 495–505 (2001).
146. Messier, C. & White, N. M. Contingent and non-contingent actions of sucrose and saccharin reinforcers: effects on taste preference and memory. *Physiol. Behav.* **32**, 195–203 (1984).
147. Di Ciano, P. & Everitt, B. J. Differential control over drug-seeking behavior by drug-associated conditioned reinforcers and discriminative stimuli predictive of drug availability. *Behav. Neurosci.* **117**, 952–960 (2003).
148. Changizi, M. A., McGehee, R. M. & Hall, W. G. Evidence that appetitive responses for dehydration and food-deprivation are learned. *Physiol. Behav.* **75**, 295–304 (2002).
149. Hall, W. G., Cramer, C. P. & Blass, E. M. Developmental changes in suckling of rat pups. *Nature* **258**, 318–320 (1975).
150. Johanson, I. B. & Hall, W. G. Appetitive learning in 1-day-old rat pups. *Science* **205**, 419–421 (1979).
151. Balleine, B. Instrumental performance following a shift in primary motivation depends on incentive learning. *J. Exp. Psychol. Anim. Behav. Process.* **18**, 236–250 (1992).
152. Landauer, T. K. Reinforcement as consolidation. *Psychol. Rev.* **76**, 82–96 (1969).
153. Pfaff, D. Parsimonious biological models of memory and reinforcement. *Psychol. Rev.* **76**, 70–81 (1969).
154. Huston, J. P., Mondadori, C. & Waser, P. G. Facilitation of learning by reward of post-trial memory processes. *Experietia* **30**, 1038–1040 (1974).
155. Kandel, E. R. The molecular biology of memory storage: a dialogue between genes and synapses. *Science* **294**, 1030–1038 (2001).
156. Frey, U., Schroeder, H. & Matthies, H. Dopaminergic antagonists prevent long-term maintenance of posttetanic LTP in the CA1 region of rat hippocampal slices. *Brain Res.* **522**, 69–75 (1990).
157. Frey, U., Matthies, H., Reymann, K. G. & Matthies, H. The effect of dopaminergic D1 receptor blockade during tetanization on the expression of long-term potentiation in the rat CA1 region *in vitro*. *Neurosci. Lett.* **129**, 111–114 (1991).
158. Li, S., Cullen, W. K., Anwyl, R. & Rowan, M. J. Dopamine-dependent facilitation of LTP induction in hippocampal CA1 by exposure to spatial novelty. *Nature Neurosci.* **6**, 526–531 (2003).
159. Swanson-Park, J. L. *et al.* A double dissociation within the hippocampus of dopamine D1/D5 receptor and β-adrenergic receptor contributions to the persistence of long-term potentiation. *Neuroscience* **92**, 485–497 (1999).
160. Otmakhova, N. A. & Lisman, J. E. D1/D5 dopamine receptors inhibit depotentiation at CA1 synapses via cAMP-dependent mechanism. *J. Neurosci.* **18**, 1270–1279 (1998).
161. Chen, Z. *et al.* Roles of dopamine receptors in long-term depression: enhancement via D1 receptors and inhibition via D2 receptors. *Recept. Channels* **4**, 1–8 (1996).
162. Calabresi, P., Maj, R., Pisani, A., Mercuri, N. B. & Bernardi, G. Long-term synaptic depression in the striatum: physiological and pharmacological characterization. *J. Neurosci.* **12**, 4224–4233 (1992).
163. Centonze, D., Picconi, B., Gubellini, P., Bernardi, G. & Calabresi, P. Dopaminergic control of synaptic plasticity in the dorsal striatum. *Eur. J. Neurosci.* **13**, 1071–1077 (2001).
164. Bissiere, S., Humeau, Y. & Luthi, A. Dopamine gates LTP induction in lateral amygdala by suppressing feedforward inhibition. *Nature Neurosci.* **6**, 587–592 (2003).
165. Huang, Y. Y., Simpson, E., Kellendonk, C. & Kandel, E. R. Genetic evidence for the bidirectional modulation of synaptic plasticity in the prefrontal cortex by D1 receptors. *Proc. Natl Acad. Sci. USA* **101**, 3236–3241 (2004).
