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Opiate versus psychostimulant addiction: the differences do matter

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Abstract

The publication of the psychomotor stimulant theory of addiction in 1987 and the finding that addictive drugs increase dopamine concentrations in the rat mesolimbic system in 1988 have led to a predominance of psychobiological theories that consider addiction to opiates and addiction to psychostimulants as essentially identical phenomena. Indeed, current theories of addiction — hedonic allostasis, incentive sensitization, aberrant learning and frontostriatal dysfunction — all argue for a unitary account of drug addiction. This view is challenged by behavioural, cognitive and neurobiological findings in laboratory animals and humans. Here, we argue that opiate addiction and psychostimulant addiction are behaviourally and neurobiologically distinct and that the differences have important implications for addiction treatment, addiction theories and future research.

In 1950, addiction experts in the World Health Organization proposed that drug addiction is fundamentally characterized by psychic dependence, independent of drug class[1]. Subsequently, early psychobiological theories identified common denominators of addiction

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in phenomena such as psychic tolerance (the presumed cause of escalating drug intake) and psychic withdrawal or abstinence agony (the presumed main obstacle to abstinence)[2–4]. In the 1970s and 1980s, building on the discovery that electrical stimulation of specific brain areas can induce reward[5], investigators proposed that the mesotelencephalic dopamine system is the neurobiological substrate for the rewarding effects of both opiates (for example, heroin and morphine) and psychostimulants (for example, cocaine, amphetamine and metamphetamine)[6,7]. The same system was also implicated in the motivational effects of drug-associated cues[8] and in the development of psychomotor sensitization to addictive drugs[9]. These neuropharmacological developments were the basis for the influential 1987 psychomotor stimulant theory of addiction[10] (BOX 1), as well as for subsequent theories that emphasize shared psychobiological substrates for addiction, across drug classes: incentive sensitization[11], aberrant learning[12–14], frontostriatal dysfunction[15–17] and hedonic allostasis[18] (BOX 1). A unified view is at the core of current clinical definitions of drug addiction[19].

Unified theories of drug addiction have led to many important discoveries, some of which are described below, but they have also diverted investigators' attention away from psychological and neurobiological processes that distinguish opiate addiction from psychostimulant addiction. For example, in the mid 1980s, studies using the intravenous drug self-administration (BOX 2) procedure in rats showed that dopamine-receptor blockade or lesions of the mesotelen-cephalic dopamine system decrease cocaine or amphetamine reward but not heroin or morphine reward[20,21] (BOX 3; FIG. 1). The controversy that was stirred by these findings was quickly swept away by the tide of evidence (some of which is discussed below) that was used to support a unitary account of addiction.

In this Perspective, our goal is to highlight differences between opiate and psycho-stimulant addictions, using behavioural, cognitive and neurobiological data from laboratory animals and humans. We first discuss differences in the cognitive and neurobiological effects of opiate and psychostimulant administration. We then review data from animal models of addiction showing behavioural and neurobiological differences between opiates and psychostimulants. Next, we consider selected studies in humans that also point to differences between opiate and psychostimulant addiction. We conclude by discussing how behavioural and neurobiological differences between opiates and psychostimulants may have implications for addiction treatment, addiction theories and future research on drug addiction. We restrict the discussion in this Perspective to differences between opiates and psycho-stimulants, but our argument that there are substantial differences in the neurobiological mechanisms of these two classes of drugs is also likely to apply to other classes of drugs of abuse, including nicotine, alcohol, cannabis, benzodiazepine and barbiturates.

Cognitive and neurobiological effects

Cognitive effects

Addiction is associated with impairments in prefrontal cortex (PFC)-dependent cognitive functions; it is thought that these impairments promote compulsive drug use and relapse[15,17]. Opiate addicts and psychostimulant addicts share some deficits in memory, cognitive flexibility and decision making[22–25]. Studies using laboratory animals have shown that repeated exposure to cocaine or heroin impairs spatial memory[26,27] (however, see REF. 28 for different results) and causes transient deficits in attention[29,30]. These data suggest common neurobiological substrates for opiate- and psychostimulant-induced cognitive impairment. However, there is evidence that indicates that for some cognitive functions, particularly those related to impulsivity (a personality trait that is associated with drug addiction[31,32]), there are some fundamental differences between opiates and

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psychostimulants. For example, cocaine and amphetamine addicts are more impulsive and show more pronounced deficits in attention and cognitive flexibility than heroin addicts[33–37]. These behavioural differences resonate with observations that functional and structural abnormalities in the prefrontal cortex are less pronounced in heroin addicts than in cocaine addicts[38].

It is unclear whether differences between heroin and cocaine addicts are due to drug use or pre-existing differences. Studies in laboratory animals, however, support the former possibility, and they specifically indicate that opiates and psychostimulants have different effects on impulsivity. Withdrawal from cocaine self-administration impaired inhibitory control in both rats[39] and non- human primates[40], whereas increased impulsivity was not observed in rats after withdrawal from heroin[29]. Furthermore, non-contingent experimenter-administered cocaine and amphetamine[41] increased impulsivity in rats, whereas heroin did not[42].

In conclusion, in both humans and laboratory animals, chronic exposure to psycho-stimulants seems to cause more pronounced deficits in impulse control and cognitive flexibility than chronic exposure to opiates.

Neurochemical and neurophysiological effects

Opiates and psychostimulants have very different pharmacodynamic profiles[10,12,43] but they share the ability to increase dopamine levels in the nucleus accumbens (NAc)[7] — one of the terminal regions of the mesocorticolimbic dopamine system — and this increase plays an important part in the rewarding effects of drugs and non-drug stimuli[44,45]. Psychostimulants do so by blocking dopamine reuptake or inverting dopamine transport[43], whereas opiates indirectly activate dopaminergic neurons in the ventral tegmental area (VTA) — the cell-body region of the mesocorticolimbic dopamine system — through inhibition of GABAergic interneurons[46,47].

Such similarities in the neurochemical effects of opiates and psychostimulants help to explain why these drugs produce similar effects on neuronal activity in the NAc and in the medial PFC (mPFC) — another terminal region of the mesocorticolimbic dopamine system that has been implicated in the behavioural and cognitive effects of addictive drugs[31,48] and in relapse to drug use (see below). *In vivo* extracellular recording has been used to show that small populations of neurons in these regions are in fact either excited or inhibited during heroin or cocaine self-administration in the rat[49,50]. However, when neural activity was assessed using multiple-channel single-unit recordings in rats that consecutively self-administered heroin and cocaine (in the same session), only a small number of drug-responsive neurons (~20%) in the mPFC and NAc showed similar responses to both drugs[51]. Thus, the rewarding effects of heroin and cocaine seem to be encoded by distinct neuronal subpopulations.

Neuroadaptations

Since the early 1990s[52,53], a central neurobiological framework for addiction research has been that compulsive drug use and relapse are due to drug-induced neuroadaptations in the mesocorticolimbic dopamine system and in the glutamatergic corticolimbic circuitry in which the dopamine projections are embedded[54–56]. An implicit assumption has been that the neuroadaptations are independent of drug class[11,54], and indeed, some are. For example, both opiates and psychostimulants induce changes in intracellular signal transduction pathways in the mesocorticolimbic dopamine system[54,57], induce long-term potentiation (LTP) of glutamatergic synapses in the VTA[58–60] impair LTP in the bed nucleus of stria terminalis (BNST)[61], and cause sensitization of dopamine and glutamate transmission in the

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terminal regions of the mesotelencephalic dopamine system[52,62]. In addition, withdrawal from both opiates and psychostimulants is associated with short-term decreases (a few days) in NAc dopamine levels[63]. However, there are also notable neurobiological differences, which are discussed below.

One difference concerns drug-induced synaptic plasticity. Studies using *ex vivo* whole-cell electrophysiology have shown that morphine and cocaine differ in their ability to induce LTP and long-term depression (LTD) at GABAergic synapses (LTP_{GABA} and LTD_{GABA}) on VTA dopamine neurons. Morphine exerts bidirectional control on such synapses: a single non-contingent injection of morphine in rats abolished both LTP_{GABA} and LTD_{GABA}[64,65] in brain slices. By contrast, cocaine seems to downregulate the strength of such synapses: in rats, a single injection of cocaine had only modestly attenuating effects on LTP_{GABA}[65], and repeated injections occluded endocannabinoid-dependent LTD[66], suggesting an induction of an LTD-like state by cocaine *in vivo*.

Additional differences in synaptic plasticity between opiates and psychostimulants are seen in the consequences of drug withdrawal on LTP in the mPFC. Facilitation of LTP in the mPFC of rats occurred after withdrawal from repeated cocaine exposure[67,68]. By contrast, withdrawal from heroin self-administration in rats had no effect on LTP as measured by the AMPA:NMDA ratio in the mPFC[69]. Furthermore, exposure to cues that had previously been associated with heroin intake reduced the AMPA:NMDA ratio in this area, suggesting decreased LTP[69]. These discrepancies should be interpreted with caution, however, as there were several important experimental differences between the studies, including the age of the rats, the route and type of drug administration (self-administration versus experimenter-delivered), the length of the withdrawal period, the electrophysiological end-points and the mPFC subregions. Nevertheless, the LTP results suggest that exposure to opiates and exposure to psychostimulants can cause qualitatively different changes in mPFC synaptic plasticity.

A second notable difference between opiates and psychostimulants concerns their effects on structural plasticity. In 1997, Robinson and Kolb[70] found that repeated non-contingent injections of amphetamine in rats induce persistent increases in dendrite branching and spine density in NAc medium spiny neurons and mPFC layer III pyramidal neurons. These findings were extended to cocaine and amphetamine self-administration[71,72]. By contrast, morphine self-administration had the opposite effect; it causes long-lasting decreases in the complexity of dendritic branching and in the number of dendritic spines in NAc and mPFC[71] (FIG. 2).

