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Dopamine "ups and downs" in addiction revisited

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Abstract

Repeated drug use can change dopamine function in ways that promote the development and persistence of addiction. But in what direction? By one view, drug use blunts dopamine neurotransmission, producing a hypodopaminergic state that fosters further drug use to overcome a dopamine deficiency. Another view is that drug use enhances dopamine neurotransmission, producing a sensitized, hyperdopaminergic reaction to drugs and drug cues. According to this second view, continued drug use is motivated by sensitization of drug 'wanting'. Here we discuss recent evidence supporting the latter view, both from preclinical studies using intermittent cocaine self-administration procedures that mimic human patterns of use, and related human neuroimaging studies. These studies have implications for modeling addiction in the laboratory, and for treatment.

Keywords

Dopamine; Cocaine; Rat; Self-Administration; Tolerance; Sensitization

Animal Models to Isolate Causes of Addiction

Addictions to psychoactive drugs (substance use disorders) are multifaceted disorders, and the propensity for addictions is determined by complex interactions amongst social, psychological, environmental and biological factors. Here we address one of these susceptibility factors; the ability of drugs themselves to produce persistent alterations in brain function, and thereby psychological function(s), in ways that promote and sustain problematic patterns of drug use and addiction. It is hard to specify how drugs change brain and behaviour in humans to promote the transition to addiction, primarily because of the

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challenge in isolating the consequences of drug use from the effects of many other conditions often associated with addiction (e.g., poor nutrition, high stress, incarceration, poly-drug use, co-morbidities, etc.). For this reason, there has been considerable effort to develop animal models of addiction where causal factors and drug effects can be isolated. Most drug self-administration procedures used in preclinical studies of addiction involve one of three procedures that we will refer to as: Short Access (ShA), Long Access (LgA) or Intermittent Access (IntA). Here we focus on the ways that these different procedures change dopamine (DA) neurotransmission, and we attempt to integrate preclinical studies with neuroimaging studies in human drug users.

Drug Self-Administration in Laboratory Animals

Laboratory animals will expend considerable effort to self-administer most drugs used by humans, and much is known at this stage about the neural systems that mediate the reinforcing and motivational effects of drugs. Drug reward is a multifactorial psychological process [1] involving complex interactions between many different neural systems. Still, much research has pointed to a central role for mesotelencephalic dopamine (DA) systems [2]. Here we focus primarily on ways in which cocaine self-administration can change DA activity, and how this might contribute to the development of addiction-like behaviours. It should be noted that different dopaminergic neuron subpopulations can contribute to different behavioural and psychological aspects of reward-seeking behaviour [5]. We do not address this complexity here. Instead, our focus is on how drug-induced changes in dopamine neurotransmission more generally contribute to the development of addiction.

There are two polarized views concerning which form of cocaine-induced change in DA neurotransmission is critical for promoting addiction – the “Ups and Downs” described by Leyton and Vezina [3, 4] and alluded to in the title of this paper. One view is that repeated cocaine use *decreases* the ability of rewards, including cocaine, to enhance DA neurotransmission, leading to ‘anhedonia’ [5, 6]. By this view, continued (and escalated) cocaine use is motivated primarily by a desire to overcome this ‘DA deficiency’. As put by Volkow et al.:

> “drug consumption triggers much smaller increases in dopamine levels in the presence of addiction (in both animals and humans) than in its absence (…). This attenuated release of dopamine renders the brain’s reward system much less sensitive to stimulation by both drug-related and non–drug-related rewards. As a result, persons with addiction no longer experience the same degree of euphoria from a drug as they did when they first started using it” [7, p. 366]. In other words, “the down-regulation of dopamine signaling (…) dulls the reward circuits’ sensitivity to pleasure”
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> [7, p. 367].

Note that this seems to adopt the view that DA mediates pleasure (hedonia), because it is otherwise difficult to imagine how a ‘DA deficiency’ could motivate drug seeking. However, that view is incompatible, many would argue, with a large body of evidence showing that DA does not mediate pleasure[8, 9].