166. Otani, S., Daniel, H., Roisin, M. P. & Crepel, F. Dopaminergic modulation of long-term synaptic plasticity in rat prefrontal neurons. *Cereb. Cortex* **13**, 1251–1256 (2003).
167. Law-Tho, D., Desce, J. M. & Crepel, F. Dopamine favours the emergence of long-term depression versus long-term potentiation in slices of rat prefrontal cortex. *Neurosci. Lett.* **188**, 125–128 (1995).
168. Pennartz, C. M., Ameerun, R. F., Groenewegen, H. J. & Lopes da Silva, F. H. Synaptic plasticity in an *in vitro* slice preparation of the rat nucleus accumbens. *Eur. J. Neurosci.* **5**, 107–117 (1993).
169. Kombian, S. B. & Malenka, R. C. Simultaneous LTP of non-NMDA- and LTD of NMDA-receptor-mediated responses in the nucleus accumbens. *Nature* **368**, 242–246 (1994).
170. Overton, P. G., Richards, C. D., Berry, M. S. & Clark, D. Long-term potentiation at excitatory amino acid synapses on midbrain dopamine neurons. *Neuroreport* **10**, 221–226 (1999).
171. Bonci, A. & Malenka, R. C. Properties and plasticity of excitatory synapses on dopaminergic and GABAergic cells in the ventral tegmental area. *J. Neurosci.* **19**, 3723–3730 (1999).
172. Thomas, M. J., Malenka, R. C. & Bonci, A. Modulation of long-term depression by dopamine in the mesolimbic system. *J. Neurosci.* **20**, 5581–5586 (2000).
173. Saal, D., Dong, Y., Bonci, A. & Malenka, R. C. Drugs of abuse and stress trigger a common synaptic adaptation in dopamine neurons. *Neuron* **37**, 577–582 (2003).
174. White, N. M. & Viaud, M. Localized intracaudate dopamine D2 receptor activation during the post-training period improves memory for visual or olfactory conditioned emotional responses in rats. *Behav. Neural Biol.* **55**, 255–269 (1991).
This paper shows that dopamine enhances memory consolidation involving different sensory modalities in different portions of the striatum.
175. Packard, M. G., Cahill, L. & McGaugh, J. L. Amygdala modulation of hippocampal-dependent and caudate nucleus-dependent memory processes. *Proc. Natl Acad. Sci. USA* **91**, 8477–8481 (1994).
176. Hitchcott, P. K. & Phillips, G. D. Double dissociation of the behavioural effects of R(+) 7-OH-DPAT infusions in the central and basolateral amygdala nuclei upon Pavlovian and instrumental conditioned appetitive behaviours. *Psychopharmacology* **140**, 458–469 (1998).
177. Wise, R. A. Drug-activation of brain reward pathways. *Drug Alcohol Depend.* **51**, 13–22 (1998).
178. Sesack, S. R., Carr, D. B., Omelchenko, N. & Pinto, A. Anatomical substrates for glutamate-dopamine interactions: evidence for specificity of connections and extrasynaptic actions. *Ann. NY Acad. Sci.* **1003**, 36–52 (2003).
179. You, Z.-B., Tzschentke, T. M., Brodin, E. & Wise, R. A. Electrical stimulation of the prefrontal cortex increases cholecystokinin, glutamate, and dopamine release in the nucleus accumbens: an *in vivo* microdialysis study in freely moving rats. *J. Neurosci.* **18**, 6492–6500 (1998).
180. Goeders, N. E. & Smith, J. E. Intracranial cocaine self-administration into the medial prefrontal cortex increases dopamine turnover in the nucleus accumbens. *J. Pharmacol. Exp. Ther.* **265**, 592–600 (1993).
181. Williams, G. V. & Goldman-Rakic, P. S. Modulation of memory fields by dopamine D1 receptors in prefrontal cortex. *Nature* **376**, 572–575 (1995).
182. McFarland, K. & Kalivas, P. W. The circuitry mediating cocaine-induced reinstatement of drug-seeking behavior. *J. Neurosci.* **21**, 8655–8663 (2001).