These opposing effects might be explained by the differential engagement of the direct and indirect striatal pathways[73], as indicated by changes in expression of immediate early genes such as FBJ osteosarcoma oncogene (*Fos*)[74–76]. In neurons of the direct pathway, both opiates and psychostimulants increase the expression of *Fos*[74–76]. In neurons of the indirect pathway, only psycho-stimulants increase *Fos* expression, whereas opiates (in this case, morphine) reduce it[74–76]. This differential regulation of *Fos* expression is potentially important because repeated drug-induced FOS (the protein product of the *Fos* gene) induction in the NAc leads to the formation of a more stable form of the FOS protein called ΔFOSB[77], which plays a major part in drug-induced neuroadaptations in the striatum[54], including the regulation of dendritic branches and spines[78,79].

Lastly, a post-mortem study in cocaine and heroin addicts supports the idea that chronic exposure to these drugs leads to dissociable neuroadaptations: out of approximately 39,000 gene transcripts that were investigated in the NAc, only 25 genes showed changed expression in both cocaine and heroin abusers and in nearly half of these cases, the drugs

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had opposite effects on expression[80]. A question for future research is whether opposing cocaine- and heroin-induced changes in neuronal morphology and gene expression help to explain the drugs' differing behavioural effects in animal models, which are described below.

Animal models

Drug addiction is not an automatic outcome of drug use. Only approximately 20% of people who use addictive drugs will switch from controlled to compulsive use[81]. Thus, one of the aims of modelling drug addiction in the laboratory is to identify the mechanisms that are responsible for the transition from one stage of the disorder to the next: from initial drug use to chronic drug use and then to compulsive, relapsing drug abuse. Vulnerable individuals often exhibit distinct personality traits or psychiatric profiles that are thought to facilitate this transition[82]. Not surprisingly, this vulnerability seems to be influenced not only by genes but also by environmental factors[83], including adverse life experiences (especially in childhood), acute exposure to stressors, drug-associated contextual and discrete cues (acting as conditioned stimuli), and other, more subtle aspects of the environment[84]. Indeed, the behavioural and subjective effects of addictive drugs should be seen as the result of complex interactions among the drug, the user's physiological and mental state (also referred to as 'set'), and the circumstances of drug taking (referred to as 'setting')[84–86]. Current animal models of drug addiction can help to clarify how drug, set and setting interact to produce the transition from controlled to compulsive drug use[84]. Under certain conditions, these models reveal important differences between opiates and psychostimulants.

Vulnerability to initial drug use

There are several similarities between the initiation of opiate self-administration and the initiation of psychostimulant self-administration. At the most fundamental level, many studies that use intravenous drug self-administration (the gold-standard procedure for assessment of abuse liability) show that agonists of both drug classes are self-administered by rodents and monkeys[87–89]. In addition, food restriction strongly facilitates the acquisition of self-administration of both opiates and psychostimulants[90], as do other environmental stressors, under certain conditions[91,92]. Furthermore, repeated non-contingent administration (which causes psychomotor sensitization) facilitates the acquisition of self-administration of both opiates and psychostimulants, as well as inducing conditioned place preference (CPP)[93–95](BOX 2). Moreover, for both drug classes, the speed with which self-administration is acquired can be predicted by certain behavioural traits, including high preference for sweet solutions[96] and high locomotor response to a novel environment (which is thought to model novelty seeking; a psychological trait that is associated with the initiation of drug use in humans)[97–99]. Furthermore, for both drugs, inter-individual differences in the propensity to acquire self-administration are associated with inter-individual differences in the extent to which drug-induced dopamine release in the NAc is modulated by the stress hormone corticosterone (through its actions on glucocorticoid receptors in the VTA and the NAc for opiates and psychostimulants, respectively)[100,101].

However, there are several fundamental differences in the behavioural effects of opiates and psychostimulants. For example, in rats, exposure to cocaine causes an approach–avoidance conflict towards places that are associated with injection of the drug, whereas exposure to heroin does not. Studies that use a runway model (BOX 2) suggest that intravenous heroin induces an appetitive incentive motivational state that causes an approach behaviour, similar to that induced by palatable food in hungry rats[102,103]. By contrast, intravenous cocaine induces a motivational state with both an appetitive and an aversive component, leading to approach–avoidance behaviour similar to that caused by simultaneous exposure to food and shock in hungry rats[104,105] (FIG. 3a). The mixed motivational state that is induced by

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cocaine is also observed in the CPP procedure: immediate intravenous cocaine administration (within the 5 min preceding a CPP training session) causes place preference, but delayed cocaine administration (15 min before a training session) causes place aversion[106]. These data from rats seem consistent with human epidemiological data that show an association between cocaine use and anxiety disorders[107,108], and with human laboratory studies in which immediate self-reports of a cocaine high were followed by delayed (~8 min) negative affect-related self-reports of anxiety, paranoia, dysphoria or anhedonia[109].

A second example is that sex hormones seem to have different effects on the initiation of cocaine self-administration and the initiation of heroin self-administration. Female rats acquire cocaine self-administration faster than males; this sex difference is mediated by ovarian hormones[110,111]. For heroin, evidence for a sex difference is mixed. Two studies have shown that intact female rats acquire heroin self-administration faster than males[96,112]. By contrast, a study in which male rats were compared with intact females and with ovariectomized females that were given hormonal replacement found neither sex differences nor a role of ovarian hormones in the acquisition of heroin self-administration[113]. What might account for the mixed results? One issue to consider is that the rats in the 'positive outcome' studies received non-contingent injections of heroin before the daily sessions[96,112], whereas the rats in the 'negative outcome' study did not[113]. Repeated non-contingent drug exposure is known to produce psychomotor sensitization and to facilitate the acquisition of drug self-administration[94,95]. As female rats develop faster morphine-induced psychomotor sensitization[114], the observed sex differences in heroin intake in the 'positive' studies may simply be attributable to the experimental procedures.

Taken together, results from studies on the initiation of cocaine and heroin self-administration in rats suggest that initial cocaine exposure induces a mixed approach–avoidance motivational state that is not observed with heroin, and that sex differences and ovarian hormones may play a more prominent part in the initiation of cocaine self-administration than in the initiation of heroin self-administration.

Transition to compulsive drug use

Researchers have attempted to model in animals the loss of control over drug intake that characterizes addiction in humans[19]. One approach is to give rats prolonged (for example, 6 h per day)[115,116] or unlimited daily access to the drug[117–119]. Under such conditions, most rats progressively escalate their drug intake, a phenomenon that is not observed in rats with limited drug access (for example, 1 h per day)[115,116]. Compulsive drug use has also been modelled in laboratory animals by imposing negative consequences on drug seeking and drug taking[120]. These include adding quinine (a bitter, aversive substance) to rewarding alcohol solutions[121], administering shock to punish drug-taking or drug-seeking responses[122–124], or exposing rats to fear-inducing conditioned cues that would normally inhibit operant responding[125]. Under these circumstances, some of the rats persist in drug seeking or drug taking.

These models show several similarities between heroin and cocaine, at least at the behavioural level[29,115,121,126]. There are, however, important differences. For example, in rats that are given prolonged drug access, escalation of heroin self-administration does not predict escalation of cocaine self-administration, and vice versa[127]. In addition, extended access to heroin self-administration is associated with increased resistance to extinction (that is, after extended access, animals show more persistent attempts to obtain the drug when it is no longer available), whereas this is not the case for cocaine self-administration[115].

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Another well-established difference is that rats that are given unlimited access to opiates gradually increase drug intake, whereas rats that are given unlimited access to psychostimulants cycle between days of binge intake and days of markedly reduced intake[118,128]. The consequences of this difference were shown in a study in which cocaine- and heroin-trained rats were given unlimited access to their drug: the heroin-trained rats gradually increased their intake over days and then maintained stable intake, whereas the cocaine-trained rats rapidly lost control over intake and, within 12 days, died of overdose[117] (FIG. 3b).

A third difference is that social defeat promotes escalation of psychostimulant self-administration but not opiate self-administration. Social-defeat stress (intermittent exposure to a dominant male) promotes the development of psychomotor sensitization to both opiates and psycho-stimulants[129]; this effect is mediated by VTA NMDA receptors[130], which control mesolimbic dopamine activity[131]. However, social-defeat stress facilitated the progression to binge-like drug intake in rats that had unlimited access to cocaine but not in those that had unlimited access to heroin[132]. This finding suggests a dissociation between psychomotor sensitization and drug-taking behaviour for opiates but not for psycho-stimulants. The difference between cocaine intake and heroin intake in the social-defeat paradigm might reflect the differential roles of the mesolimbic dopamine system in heroin self-administration versus cocaine self-administration[20,21] (BOX 3).

Lastly, escalation of cocaine self-administration is predicted by high trait impulsivity, whereas escalation of heroin self-administration is not. As described earlier, cocaine and heroin have different effects on the expression of impulsive behaviours in rats. There is also evidence that trait impulsivity, which can be assessed before drug self-administration, predicts escalation of cocaine but not heroin intake. Thus, high trait impulsivity, reflected in premature responses in a five-choice serial reaction-time test, predicted escalation of cocaine self-administration but not heroin self-administration[29,133] (FIG. 3c). In the cocaine study, trait impulsivity was also associated with low expression of D2 dopamine receptors in the NAc[133]. This indicates that the observed differences between the effects of cocaine and heroin may be yet another illustration of the differential role of the mesolimbic dopamine system in psycho-stimulant but not opiate self-administration (BOX 3).

Taken together, data from animal models indicate that when rats are given unlimited access to psychostimulants, they develop uncontrolled binge intake behaviour that is not seen in rats that are given unlimited access to opiates. In addition, prior exposure to social stress promotes escalation of cocaine self-administration but not heroin self-administration. Lastly, trait impulsivity predicts escalation of cocaine intake but not heroin intake.