In contrast, a second view of addiction is that repeated exposure to addictive drugs, like cocaine, *increases* DA activity evoked by drug and drug cues (i.e., produces *sensitization*). This sensitized DA response, in turn, by interacting with glutamate and other signals, leads to heightened motivation for drugs ('wanting'), but not higher drug 'liking' [10–12]. Importantly, more recent studies in rats using an intermittent self-administration procedure that reflects human patterns of cocaine use, have led to a re-examination of hypo- versus hyperdopaminergic states in addiction, in part because this procedure sensitizes DA activity [13, 14].

Preclinical Models of Addiction: Long Access (LgA) versus Short Access (ShA)

One goal of preclinical models is to capture behavioural features of human addiction ("addiction-like behaviours"). DSM-5 criteria for addiction include progressive increases in drug use (i.e., escalation), continued use despite adverse consequences, unsuccessful efforts to cut down and persistent drug craving [15]. Many early drug self-administration studies, especially with cocaine, used Short Access procedures (ShA). With ShA, rats have continuous access to drug for 1–3 hours per day [16, 17]. This usually results in stable cocaine intake across many sessions [18], which is not reflective of addiction. By contrast, early studies using prolonged (many months) oral administration of amphetamine or an opioid (etonitazene) described the emergence of escalated and dysregulated intake, that appeared to much better reflect addiction-like behaviour [19, 20]. But recreational drug users typically prefer routes of administration that produce a more rapid rise in brain drug levels, such as smoking or injection, and this pharmacokinetic variable is very important in determining both the neurobiological response to drugs and the transition to addiction [21]. Thus, a significant advance came with a study that compared rats allowed to continuously self-administer *intravenous* cocaine for 1 hour/day (ShA), with those allowed to continuously self-administer for 6 h/day (Long Access, LgA) [18]. ShA rats maintained stable levels of drug intake over 22 sessions, as expected. In contrast, LgA rats escalated their intake across sessions. Given that escalation of intake is a central feature of addiction, it was suggested that LgA, "*may provide an animal model for studying the development of excessive drug intake and the basis of addiction*" [18, p. 298].

Indeed, not only has escalation of intake during LgA been replicated many times [22–25], but LgA cocaine experience is also reported to be more effective than ShA at producing addiction-like behaviours in rats, including: *i*) a greater increase in motivation for cocaine, as measured by breakpoint on a progressive ratio schedule [26], behavioural economic indicators of cocaine demand [27, 28], running speed in a runway [22] and drug-seeking behaviour [23]; *ii*) greater drug-taking in the face of an adverse consequence [29]; and *iii*) greater reinstatement of cocaine-seeking behaviour evoked by re-exposure to the drug [24, 30]. Similarly, LgA more effectively produces addiction-like behaviours following the self-administration of heroin [31], methamphetamine [32], or nicotine [33]. These results have led to widespread adoption of the LgA procedure as a preferred preclinical model of addiction.

Given that LgA and ShA differ in their ability to produce addiction-like behaviours, and the established role for DA in the reinforcing/motivational effects of drugs, there has been considerable focus on determining how LgA may alter DA systems to produce addiction-like behaviours. There are several reports that LgA experience reduces DA transmission, particularly in brain regions that mediate drug-seeking and drug-taking behaviours, like the Nucleus accumbens (NAc; Figure 1). For example, in brain slices taken from rats following LgA experience, stimulated DA release and cocaine-induced inhibition of DA uptake is reduced within the NAc core [14, 34]. This is consistent with decreases in both cocaine-induced DA overflow assessed using *in vivo* microdialysis, and cocaine-induced psychomotor activity [34]. The findings are also consistent with studies showing that very extended (24 h) [35] or high-dose [36] cocaine self-administration sessions reduce cocaine's efficacy at the DA transporter and also produce a blunted DA response to the drug. Finally, the phasic DA response that typically accompanies cocaine-seeking behaviour decreases across LgA sessions [37]. These LgA studies seem to support the reward deficiency view that a drug-induced *hypo*-dopaminergic state (tolerance) promotes the development of addiction-like behaviours. However, as we detail in Box 1, there is evidence that both tolerance and sensitization can develop in parallel, and that tolerance can mask sensitization [38]. Time since the last drug exposure determines which is dominant. Tolerance dissipates after a period of abstinence, revealing sensitization-related changes in brain and behaviour, as indicated for example, by the incubation of cocaine craving after LgA experience in rats [39] (an 'unmasking' of DA sensitization can also be seen after ShA cocaine experience [16]). Thus, the LgA model provides evidence for both tolerance and sensitization depending on when measures are made, highlighting the importance of examining DA responses both early and late following the discontinuation of self-administration.