183. McFarland, K., Lapish, C. C. & Kalivas, P. W. Prefrontal glutamate release into the core of the nucleus accumbens mediates cocaine-induced reinstatement of drug-seeking behavior. *J. Neurosci.* **23**, 3531–3537 (2003).
184. Capriles, N., Rodaros, D., Sorge, R. E. & Stewart, J. A role for the prefrontal cortex in stress- and cocaine-induced reinstatement of cocaine seeking in rats. *Psychopharmacology* **168**, 66–74 (2003).
185. Sanchez, C. J., Bailie, T. M., Wu, W. R., Li, N. & Sorg, B. A. Manipulation of dopamine d1-like receptor activation in the rat medial prefrontal cortex alters stress- and cocaine-induced reinstatement of conditioned place preference behavior. *Neuroscience* **119**, 497–505 (2003).
186. Cador, M., Robbins, T. W. & Everitt, B. J. Involvement of the amygdala in stimulus-reward associations: interaction with the ventral striatum. *Neuroscience* **30**, 77–86 (1989).
187. Whitelaw, R. B., Markou, A., Robbins, T. W. & Everitt, B. J. Excitotoxic lesions of the basolateral amygdala impair the acquisition of cocaine-seeking behaviour under a second-order schedule of reinforcement. *Psychopharmacology* **127**, 213–224 (1996).
188. Hall, J., Parkinson, J. A., Connor, T. M., Dickinson, A. & Everitt, B. J. Involvement of the central nucleus of the amygdala and nucleus accumbens core in mediating Pavlovian influences on instrumental behaviour. *Eur. J. Neurosci.* **13**, 1984–1992 (2001).
189. Pears, A., Parkinson, J. A., Hopewell, L., Everitt, B. J. & Roberts, A. C. Lesions of the orbitofrontal but not medial prefrontal cortex disrupt conditioned reinforcement in primates. *J. Neurosci.* **23**, 11189–11201 (2003).
190. Hutcheson, D. M. & Everitt, B. J. The effects of selective orbitofrontal cortex lesions on the acquisition and performance of cue-controlled cocaine seeking in rats. *Ann. NY Acad. Sci.* **1003**, 410–411 (2003).
191. Schoenbaum, G., Setlow, B., Saddoris, M. P. & Gallagher, M. Encoding predicted outcome and acquired value in orbitofrontal cortex during cue sampling depends upon input from basolateral amygdala. *Neuron* **39**, 855–867 (2003).
192. Prado-Alcala, R. & Wise, R. A. Brain stimulation reward and dopamine terminal fields. I. Caudate-putamen, nucleus accumbens and amygdala. *Brain Res.* **297**, 265–273 (1984).
193. Ursin, R., Ursin, H. & Olds, J. Self-stimulation of hippocampus in rats. *J. Comp. Physiol. Psychol.* **61**, 353–359 (1966).
194. Phillips, A. G., Mora, F. & Rolls, E. T. Intracerebral self-administration of amphetamine by rhesus monkeys. *Neurosci. Lett.* **24**, 81–86 (1981).
195. Stevens, K. E., Shiotsu, G. & Stein, L. Hippocampal μ-receptors mediate opioid reinforcement in the CA3 region. *Brain Res.* **545**, 8–16 (1991).
196. Fallon, J. H. & Moore, R. Y. Catecholamine innervation of the basal forebrain. IV. Topography of the dopamine projection to the basal forebrain and neostriatum. *J. Comp. Neurol.* **180**, 545–580 (1978).
This classic paper first characterized the midbrain dopamine system as a single system with topologically graded projections rather than a set of independent, non-overlapping systems. This anatomical perspective is fundamental to the suggestion that dopamine plays similar parts in various of its projection fields.
197. Heimer, L., Zahm, D. S. & Alheid, G. F. in *The Rat Nervous System* (ed. Paxinos, G.) 579–628 (Academic, New York, 1995).
198. Ito, R., Dalley, J. W., Robbins, T. W. & Everitt, B. J. Dopamine release in the dorsal striatum during cocaine-seeking behavior under the control of drug-associated cue. *J. Neurosci.* **22**, 6247–6253 (2002).

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Competing interests statement

The author declares that he has no competing financial interests.

Online links

FURTHER INFORMATION
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