Drug seeking and relapse

In humans, drug craving and relapse during abstinence are often triggered by acute re-exposure to the self-administered drug[134], drug-associated cues[135] or stress[136,137]. This clinical scenario can be modelled using a reinstatement procedure (BOX 2) in which laboratory animals are exposed to non-contingent injections of the self-administered drug or related drugs (a drug priming manipulation)[138], drug cues[139] or stress[140]. Cue-induced drug seeking and drug craving can also be modelled using second-order schedules of reinforcement[141] and extinction[142] procedures. The use of reinstatement and extinction procedures has led to the discovery of incubation of drug craving[143], which seems relevant to human addiction[144].

These animal models have not provided much evidence for a difference between cocaine and heroin relapse at the behavioural level, except for a finding that is discussed in the next section. Studies in rats have shown that after extinction, seeking of cocaine and heroin is

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reliably reinstated by acute injections of the drug, by different types of cues (discrete, discriminative or contextual) that are associated with the drug or by stressors such as intermittent footshock or yohimbine (a drug that induces stress-like responses in humans and non-human animals)[145–148]. Discrete cues that are paired with either cocaine or heroin injections also maintain robust drug seeking in second-order schedules of reinforcement[141,149], and incubation of drug craving is equally robust for cocaine, methamphetamine and heroin[150–152].

There is also evidence of similarities at the neurobiological level (FIG. 4b). Reinstatement of both heroin and cocaine seeking induced by drug priming and different cue types requires dopaminergic projections from the VTA to the NAc and mPFC[147,153,154]. Cue-induced seeking of both heroin and cocaine also seem to require the dorsolateral striatum[155–157]. In addition, drug priming-induced and discrete cue-induced reinstatement of both cocaine and heroin seeking require glutamatergic projections from the dorsal mPFC to the NAc core[147,158,159]. Lastly, reinstatement of both cocaine seeking and heroin seeking induced by intermittent-footshock stress requires activity in extrahypothalamic corticotropin releasing factor (CRF) and central noradren-aline systems[160,161].

However, there are also several differences (FIG. 4c). First, reinstatement of heroin seeking seems to involve more brain sites compared to reinstatement of cocaine seeking. Cocaine priming-induced reinstatement is attenuated by reversible inactivation of the VTA, dorsal mPFC, NAc core or ventral pallidum, but not of the ventral mPFC, NAc shell, substantia nigra, central and basolateral amygdala or mediodorsal thalamus[159]. By contrast, heroin priming-induced reinstatement is attenuated by reversible inactivation of any of the above brain areas, as well as the BNST[162].

Second, pre-training excitotoxic (that is, permanent) lesions of the basolateral amygdala attenuated discrete cue-induced cocaine seeking but not discrete cue-induced heroin seeking in a second-order schedule of reinforcement[163,164]. No such dissociation was found after local reversible inactivation[165,166]. The discrepant results may reflect differences in the experimental procedures: although both second-order schedule and cue-induced reinstatement procedures assess the conditioned reinforcing effects of reward cues[142], cue-induced reinstatement does not include drug delivery. Another possible explanation for the discrepancy is the use of different lesion and inactivation methods, and differences in the timing of their application (permanent cell-specific excitotoxic lesions before training[163,164] versus acute reversible inactivation of both cell bodies and fibres of passage by tetrodotoxin[165,166]). A question for future research is whether reversible inactivation of the basolateral amygdala after training would decrease cue-induced heroin seeking in the second-order schedule, as it did with cue-induced heroin seeking in the reinstatement model[165].

Third, context-induced reinstatement of cocaine seeking seems to involve subregions of mPFC and NAc that are functionally dissociable from those involved in context-induced reinstatement of heroin seeking. For cocaine, context-induced reinstatement is attenuated by reversible inactivation of the dorsal but not the ventral mPFC[167], whereas the opposite is the case for heroin[168]. In addition, context-induced reinstatement of cocaine seeking is attenuated by reversible inactivation of either the NAc core or shell[169], whereas context-induced reinstatement of heroin seeking is attenuated by manipulations of the NAcc shell and not by manipulations of the NAc core[170,171]. This possible difference between heroin and cocaine reinstatement should be interpreted with caution, because the manipulations that were used to test heroin reinstatement (dopamine-receptor blockade and inhibition of glutamate transmission) differed from those used to test cocaine reinstatement (muscimol in combination with baclofen), and these manipulations can have different effects on

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behaviour[172]. Furthermore, studies by Bossert *et al.*[146,168], described above, indicate that reinstatement of heroin seeking requires activity in the ventral mPFC and NAc shell. By contrast, reinstatement of cocaine seeking is induced by reversible inactivation of the ventral mPFC (infralimbic area) or NAc shell[169,173] and is attenuated by ventral mPFC AMPA receptor activation[173]. Functionally disconnecting these two brain regions by a unilateral inhibition of ventral mPFC and simultaneous unilateral inactivation of the NAc shell mimics the reinstatement of cocaine seeking induced by bilateral inactivation of either brain area[173], suggesting that activation of projections from the ventral mPFC to the NAc shell inhibits cocaine seeking after extinction[174].

Lastly, recent data suggest that incubation of psychostimulant craving and incubation of opiate craving have different underlying mechanisms[143]. In this regard, glial cell line-derived neurotrophic factor (GDNF) activity in the VTA is crucial for incubation of cocaine but not heroin craving[175,176].

What might account for a divergence between the circuits that mediate the reinstatement of cocaine seeking versus heroin seeking? A possible explanation is the differences in the psychological states that are induced by cocaine versus heroin, and by extension, in the psychological states that are induced by cues associated with them. As mentioned above, runway studies by Ettenberg and colleagues[102,177] (FIG. 3a) suggest that heroin induces seemingly pure approach behaviour, whereas cocaine induces approach–avoidance conflict behaviour. We speculate that the partial dissociation of brain circuits that control cocaine and heroin seeking (FIG. 4) may mirror this difference in motivational states. Given the evidence for a substantial aversive component in the response to cocaine[177], it is perhaps not surprising that the circuits that control inhibition of cocaine seeking after extinction are more similar to the circuits that control fear inhibition[174] than are those that control inhibition of heroin seeking.

In conclusion, although there are similarities between the brain circuits that control opiate and psychostimulant seeking in animal models of relapse, there are some notable differences with regard to drug-priming and context-induced reinstatement of drug seeking, and incubation of drug craving.

The setting of drug taking

It has been known for many years that environmental contexts or places in which drugs are taken play an important part in human addiction[84–86,178]. So far, animal research has focused mostly on the ability of the environmental context to alter drug seeking or drug taking by inducing stress or conditioned responses. In the previous section, we provided several examples of this. However, setting can also affect drug taking in ways that are not easily attributable to stress or conditioning. For example, the presence of novel objects can reduce intake of amphetamine[179,180], and high temperatures can increase intake of 3,4-methylenedioxymethamphetamine[181].

Even non-physical, seemingly negligible differences in setting can powerfully alter drug-taking behaviour, as indicated by a series of studies in which rats were trained to self-administer heroin or cocaine under two deceptively similar environmental conditions. Some rats were transferred to self-administration chambers immediately before experimental sessions (non-resident rats), a procedure commonly used in most self-administration studies. Other rats were kept in the self-administration chambers at all times (resident rats). Thus, the physical characteristics of the self-administration environment for resident versus non-resident rats were virtually identical, with all differences being purely a function of familiarity[84] (FIG. 5). These studies yielded three major findings that challenge the

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prevailing view that environmental contexts influence opiate and psychostimulant drug taking and drug seeking in a similar way.

First, cocaine and amphetamine self-administrations were greater and seemed to be more rewarding (when tested in a progressive-ratio schedule) in non-resident rats than in resident rats (FIG. 5). By contrast, heroin self-administration was greater and more rewarding in resident rats than in non-resident rats[182,183]. Second, when rats with double-lumen catheters were permitted to self-administer either cocaine or heroin within the same session, most resident rats preferred heroin over cocaine, whereas most non-resident rats preferred cocaine over heroin[184] (FIG. 5). Third, preliminary data suggest that resident and non-resident rats show differential reinstatement of drug seeking after cocaine or heroin priming[185]. Resident and non-resident rats were first trained to self-administer heroin and cocaine on alternate days. After extinction, heroin priming had a stronger effect on reinstatement in the resident rats than in the non-resident rats. By contrast, cocaine priming had a stronger effect on reinstatement in the non-resident rats than in the resident rats.

Additional experiments using the drug-discrimination procedure[186] suggest that opiates and psychostimulants produce interoceptive cues of different strength in resident rats and non-resident rats. Non-resident rats discriminated amphetamine or cocaine from saline more readily than resident rats, whereas resident rats discriminated heroin from saline more readily than non-resident rats[84,187]. Thus, the setting of drug exposure seems to modulate the effects of opiates and psychostimulants in opposite directions with regard to two major attributes of addictive drugs: the degree of reward and the strength of subjective effects[186].

Why do the environmental settings differentially affect heroin and cocaine taking, as well as the propensity to relapse to drug seeking? At a proximal, neurobiological level, there is evidence that the initial exposure to low doses of intravenous heroin and cocaine (such as those used in self-administration experiments) differentially activate dorsal striatum neurons in resident and non-resident rats, respectively[188] (FIG. 5). The functional significance of this differential neuronal activation is a subject for future research.

At a more distal level, it is tempting to view the setting as an ecological backdrop against which drug effects are appraised as adaptive or maladaptive[184]. Thus, the sedative effects of heroin may facilitate introspection in a safe, non-challenging home environment, but may be appraised as performance impairing in a potentially unsafe non-home environment. By contrast, the arousing and activating effects of cocaine may be appraised as performance enhancing in a challenging non-home environment, whereas the same state may be appraised as mainly anxiogenic in the home environment. This hypothesis requires rigorous testing but initial evidence in support of this idea comes from studies showing that ketamine — which, like cocaine, has activating and sympathomimetic effects — is more readily self-administered by rats in the nonresident environment[189]. By contrast, alcohol — which, like heroin, initially causes drowsiness and sedation — is more readily self-administered in the resident environment[190].