Preclinical Models of Addiction: Intermittent Access (IntA)

With the ShA and LgA procedures, cocaine is continuously available. This produces high and sustained brain concentrations of cocaine throughout each self-administration session [40–42] (Figure 1). Yet as human users become addicted, they seldom take cocaine continuously in LgA fashion over many hours and days. Instead, they usually consume drug more intermittently, with periods of ingestion spaced apart, both between and within bouts of use [21, 43–45]. This results in a "spiking" pattern of brain cocaine levels over time. To reproduce this spiking pattern within a bout of use, Intermittent Access (IntA) self-administration procedures were developed, whereby periods during which drug is available (5–6 min for cocaine) are interspersed with periods when drug is not available (e.g., 25 min) during a self-administration session [40] (see also [46]; Figure 1).

Crucially, comparing effects of IntA versus LgA indicates that the temporal pattern of drug self-administration may be more important for promoting addiction than the total amount of drug consumed. Previous reviews have compared the ability of these procedures to produce addiction-like behaviour [13, 21]. Specifically, IntA is even more effective than LgA in producing addiction-like behaviours, even though IntA results in much less total cocaine intake/session, with intake levels comparable to ShA [13, 21]. For example, the large amount of cocaine consumption associated with LgA was thought to be necessary for escalation, however IntA experience—which achieves much lower levels of cocaine intake—also results

in escalation [42, 47]. In addition, compared to LgA, IntA produces *i*) a greater and longer-lasting increase in subsequent motivation to obtain cocaine [42, 48], *ii*) increased drug taking in the face of an adverse consequence ([48] also see [49]), *iii*) more robust cue-induced reinstatement of cocaine-seeking behaviour ([48, 50, 51] also see [47, 49, 52, 53]), and *iv*) continued drug seeking when drug is known to no longer be available [47]. Beyond cocaine and other psychostimulants, IntA exposure to other drugs, including alcohol [54] and opioids [55, 56] is also especially effective in producing addiction-like behaviours.

Although admittedly few, studies examining the effects of IntA cocaine experience on DA are consistent with enhancements (sensitization), rather than reductions (tolerance) in drug-evoked DA activity [51] (Figure 1). Initial studies using *ex vivo* slices showed that IntA cocaine self-administration increases cocaine-induced DA transporter (DAT) inhibition (LgA had the opposite effect) and increases electrically-stimulated DA release in the NAc [14]. As few as 3 IntA cocaine sessions sensitize cocaine's effects at the DAT in the NAc, and after one week of abstinence, both cocaine potency and stimulated DA release are increased even further [57]. Using *in vivo* microdialysis in freely moving rats, it has recently been reported that 1–3 days after the last self-administration session, IntA and LgA rats do not differ in basal extracellular DA concentrations, but IntA (not LgA) rats show sensitization of cocaine-induced overflow in the NAc core [51]. Furthermore, IntA cocaine experience enhances amphetamine and methylphenidate's effects at the DAT [58], and IntA methylphenidate experience produces DA sensitization effects similar to those produced by cocaine [59]. Finally, IntA experience also produces psychomotor sensitization [60–63], which has been related to increased DA neurotransmission [11], and psychomotor sensitization often predicts later motivation for cocaine [61, 62]. Indeed, there is a large literature showing that intermittent treatment with many drugs of abuse produces sensitization of psychomotor activity and of DA [64, 65]. Thus, the available evidence suggests that LgA can produce tolerance, reductions in DA (although see Box 1), and addiction-like behaviours, whereas IntA increases (sensitizes) DA activity and is more effective in producing addiction-like behaviours than LgA, despite less total drug consumption (Figure 1).