The ability of setting to differentially affect heroin and cocaine reward may have important implications for the incentive sensitization theory of addiction. Earlier studies have shown in fact that repeated administrations of heroin or morphine produce greater psychomotor sensitization in non-resident than in resident rats[191,192]. Thus, it appears that psychomotor sensitization and drug reward can be modulated in opposite directions, at least under certain circumstances. This discrepancy goes beyond the reports of mere dissociation between psychomotor sensitization and drug reward[193,194].

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In conclusion, in laboratory rats, the setting of drug availability affects heroin taking and seeking, and cocaine taking and seeking in a different way. Below, we discuss results that suggest that this is also the case in humans.

Epidemiological and clinical aspects

At the epidemiological level, heroin and smoked cocaine seem similar in terms of the severity and type of harm that they are likely to cause to drug users[195], although the proportion of users who become addicted is somewhat higher for heroin (~23%) than for cocaine (~17%)[196]. Users of these drugs also show similar likelihoods of relapse in the year following treatment[197]. Non-pharmacological treatments, such as contingency management or cognitive behavioural therapy, are moderately effective in both types of addiction[198,199]. Lastly, attempts to identify trait determinants of the 'drug of choice', in terms of self-medication hypotheses[200], have not fared well[201–203], and it has even been suggested that an addicted person's choice of drug is largely determined by chance[204].

Nevertheless, there is ample evidence that psychostimulant addiction and opiate addiction have distinct profiles, and in the following sections we briefly discuss selected studies that point to fundamental differences between these two drug classes in human addicts.

Genetic and environmental factors in the vulnerability to opiate and psychostimulant use

There is some evidence that shared genetic and environmental influences contribute to a generalized vulnerability to drug abuse and dependence[83,205]. However, there is also evidence that unique genetic and environmental factors underlie a differential vulnerability to heroin versus cocaine use.

Data from the Vietnam Era Twin Registry, for example, suggest that vulnerability to heroin use is more strongly influenced by unique genetic factors compared to vulnerability to other drugs, including cocaine[83]. This finding was not replicated in a cohort study based on the Virginia Twin Registry[205], suggesting that it may have been specific to the all-military Vietnam-era cohort. However, small-scale linkage studies and genome-wide association studies also support the idea that specific genetic variants are differentially associated with opiate and psychostimulant use[206].

Lastly, both the Vietnam Era Twin Registry and the Virginia Twin Registry cohort studies indicate that a sizeable portion of the variability in the susceptibility to drug use is due to environmental influences that are unique to opiates versus psychostimulants[83,205]. A host of environmental factors are thought to influence the initiation and maintenance of drug addiction, including price and availability of drug and non-drug rewards, peer pressure, aversive life experiences and occurrence of negative consequences. What is not clear is which of these environmental factors can differentially influence opiate and psychostimulant use. In the next section, we examine at least one way in which environmental context has been shown to interact differently with heroin and cocaine taking in humans.

Patterns of heroin or cocaine use in drug addicts

As discussed above, studies conducted using rats have shown differential preferences for heroin and cocaine as a function of the environmental setting or context[184,188]. These preclinical findings are supported by a study in human addicts (outpatients at an addiction clinic), who were heroin and cocaine co-abusers. Retrospective self-reports[184] and written diaries[207] showed that the respondents used cocaine in different settings from those in which they used heroin. In most cases, heroin was used at home, whereas cocaine was used outside the home; respondents said that these choices of location reflected real preferences rather than social or practical constraints. The route of drug taking did not play a major part in

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these findings, as comparable results were obtained when the analysis was limited to subgroups of respondents who injected or snorted heroin and cocaine separately, often on the same day (FIG. 5). The within-subject design of this study makes the findings especially compelling, because the difference in preferred settings for heroin use compared to cocaine use cannot readily be attributed to differences in drug availability, peer influence or other socio-demographic factors.

Other studies conducted with heroin and cocaine co-abusers[208], using real-time electronic diary reports, have examined the predictive value of potential triggers of craving and relapse, such as negative moods, positive moods and exposure to drug-associated cues[209,210]. Episodes of cocaine use, but not craving, were reliably predicted by any of these triggers on a timescale of 5 hours. For heroin, the results were nearly the opposite: episodes of craving, but not use, were reliably predicted by increases in triggers that induced negative mood. These findings suggest that heroin and cocaine differ in terms of the factors that induce craving and in terms of their use in daily life. A caveat to this interpretation is that the participants were all in methadone maintenance therapy, which may have partly decoupled heroin craving from heroin use.

In summary, the human data reviewed here suggest that there are differences between aspects of heroin and cocaine use, abuse and craving. Indeed, there are no pharmacological treatments that are similarly effective for heroin addiction and cocaine addiction. For example, the effectiveness of agonist maintenance therapy (for example, methadone treatment) for heroin addiction[211] has no clear parallel in cocaine addiction, although efforts to find such a therapy continue[212].

Conclusions and future directions

Opiate addiction, psychostimulant addiction and other types of addiction are often seen as mere variants of the same disorder. Indeed, current diagnostic criteria for addiction cut across drug classes[19], and influential theories of addiction emphasize the shared psychological processes and neurobiological substrates of different types of drug addiction (BOX 1). Here, we have attempted to offer a different perspective. We argue that although there are commonalities in the ways in which opiates and psychostimulants affect brain and behaviour, much can be learned from considering the distinctive features of each type of addiction. The human and animal studies reviewed here suggest that there are substantial differences in the neurobiological and behavioural mechanisms underlying opiate addiction and psychostimulant addiction (Supplementary information S1 (box)).

At the neurobiological level, the most fundamental difference is that mesocor-ticolimbic dopamine transmission seems to be crucial for psychostimulant self-administration but not opiate self-administration (BOX 3). By contrast, the mu opioid receptor is crucial in mediating the effects of intravenous opiate self-administration but plays only a minor part in psychostimulant self-administration[20,213]. Other notable differences include the distinct populations of mPFC and NAc neurons that are associated with heroin self-administration compared to cocaine self-administration[51], the opposite synaptic and structural plasticity changes in the PFC after withdrawal from opiates and psychostimulants[67–69,71,72], the opposite regulation of immediate-early gene expression in the striatal neurons of the indirect pathway by opiates and psychostimulants[74–76], and the differential roles of mPFC subregions in context-induced relapse to heroin seeking and cocaine seeking[167,168]. Lastly, human studies suggest that there is minimal overlap between the genes that are associated with opiate and psychostimulant addiction[83,206,214], as well as minimal overlap between the profiles of post-mortem gene-expression changes in the striatum of opiate and psychostimulant users[80].

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At the behavioural and psychological levels, perhaps the two most fundamental differences between cocaine and heroin (and by implication other psychostimulants and opiates) were revealed in rat models: cocaine exposure leads to a mixed motivational state characterized by approach–avoidance conflict towards drug-associated places, and unlimited cocaine access leads to complete loss of control over drug intake. By contrast, heroin exposure leads to a classical approach behaviour similar to that observed in hungry rats seeking food, and unlimited heroin access does not lead to loss of control over drug intake[102,117] (FIG. 3). There are also fundamental differences in the way in which the environment interacts with opiate and psychostimulant reward: in both rats and humans, the preferred setting for opiate use is the home environment, whereas the preferred setting for psychostimulant use is outside of the home environment[182–184] (FIG. 5). These findings may help to account for data from population studies that suggest that there are unique environmental influences on opiate addiction and psychostimulant addic-tion[83,214]. Furthermore, in rats, escalation of cocaine self-administration is predicted by high trait impulsivity, whereas escalation of heroin self-administration is not[29,133]. Lastly , in humans, psychostimulants cause more pronounced deficits in impulse control and cognitive flexibility than do opiates[33–37].

The neurobiological, behavioural and psychological differences between opiates and psychostimulants have implications for addiction treatment. These differences may account for the fact that no known medication effectively treats both opiate and psychostimulant addiction. For example, approved treatments for opiate addiction, such as methadone and buprenorphine, have shown limited efficacy in decreasing cocaine use in concurrent users of heroin and cocaine[215–218] (however, see REF. 219 for different results). In addition, the realization that drug choice is crucially dependent on setting has implications for cognitive behavioural therapies in which addicts learn to identify and respond appropriately to use-provoking risk factors.

The data reviewed here also have implications for addiction theories (BOX 1), which, as mentioned above, have attempted to provide a unitary account of addiction across drug classes. It is beyond the scope of this Perspective to analyse how each of the neurobiological or behavioural differences discussed above can or cannot be accounted for by current theories. However, we argue that these theories would struggle to explain the opposite modulatory role of the environment on opiate and psychostimulant reward and choice, the finding that escalation of cocaine intake does not predict escalation of heroin use (and vice versa), the finding that opiate self-administration is mostly independent of mesocorticolimbic dopamine transmission, and the opposite structural and synaptic changes in PFC that are induced by exposure to opiates and psychostimulants.

Lastly, the data reviewed here have implications for future neuroscience research on drug addiction. Since the late 1980s and the early 1990s[52,53,220], such research has focused on a search for drug-induced neuroadaptations that can account for compulsive drug use and relapse across drug classes. In the vast majority of these studies, cocaine has been used as the prototypical, presumably representative drug of abuse[221,222]. Based on the differences across drug classes that we have discussed here, we believe that generalizations from cocaine to other drugs of abuse should be made with extreme caution, and that the field would benefit from more systematic comparisons of the roles of different signalling molecules and synaptic-plasticity mechanisms in reward and relapse across drug classes.

It is beyond the scope of this Perspective to compare and contrast similarities and differences in the behavioural and neuro-biological mechanisms of addiction across all drug classes. However, our concerns about differences between opiates and psychostimulants probably also apply to other addictive drugs. For example, to our knowledge, it has not been established in animal models or human studies that the mesocorticolimbic dopamine system

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plays a part in addiction to benzodiazepines or barbiturates. Even for nicotine and alcohol, empirical data raise questions about the centrality of the mesocorticolimbic dopa-mine system in the rewarding effects of these drugs[223–226].

We hope that this Perspective will serve as a starting point for more balanced future research that will avoid the Scylla of rigidly unified models and the Charybdis of excessively compartmentalized ones. In particular, we believe that it is crucial for models of drug addiction to be formulated and validated on the basis of empirical results from comparative studies that include several classes of addictive drugs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Glossary

AMPA:NMDA ratio	A measure of postsynaptic changes in synaptic strength. It is defined as the peak synaptic AMPA receptor current relative to the peak synaptic NMDA receptor current
Craving	An affective state that can be induced in human drug users by exposure to the drug itself, drug-associated cues or stress. In laboratory animals, craving is often inferred from the subjects' behavioural response (for example, lever-pressing) to drugs, drug-associated cues or stress
Direct and indirect striatal pathways	The two efferent pathways in the basal ganglia. The direct pathway connects the striatum with the substantia nigra pars reticulata and entopeduncular nucleus. The indirect pathway connects the striatum with the globus pallidus and ventral pallidum
Extinction	The decrease in the frequency or intensity of learned responses after the removal of the unconditioned stimulus (for example, food or a drug) that has reinforced the learning
Incentive motivational state	A motivational state that is induced by exposure to unconditioned aversive or appetitive stimuli or cues that become associated with these stimuli
Incubation of drug craving	A hypothetical motivational process that is inferred from findings of time-dependent increases in cue-induced drug seeking after withdrawal from drug self-administration in rats
***In vivo* extracellular recording**	A set of methods in which bundles of microwires are targeted to specific areas of the brain to allow measurement of extracellular currents (action potentials) of single cells

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Long-term depression	(LTD). A form of synaptic plasticity that is defined by a persistent weakening of synaptic strength
Long-term potentiation	(LTP). A form of synaptic plasticity that is defined by a persistent increase in synaptic strength
LTD_{GABA}	A form of long-term depression (LTD) that is observed in dopaminergic neurons in the ventral tegmental area and that reduces synaptic efficacy between presynaptic GABAergic neurons and postsynaptic dopaminergic neurons
LTP_{GABA}	A form of long-term potentiation (LTP) that is observed in dopaminergic neurons in the ventral tegmental area. It results in increased GABA release and in the strengthening of inhibitory synapses
Mesotelencephalic dopamine system	Also known as the mesocorticolimbic dopamine system. A major ascending dopaminergic pathway that originates in the ventral tegmental area and projects to, among other regions, the nucleus accumbens, the bed nucleus of the stria terminalis, the amygdala, the olfactory tubercle and the medial prefrontal cortex
Psychic (or psychological) dependence	A concept, established early in the addiction field, that refers to a compulsion that requires periodic or continuous intake of an abused drug to produce psychological pleasure or to avoid psychological distress, regardless of whether physical dependence is also present
Psychomotor sensitization	A progressive increase in locomotor or activity or stereotypy with repeated drug (for example, cocaine) administration
Relapse	The resumption of drug-taking behaviour after self-imposed or forced abstinence in humans with a history of abuse or dependence
Second-order schedule of reinforcement	A complex reinforcement schedule in which the completion of the response requirement of one schedule is treated as a unitary response that is reinforced according to another schedule
Stress	n animal models, stress typically refers to forced exposure to events or conditions that the animal would normally avoid. In humans, stress often refers to a condition in which the environmental demands exceed the coping abilities of the individual
Synaptic plasticity	Activity-dependent direct or indirect modifications of the strength of synaptic transmission at pre-existing synapses.;

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Box 1 | Theories of addiction

Over the past decades, several classes of addiction theories have been proposed by animal behaviour researchers and clinical researchers. Below, we describe some of these theories, which over the past two decades have had a substantial influence on the direction that drug addiction research has taken.

Aberrant-learning theories of addiction

These theories propose that repeated exposure to addictive drugs heightens Pavlovian and instrumental responsiveness to drug-associated cues through actions on neurons that control normal responses to non-drug conditioned cues; these actions may occur in the ventral striatum[12], dorsal striatum[14] or both[13]. A main theme of these theories is that the heightened responsiveness to drug cues is insensitive to outcome devaluation (for example, punishment), leading to continued drug use even when it has adverse consequences[227,228]. This aberrant learning process has been suggested to be mediated by a progressive dopamine-dependent ventral-to-dorsal striatal shift in control over drug seeking and drug taking[227,228].

Frontostriatal-dysfunction theories of addiction

These theories propose that repeated exposure to addictive drugs causes deficits in top-down executive control over behaviour[15–17], leading to loss of impulse control, impaired decision-making processes, exaggerated responsiveness to drug-associated cues and compulsive drug use despite adverse consequences. This idea was first advanced by Jentsch and Taylor[15], who proposed that compulsive drug use is due to drug-induced alterations in cortical and limbic circuits, leading to exaggerated responses to drugs and drug-associated cues (owing to nucleus accumbens and amygdala dysfunction) and impaired inhibitory control (owing to medial prefrontal and orbitofrontal cortex dysfunction).

Hedonic-allostasis theory of addictio*n*

A theory that is based on the opponent-process theory of motivation[4]; it proposes that although initial drug use is primarily controlled by the drug's rewarding effects, chronic drug use leads to decreases in its rewarding effects and to recruitment of stress-related systems. This leads to a new emotional state, termed the 'hedonic allostatic' state, which represents a chronic change in the normal reward setpoint[18]. According to this theory, hedonic allostasis causes loss of control over drug use through cortico– striatal–thalamic circuits that are involved in compulsive behaviour.

Incentive-sensitization theory of addiction

This theory has three main components: first, the idea that addictive drugs increase mesocorticolimbic dopamine neurotransmission; second, the idea that one psychological function of this brain system is to attribute incentive salience to contexts, cues and other events that are associated with activation of this dopaminergic system; and third, the idea that repeated exposure to addictive drugs produces long-lasting adaptations in this neural system, rendering it hypersensitive to drugs and drug-associated cues[11]. Incentive salience is defined as a psychological process that increases the valence of reward-associated cues and makes them attractive incentive cues. Robinson and Berridge[11] also argued that sensitization of neural systems that mediate incentive salience (drug 'wanting') occurs independently of changes in neural systems that control pleasurable effects of drugs (drug 'liking'). They also suggested that motivation systems that control incentive salience are independent of those controlling drug withdrawal states.

Pschomotor-stimulant theory of addiction

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This theory proposes that a common denominator of addictive drugs is their ability to cause psychomotor activation[10]. The theory is rooted in an earlier theory that all positive reinforcers activate a common biological mechanism that is associated with approach behaviours[229]. Wise and Bozarth[10] put forward the idea that the major substrate of the approach system (and of psychomotor sensitization) is the mesocorticolimbic dopamine system. They also argued that drug withdrawal symptoms, which are drug-class dependent, do not play a major part in controlling compulsive drug use.

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Box 2 | Animal models of drug reward, subjective effects and relapse

For many decades, investigators have used animal models to assess the behavioural effects of abused drugs that are potentially related to their effects in humans[186,230–233]. Below, we describe the main animal models that are currently used by addiction researchers to study the positive reinforcing (or rewarding) effects of drugs, the subjective effects of drugs and relapse to drug seeking.

Conditioned place preference (CCP) model

A Pavlovian (classical) conditioning model in which during the training phase one distinct context is paired with drug injections and another context is paired with vehicle injections. During the subsequent testing phase (which is drug-free), the animal's preference for either context is determined by allowing the animal to move between the two contexts. An increase in preference for the drug-associated context serves as a measure of the drug's Pavlovian reinforcing (or rewarding) effects.

Intravenous drug self-administration model

In this model, animals typically make a lever press or nose poke to receive contingent drug injections. The premise of this procedure is that drugs of abuse control behaviour by functioning as operant positive reinforcers.

Reinstatement model

An animal model of relapse to drug seeking. In the operant-conditioning version of this model, laboratory animals are first trained to self-administer drugs by making a lever press or nose poke, with drug injections typically paired with discrete cues (for example, a tone or a light). Subsequently, the animals undergo extinction training, during which lever presses (or nose pokes) are not reinforced with drug. Reinstatement of lever pressing (or nose pokes) under extinction conditions is then determined after manipulations such as non-contingent priming injections of the drug, exposure to discrete or contextual cues that are associated with drug intake, or exposure to stressors. In the classical-conditioning version of the model, CPP is induced by a drug, extinguished and then induced again by drug priming injections or stressors.

Runway model

In this operant-conditioning model, the speed with which a laboratory animal traverses a long, straight alley for a positive reinforcer (for example, food or a drug) provides an index of the animal's motivation to seek the reinforcer. The dependent measure in this model is the run-time from a start box to the goal box in which the positive reinforcer (or the reward) is earned.

Drug-discrimination model

An animal model of the subjective effects of drugs. In this model, laboratory rodents or monkeys are trained to discriminate between a drug state and a non-drug state, or between different drug states. In a typical experiment, a food-restricted animal is trained in a two-lever operant chamber in which the food-reinforced lever differs as a function of whether drug or saline was administered before the session. After achieving a training criterion of correct responding, subjects are typically injected with various doses of the training drug to generate dose-response curves or injected with other drugs from the same or different drug classes to test for stimulus generalization.

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Box 3| Does dopamine mediate opiate reward?

It is well established that the rewarding effects of psychostimulants are mediated by dopamine projections from the ventral tegmental area (VTA) to the nucleus accumbens (NAc); evidence for this is seen in both the self-administration and the conditioned place preference (CPP) models[234–237]. However, although addiction and neuroscience experts, the popular press and the public commonly assume that this dopamine projection is also crucial for the rewarding effects of opiates, the literature does not support this general conclusion.