Little is known about the mechanism(s) by which IntA cocaine experience sensitizes DA activity. DA in the NAc arises (for the most part) from cells in the ventral tegmental area (VTA). Many neurotransmitter/neuromodulator systems regulate VTA DA neuron firing and DA activity at DA terminals in the NAc. This includes glutamate, GABA, orexin and endogenous cannabinoids and opioids. One of the forthcoming challenges is to determine how IntA drug experience affects these systems to alter DA activity. In this regard, existing studies already show that IntA cocaine ([48], and see also [66]) or fentanyl [55] experience increases the number and activity of orexin neurons in ways that could contribute to enhanced DA release in the NAc, and that this is causal in drug seeking and taking [also see 67]. Although of course, many different players could be involved.

There are well-established sex differences in the transition to addiction, as detailed in a number of reviews [68–70]. For example, in vulnerable cocaine users, women can progress more rapidly from initial drug use to addiction than men do, and women can also be more vulnerable to relapse after abstinence [71, 72]. Similarly, sex differences are seen in rats and monkeys [69, 73]. These sex differences are due largely to activational effects of hormones

in females and males, and are thought to be mediated, at least in part, by the ability of gonadal hormones to influence DA systems [74]. In the context of the current review, it is notable that after IntA experience, female rats show more robust psychomotor sensitization than male rats do [60, 62], consistent with earlier studies using experimenter-administered drug [75]. Female IntA rats also more readily develop incentive sensitization than male rats do, as indicated by earlier and greater increases in the motivation to take cocaine [76] and more cocaine seeking when drug is not available [50]. In this regard, future studies should determine the effects of IntA drug experience on DA and other brain systems in females, as there are currently no published studies on the neurobiological effects of IntA in female animals. More generally, future research in addiction should include animals of both sexes and address knowledge gaps due to biased inclusion of males vs. females in past work.

Studies in Humans

In the following, we compare results from preclinical studies to those from neuroimaging studies of DA-related systems in people with a substance use disorder. It is difficult to draw direct parallels between rodent and human studies, and studies in humans also carry many caveats. Still, integrating results across these literatures allows assessing the extent to which findings from preclinical studies are relevant to human drug addiction. As detailed next, we would argue that evidence from human neuroimaging studies is consistent with the thesis that the heightened motivation for drugs seen in addiction is primarily due to a sensitized DA response to drug cues and drugs (see [3, 77] for more thorough reviews).

D-amphetamine increases DA transmission in the human ventral striatum [78] (see also [79, 80]), as indicated by decreased [^{11}C]raclopride binding (but see Box 2 for alternative interpretations of [^{11}C]raclopride binding studies). Alcohol [81], cigarette smoking [82, 83], morphine [84] and Delta 9-tetrahydrocannabinol [85] have a similar effect. With repeated drug exposure, humans show sensitization of drug-induced DA transmission in the striatum. For example, after 3 d-amphetamine doses, there is both psychomotor and DA sensitization to the drug, such that d-amphetamine now produces increased behavioural activation and DA transmission relative to the initial dose [78]. This behavioural and neurochemical sensitization in humans is long-lasting, persisting for up to one year [78].

In addition, and as seen in rats [86], studies using [^{11}C]raclopride and positron emission tomography in humans suggest that drug-paired cues increase striatal DA transmission in humans, and this is linked to drug craving. An environmental context associated with d-amphetamine use increases DA transmission in human striatum, to the same extent as d-amphetamine itself [79]. Presentation of rich, personalized drug cues that signal cocaine availability also increases striatal (and frontocortical) DA release in human users, and the magnitude of this effect is positively correlated with their drug craving scores [87–89].