On the one hand, there is evidence that opiate drugs activate VTA dopamine neurons[47] and increase NAc dopamine release[7]. There is also evidence that fluctuations in NAc dopamine levels correlate with heroin self-administration behaviour[238]. In addition, morphine and other opiate agonists are self-administered directly into the VTA or the NAc and produce CPP following intracranial injections into either site[239–243]. Lastly, there is some evidence that morphine or heroin CPP is blocked by systemic or NAc injections of dopamine receptor antagonists[236,244,245].

On the other hand, the CPP findings are not consistent across studies: 6-hydroxydopamine (6-OHDA) or excitotoxic lesions of the NAc seem to have no effect on CPP for morphine[246,247], and dopamine receptor blockade decreases heroin CPP in heroin-dependent rats but not in non-dependent rats[248,249]. Self-administration data pose an even greater challenge to the theory of a unified, dopamine-based mechanism of drug reward. There is surprisingly little empirical evidence that dopamine transmission is crucial for self-administration of opiates. For example, systemic injections of dopamine receptor antagonists have minimal effect on self-administration of opiate agonists in rats and monkeys, unless the agonists are administered at doses that are high enough to be sedating[20,213,250,251] (FIG. 1). In addition, self-administration of heroin or morphine is only minimally reduced by NAc disruptions such as 6-OHDA lesions or local injections of dopamine receptor antagonists[250,252–254] (FIG. 1). Finally, chronic blockade of dopamine receptors with a-flupenthixol strongly potentiates, rather than inhibits, the rewarding effect of low heroin doses[255].

In conclusion, as stated 15 years ago by Mello and Negus[213], these data and related results “argue against a prominent role for dopamine in opioid self-administration.” Research that has been performed since then has not led to new empirical evidence that can be used to refute this conclusion.

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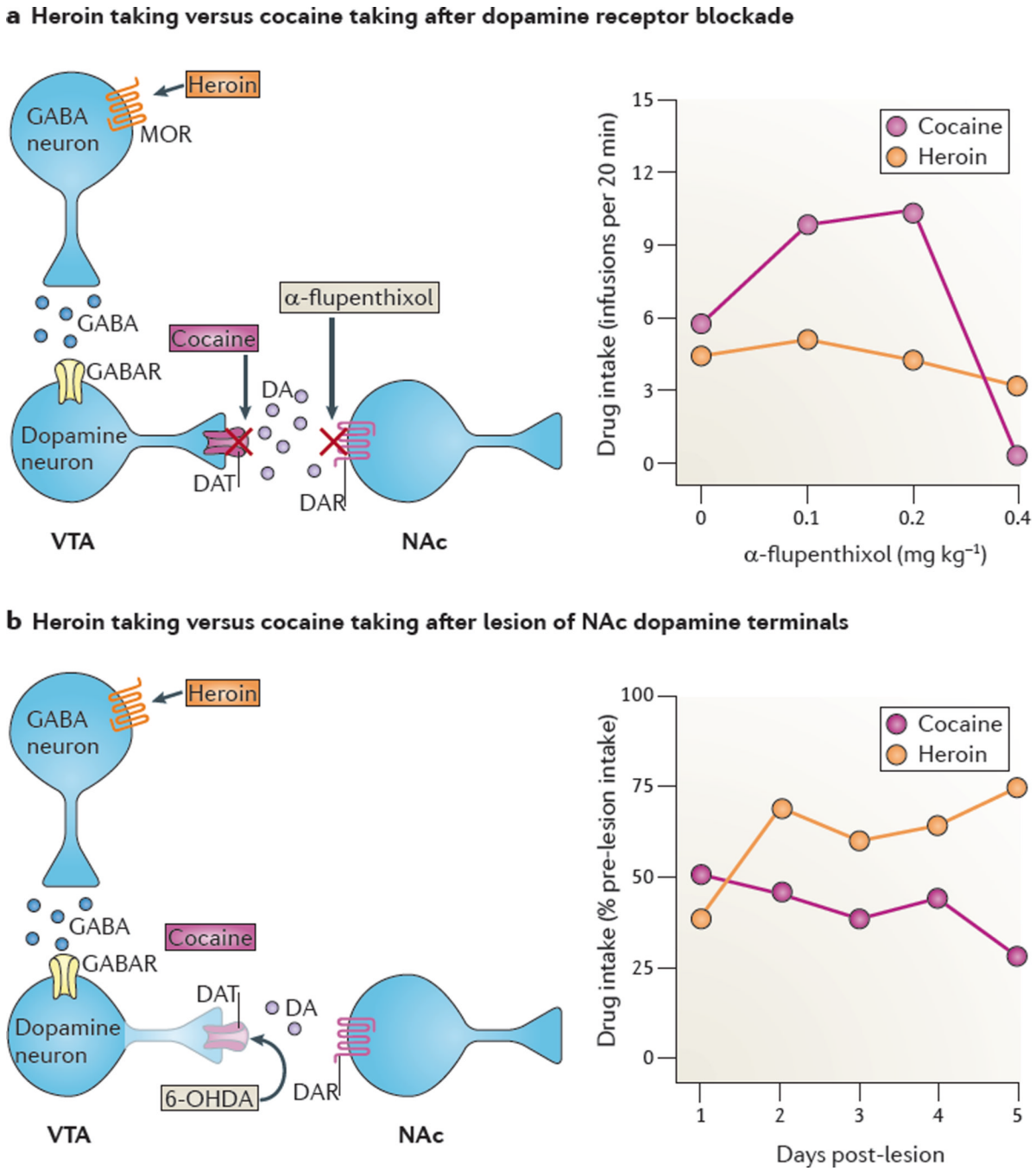

Figure 1. Dopamine receptor blockade or lesions of the mesolimbic dopamine system decrease cocaine reward but not heroin reward

a | The effect of dopamine receptor blockade: rats were trained to lever press for intravenous heroin (0.06 mg kg^{-1} per infusion) or cocaine (0.75 mg kg^{1} per infusion) on a fixed-ratio 1 (FR1) reinforcement schedule (each lever press was reinforced with drug infusion). After stable self-administration, the rats were injected on different days with different doses of the dopamine receptor antagonist a-flupenthixol (left part). Lower doses (0.1 or 0.2 mg kg^{-1}) of a-flupenthixol increased cocaine intake but not heroin intake (right part); this effect presumably reflects a compensatory response to offset a decrease in the rewarding effects of cocaine but not heroin. A higher dose of a-flupenthixol (0.4 mg kg^{-1}), which causes

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sedation, decreased both heroin and cocaine self-administration (right part). **b** | The effect of dopaminergic lesions: rats were trained to self-administer heroin or cocaine, as above. After stable self-administration, dopamine terminals in the nucleus accumbens (NAc) were lesioned with 6-hydroxydopamine (6-OHDA) (left part). Post-lesion responding for cocaine decreased over days, reflecting extinction of cocaine-reinforced responding. By contrast, post-lesion responding for heroin increased over days, reflecting recovery of the rewarding effects of heroin (right part). DA, dopamine; DAR, dopamine receptor; DAT, dopamine transporter; GABAR, GABA recptor; MOR, mu opioid receptor; VTA, ventral tegmental area. Part **a** is modified, with permission, from REF. 20 © (1982) Springer. Part **b** is modified, with permission, from REF 21 © (1984) Springer.

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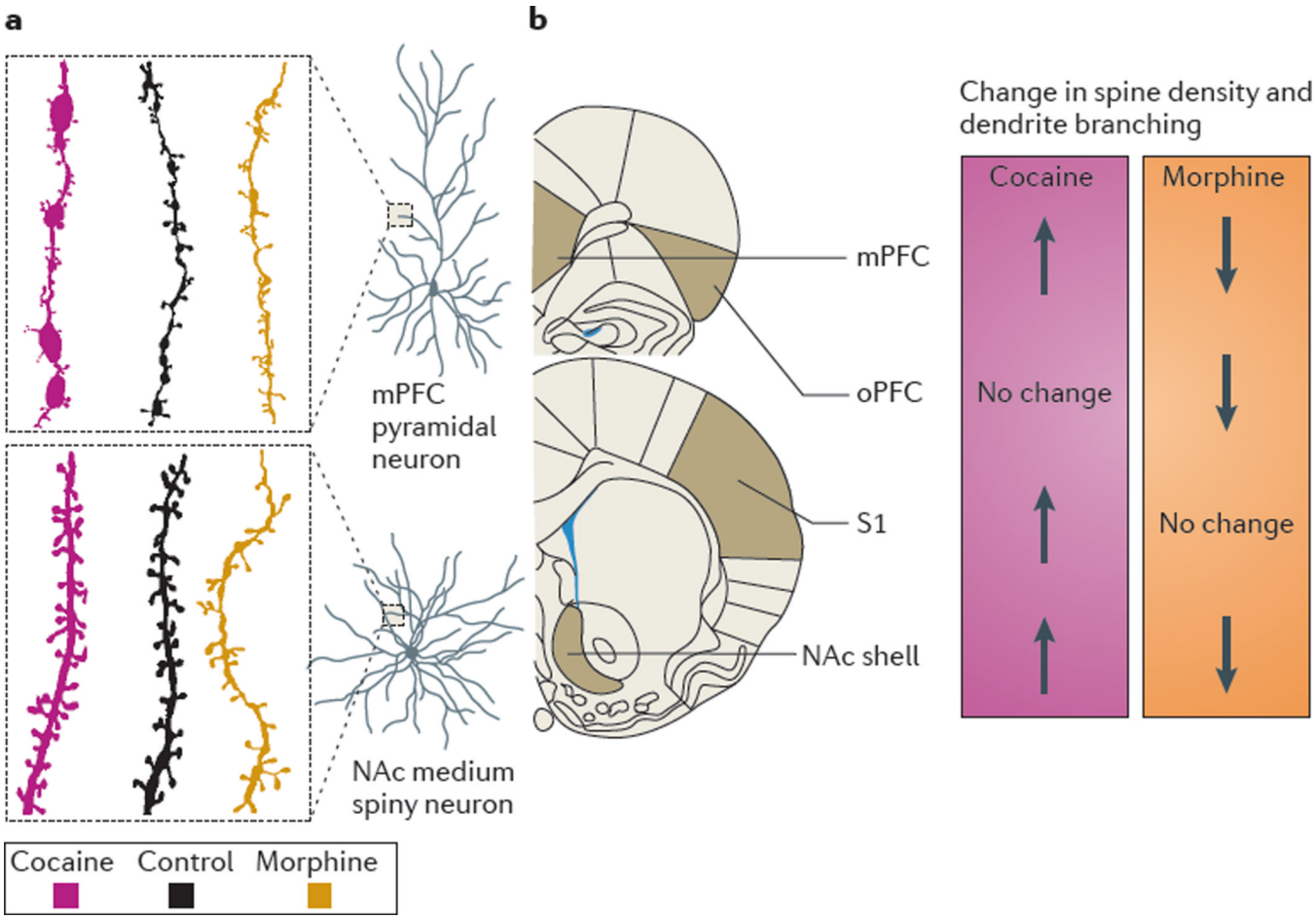