In humans with substance use disorders, drug-related cues are especially effective at capturing attention, and such cues can evoke craving and renewed drug use [90–93]. Such cue effects are especially evident during daily life outside the laboratory [94]. Some studies have used fMRI to quantify cue-induced neural activations in human users (change in the BOLD signal), and increases in DA activity are thought to be both necessary and sufficient

to increase the BOLD signal in the striatum [95–99], although see [100]. Such fMRI studies report that drug-paired cues, as well as the drug itself, produce robust activations in a number of brain regions, including mesostriatal dopamine-rich regions [77, 91, 101–103, also see 104]. These DA-related activations positively correlate with self-report of cue-evoked craving and predict subsequent relapse [105–107]. Interestingly, cocaine cues evoke activations even when people are not consciously aware of seeing the cues [108]. Together, these results further support the notion of a hyperdopaminergic state in drug addiction.

An important question is whether there are mechanistic links between enhanced DA neurotransmission and the development of addictive behaviours in humans. Studies in patients with Parkinson's Disease and with Dopamine Dysregulation Syndrome (DDS), induced by their L-Dopa or DA receptor agonist medications support such links. In some patients, DDS is accompanied by a pathologically high motivation to take excessive medication, and in many others by the development of compulsive behaviours (e.g., gambling) that abate when the medication is stopped. This has been linked to the pharmacological induction of a *hyper*dopaminergic state, particularly within the ventral striatum (NAc [109]). Thus, it is an increase, not a decrease, in DA transmission that leads to excessive motivation in DDS. As put by Dagher and Robbins,

> "the reward deficiency hypothesis appears to be directly falsified by the premorbid Parkinsonian personality syndrome and by the occurrence of addiction in PD patients when they are overdosed with dopaminergic medication. (…) This suggests that, in the general population as well as in PD patients, factors that lead to enhanced striatal dopaminergic function, whether hereditary or acquired, represent a biological substrate of addictive propensity"
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> [110, p. 508].

Thus, when DA is pharmacologically enhanced, this promotes addiction-relevant behaviours. Furthermore, these compulsive behaviours cease when pro-dopaminergic medication is terminated. Although data from patients with Parkinson's disease should be interpreted with caution, these findings nonetheless support the view that addiction involves sensitized DA responses.

The studies in humans discussed above support a role for *hyper*- and not hypo-dopaminergic states in producing pathological motivations. However, there are also studies that have been interpreted as supporting the opposite view. These latter studies report D2-like receptor downregulation and decreased stimulated DA release in people with substance use disorder [111, 112]. However, as described in Box 2, such findings do not necessarily reflect a hypodopaminergic state [3, 4, 10]. Downregulation of D2-like receptors could reflect a compensatory response to increased DA release and/or decreased D2 autoreceptors, neither of which would be consistent with a blunted DA response. Similarly, the studies showing reduced drug-induced DA release generally tested participants in the absence of drug-predictive cues and contexts, and also tested shortly after abstinence. Such conditions are known to mask the expression of sensitization.