Figure 2. Morphine and cocaine have opposite effects on structural neuroplasticity in the NAc and mPFC

a | Groups of rats were trained to self-administer morphine or cocaine intravenously for several weeks. The control groups were given daily intravenous infusions of vehicle for the same period of time. After 1 month of withdrawal from the drugs, the rats' brains were processed using the Golgi staining procedure. Rats that were exposed to cocaine showed increased dendritic branching and increased spine density in both nucleus accumbens (NAc) medium spiny neurons and medial prefrontal cortex (mPFC) pyramidal neurons. By contrast, rats that were exposed to morphine had both reduced dendritic branching and reduced spine density in these brain regions. **b** | A summary of changes in spine density and dendritic branching that occur after exposure to cocaine or morphine relative to controls. A dissociation between the effects of cocaine and morphine was also observed in the orbital prefrontal cortex (oPFC) and in the primary somatosensory cortex (S1). Data from REF. 71.

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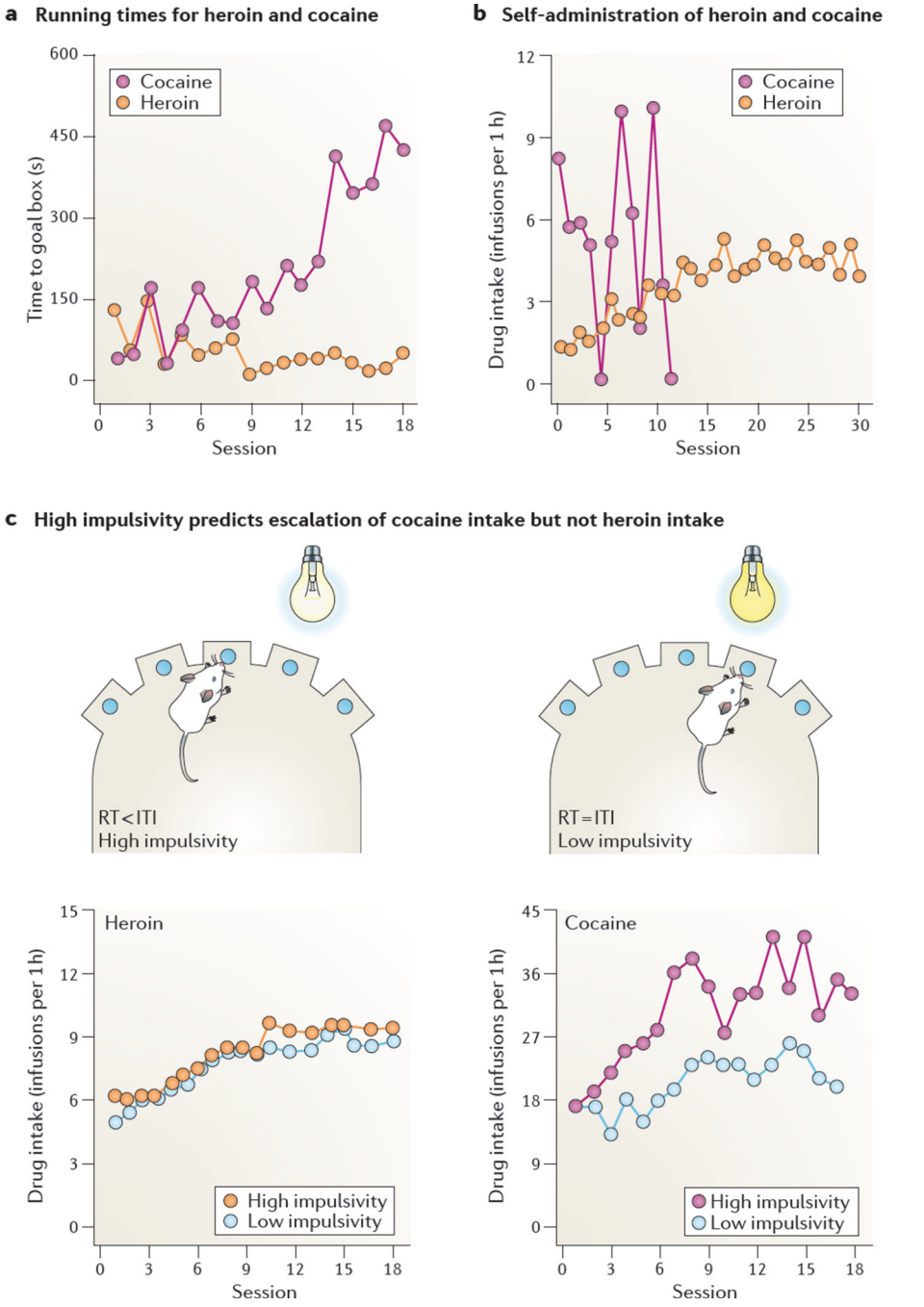

Figure 3. Initiation of drug use and transition to compulsive drug use

a | In a runway procedure, two groups of rats were trained to traverse a straight alley to obtain either five heroin injections (0.06 mg kg^{-1} per infusion) or five cocaine injections (0.75 mg kg^{-1} per infusion) in the goal box. In heroin-trained rats, the running times of rats to the goal box to obtain heroin infusions decreased over days, indicating that heroin serves as an operant reinforcer (reward). In cocaine-trained rats, the time to obtain cocaine infusions increased over days, owing to repeated cycles of forward locomotion and retreats before reaching the goal box (a behavioural pattern that mimics the behaviour of hungry rats that receive both food and shock in the goal box). **b** | In the unlimited drug self-

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administration procedure, two groups of rats were trained to lever press for intravenous heroin (0.01 mg kg^{-1} per infusion) or cocaine (1.0 mg kg^{-1} per infusion) on a fixed-ratio 1 (FR1) reinforcement schedule for 24 hours per day. Heroin-trained rats gradually increased their drug intake over days and then maintained stable drug intake, whereas cocaine-trained rats rapidly lost control over cocaine intake and died of drug overdose within 12 days. **c**To test the effect of impulsivity on self-administration, groups of naive rats were first assessed for trait impulsivity in the five-choice serial-reaction time test. Animals that showed premature responses — reaction times (RTs) were shorter than the inter-trial interval (ITI) — were classified as high impul-sivity, and animals that responded only when a stimulus appeared — reaction times were equal to the inter-trial interval — were classified as low impulsivity (top panels). They were then trained to lever press for either intravenous heroin (0.04 mg kg^{-1} per infusion) or cocaine (0.25 mg kg^{-1} per infusion). After 5 days of short access (1 h per d) to heroin or cocaine, the rats were given extended (6 h per d) access to the drugs for 18 consecutive days. High impulsivity predicted escalation of cocaine self-administration but not heroin self-administration (bottom panels). Part **a** is modified, with permission, from REF. 103 © (1993) Elsevier. Part **b**, data from REF. 117. Part **c**, left graph is modified, with permission, from REF. 29 © (2010) Springer. Part **c**, right graph is modified, with permission, from REF. 133 © (2007) American Association for the Advancement of Science.

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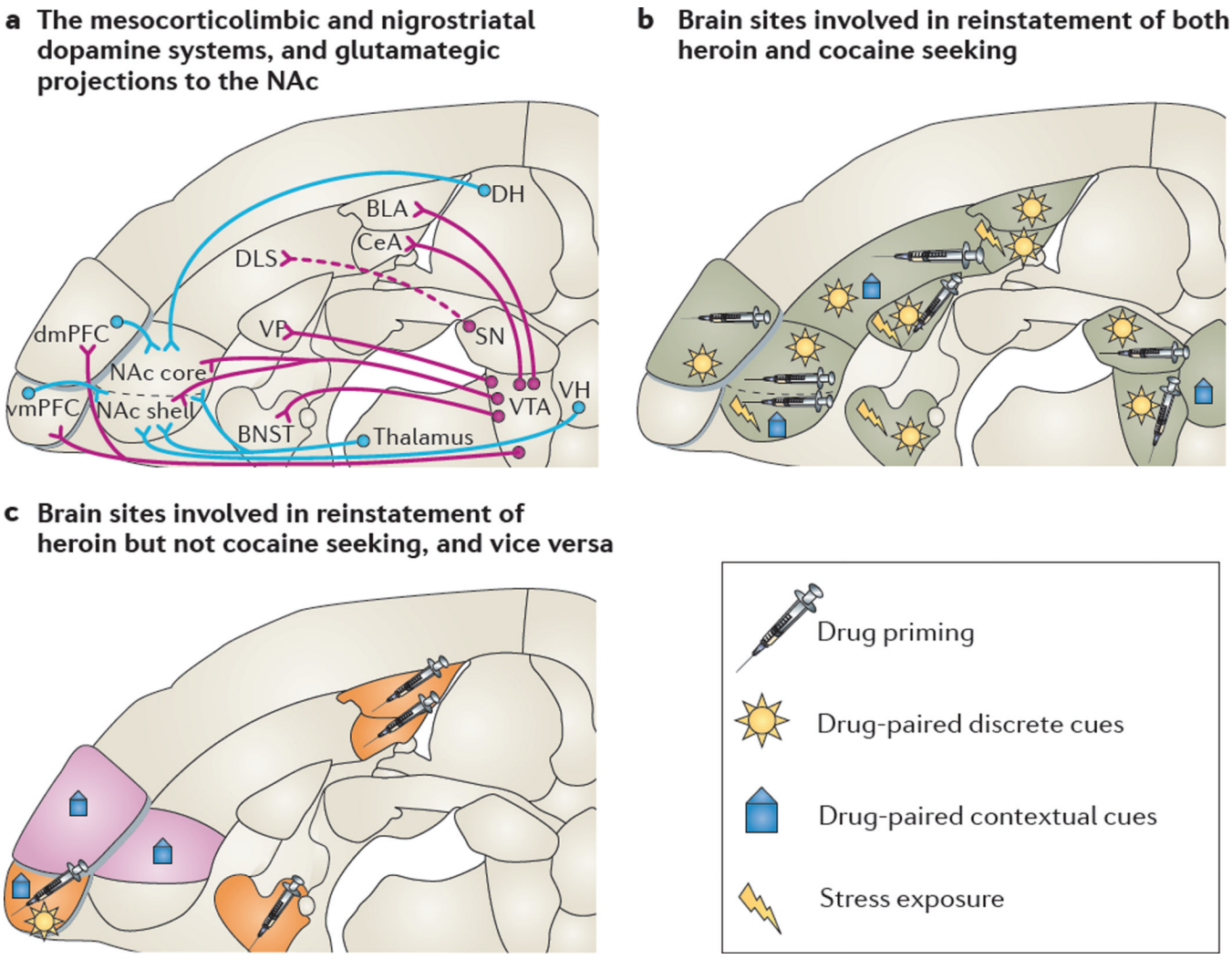

Figure 4. Similarities and differences in the brain sites controlling reinstatement of cocaine seeking and heroin seeking

a | Horizontal section showing the mesocorticolimbic dopamine pro-jections (shown by purple lines) from the ventral tegmental area (VTA) and nigrostriatal dopamine projections (shown by dashed purple lines) from the substantia nigra (SN) to various brains areas, and the glutamatergic projections (shown by blue lines) to the nucleus accumbens (NAc). **b** | Several brain sites are implicated in the reinstatement of both heroin seeking and cocaine seeking. The brain areas that are involved depend on the way in which reinstatement is induced — by exposing animals to non-contingent injections of a drug (‘drug priming’), to drug-associated discrete or contextual cues, or to stress. **c** | Some brain sites are differentially implicated in heroin reinstatement (shown in orange) and cocaine reinstatement (shown in purple), depending on how reinstatement was induced. The basolateral and central nuclei of the amygdala (BLA and CeA, respectively), the bed nucleus of the stria terminalis (BNST) and the ventromedial prefrontal cortex (vmPFC) are differentially implicated in the reinstatement of heroin seeking induced by heroin priming. The vmPFC is also differentially involved in the reinstatement of heroin seeking that is induced by exposure to heroin-paired discrete cues or contextual cues. By contrast, the dorsomedial PFC (dmPFC) and the NAc core are differentially implicated in the reinstatement of cocaine seeking induced by exposure to cocaine-associated contextual cues. DH, dorsal hippocampus; DLS, dorsolateral

striatum; VH, ventral hippocampus; VP ventral pallidum. Brain sections are modified, with permission, from REF. 256 © (2005) Elsevier.

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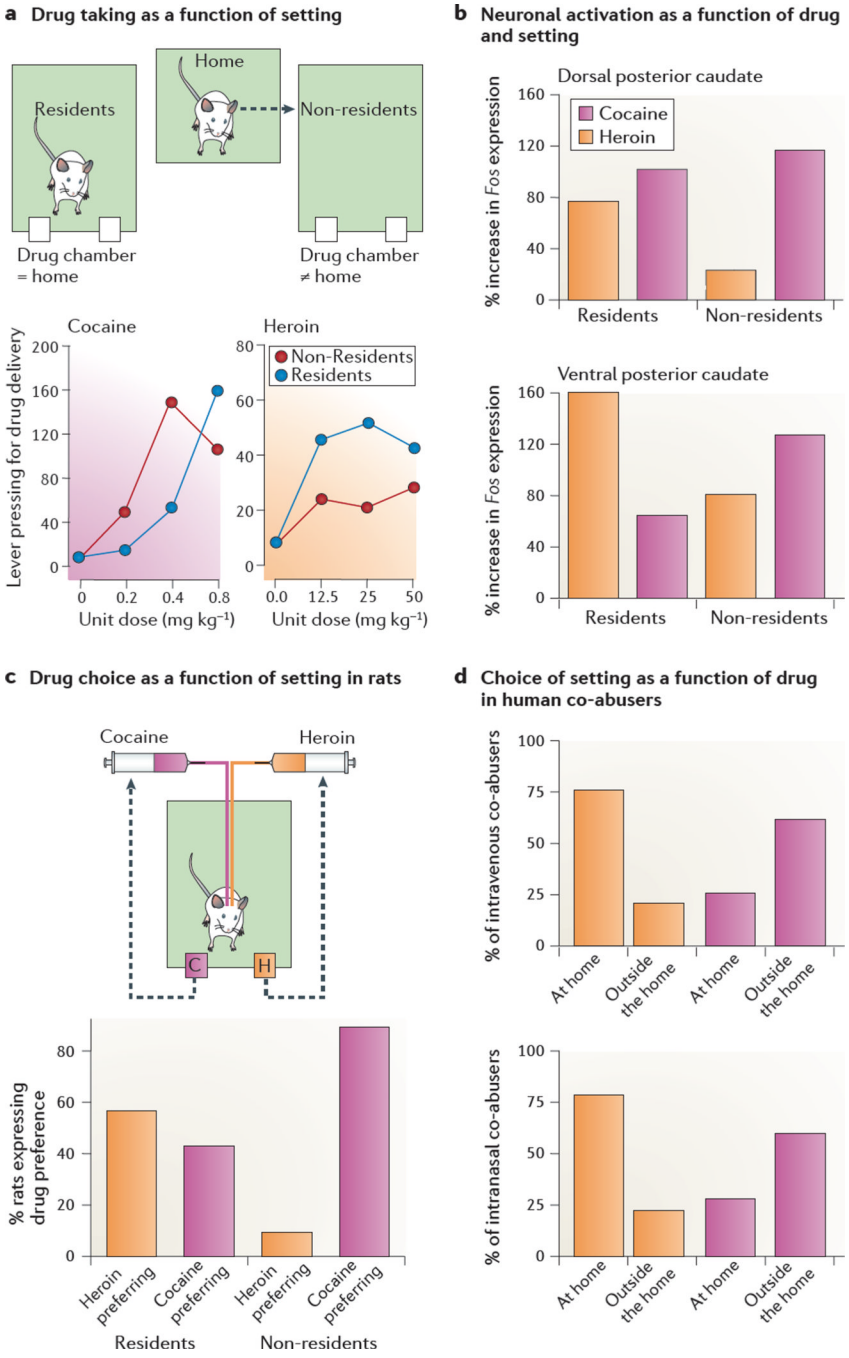

Figure 5. Setting differentially affects heroin and cocaine use in rats and humans

a | In a study that examined drug taking as a function of setting, standard two-lever self-administration chambers were used (one lever was paired with drug infusions and the other lever was inactive). Some rats were transferred to the chambers immediately before the start of the sessions (referred to as non-resident rats), whereas other rats were kept in these chambers at all times (referred to as resident rats). Heroin was more rewarding in the resident rats than in the nonresidents rats (indicated by an upward shift in the dose-response curve). By contrast, cocaine was more rewarding in the non-resident rats than in the residents rats (indicated by a left shift in the dose-response curve of non-resident rats). **b** | In

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a study that examined drug-induced neural activity in the caudate nucleus as a function of setting, drug-naive resident and non-resident rats with intravenous catheters received a single 'self-administration dose' of either heroin (25 μg kg^{-1}) or cocaine (400 μg kg^{-1}), and their brains were processed 30 min later for *in situ* hybridization of *Fos* mRNA expression. Cocaine exposure induced greater increases in *Fos* expression in the dorsal and ventral parts of the caudate nucleus of non-resident rats than in that of resident rats, whereas heroin exposure induced greater increases in *Fos* expression in resident rats than non-resident rats. **c** | In a study that examined drug preference as a function of setting, resident and non-resident rats with double-lumen catheters were first trained to self-administer heroin and cocaine on alternate days, and were then given the opportunity to choose between cocaine and heroin within the same session. Most resident rats preferred heroin over cocaine, whereas most non-resident rats preferred cocaine over heroin. **d** | In a study that examined setting preferences as a function of drug in humans, most addicts reported using heroin at home and cocaine outside the home, regardless of whether the two drugs were injected (top panel) or snorted (bottom panel). Only a minority of addicts (<10%) indicated no clear preference for the setting of drug taking. Part **a**, left graph is modified, with permission, from REF. 183 © (2007) Springer. Part **a**, right graph, data from REF. 182. Part **b** is modified, with permission, from REF. 188 © (2009) Springer. Part **c** is modified, with permission, from REF. 184. © (2009) Elsevier. Part **d**, data from REFS. 184, 207.