Concluding Remarks

Addiction cannot be reduced to drug-induced changes in DA function alone, as many other neurotransmitter systems, brain systems, and non-pharmacological factors are involved. Nevertheless, clarifying the direction of cocaine-induced changes in DA systems is fundamental for understanding addiction, and carries implications for both modeling addiction in the laboratory and for therapeutics. In this article, we argue that evidence from both rat drug self-administration studies and human neuroimaging studies supports the notion that a sensitized DA response to drugs and drug cues contributes to the development and persistence of addiction. Animal self-administration procedures that reflect the intermittency of human cocaine use are most effective at producing increased motivation for the drug and other addiction-like behaviours, and these procedures consistently produce a sensitized DA response. In parallel, neuroimaging studies in human drug users show that when personalized cues that signal drug availability are present—a condition closer to real-life drug use—the DA response to drug and drug cues is enhanced. This supports the view that drug use produces a *hyper*dopaminergic reactivity state, and that addiction involves sensitization of DA systems to the incentive effects of drugs and drug cues, leading to pathological drug wanting. In the context of therapeutic approaches, this indicates that when targeting the DA system, treatments should aim to mitigate this sensitized DA state [11]. Indeed, d-amphetamine maintenance therapy decreases cocaine use in humans [113–117], and a recent study in rats shows that d-amphetamine maintenance during IntA cocaine self-administration decreases the expression of psychomotor sensitization and subsequent motivation for cocaine, while reversing the sensitization of cocaine's action at the DAT [118]. While many questions remain to be addressed (see Outstanding Questions), this emerging literature suggests that treatments that mitigate cocaine-induced sensitization of DA systems may blunt the motivation to take the drug.

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Glossary

Addiction-like behaviours

Behaviours displayed by laboratory animal models that are analogous to DSM-5 criteria for substance use disorders. For example, escalation of drug use, considerable time/effort spent to obtain drug, continued drug use despite adverse consequences (punishment resistance) or continued drug seeking when drug is not available (resistance to extinction).

Incentive-sensitization theory

The incentive-sensitization theory of addiction posits that *i*) events that activate mesotelencephalic dopamine and associated systems are attributed with incentive salience and become 'wanted', *ii*) in vulnerable people, taking psychoactive drugs produces incremental neuroadaptations in these neural systems, making them sensitized to drugs and

drug-associated cues, *iii*) in turn, these sensitization-related changes maintain excessive drug 'wanting' (craving) even after long periods of drug abstinence.

Drug self-administration

In the context of preclinical studies, drug self-administration refers to a procedure where laboratory animals can make an instrumental behavioural response (e.g., pressing a lever) to obtain a dose of drug.

Progressive ratio

A schedule of reinforcement where the number of responses required to obtain a single drug infusion increases with each successive infusion. The rate of increase is usually exponential, but other functions can also be used. The maximum requirement met (e.g., in number of lever presses) to obtain a single dose of drug before abandoning the self-administration task is termed the 'breakpoint'. Breakpoint is used as a measure of motivation for drug, because it reflects the maximum amount of work (e.g., lever pressing) an animal will perform for a single drug infusion.

Sensitization

The process whereby repeated exposure to the same stimulus (in the context of addiction studies, a given dose of drug, for instance) comes to elicit a progressively greater response to that same stimulus.

Tolerance

The process by which repeated exposure to the same stimulus (in the context of addiction studies, a given dose of drug, for instance) comes to elicit a progressively reduced response, such that increased doses of drug are required to elicit the same initial response.

Short access (ShA)

Self-administration procedures where sessions involve continuous drug access, typically for 1–3 hours per session (usually 1 session per day).

Long access (LgA)

Self-administration procedures where sessions involve continuous drug access, typically for 6+ hours (usually 1 session per day).

Intermittent access (IntA)

Self-administration involving cycles of drug availability and unavailability within the same session. With cocaine this is achieved by interspersing 5–6 min periods of drug availability with at least 25-min periods when drug is not available. This cycle is then repeated, typically for 4–6 h/session (usually 1 session per day).

Psychomotor activating effects

The ability of a drug to enhance locomotor activity, rearing, sniffing, darting behaviours, and stereotyped head and forelimb movements. These behaviours require DA transmission in mesolimbic circuits, and changes in the intensity and frequency of these behaviours indicate neuroplasticity in these circuits and of DA in particular.

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BOX 1:

Does LgA experience reliably produce tolerance to cocaine's effects?

As discussed in more detail in the main text, while some studies have reported that LgA experience increases motivation for cocaine, decreases the psychomotor activating effects of cocaine, and decreases DA neurotransmission, the evidence in support of these effects is mixed. A relatively consistent finding is that LgA does not decrease the basal concentration of DA in the NAc [cf. 36, 51, 58, 119]. Furthermore, using *in vivo* microdialysis in the NAc of rats, LgA was found to have no effect on either the ability of experimenter-administered cocaine challenges to increase extracellular DA, or the efficacy of self-administered cocaine to increase DA [119]. In another study, a single self-administered injection of cocaine increased extracellular DA in the NAc to the same extent in rats with LgA versus ShA experience (although DA overflow was greater in rats with IntA experience), and the magnitude of the DA response to cocaine predicted motivation for cocaine [51]. Similarly, although there are reports that LgA experience increases motivation for cocaine in rats [e.g. 26, 40], there are also reports of no effect [51], of decreased motivation [120 for discussion], or when seen, only a very transient effect [27, 48].

Reports on how LgA experience influences the psychomotor activating effects of cocaine, which are thought to be largely due to increased DA activity, are also mixed. Some early studies suggested LgA produces tolerance to the psychomotor activating effects of cocaine [e.g. 34, 121]. In contrast, ShA and LgA experience have been reported to produce the same degree of psychomotor sensitization, rather than tolerance [30]. A more recent study reported no change in the psychomotor activating effects of cocaine following LgA experience, when rats were tested soon (3 days) after the last self-administration session [60]. However, when tested after 30 days of abstinence, rats with LgA experience showed robust psychomotor sensitization, consistent with an earlier study [23]. It is possible that in some situations the self-administration of very large amounts of cocaine can produce tolerance to a number of cocaine's effects, which can mask the expression of sensitization [38]. However, tolerance is short-lived, and when it dissipates, underlying sensitization-related neurobehavioural adaptations become evident, similar to what is seen when psychomotor stimulant drugs are experimenter-administered [11, 122], and with incubation of cocaine craving after LgA experience [39].

BOX 2:

Do people with addiction have decreased dopamine neurotransmission?

Stimulant drug users are consistently reported to have "*a significant decrease in D2/D3 [receptor] availability*", and in "*in striatal dopamine release*" [111] [also see 112]. This has been interpreted by some to suggest that long-term drug use renders the mesostriatal DA system *hypo*active [123]. However, one could make the case that these studies do not provide unambiguous or compelling evidence for this conclusion [3, 4, 10]. There are alternative interpretations for the decrease in D2/D3 binding. *i*) It could be a compensatory response to increased DA release, or a simple competition effect due to enhanced DA release competing with the neuroimaging tracer, neither of which would be reflective of decreased DA. *ii*) It could reflect decreased DA autoreceptors (which are also D2-type receptors), which would result in enhanced DA. *iii*) D2/D3 receptors may be low before drug use, rather than a consequence of drug use—or both. Also, most studies reporting a decrease in D2/D3 receptor availability use ligands like raclopride, a D2/D3 receptor antagonist. However, studies using agonist ligands, such as [11C]-(+)-propyl-hexahydro-naphtho-oxazin (PHNO), which has greater affinity for the postsynaptic, D3 receptor [124], do not support a decrease in D2/D3 receptor availability in addiction [125–128].

Reports of decreased stimulated DA release in people with addiction appear to provide more compelling evidence for DA hypoactivity, but this interpretation has also been questioned [3, 4]. Studies showing blunted DA release typically provide drug in an environment where drug was never experienced before (i.e., in the scanner/laboratory). Thus, they are conducted in the absence of drug-predictive cues, and when drug is known to be unavailable, because users have generally not taken drug in the laboratory environment before. Sensitization is typically not expressed under such conditions, even in rats, because sensitization can be highly context-dependent [3, 77, 122, 129–131]. Indeed, providing drug in the presence of drug-associated cues, or cues signaling drug availability, increases DA release [3, 4, 77, 88]. Furthermore, most studies showing blunted DA release are conducted shortly after abstinence, when preclinical studies indicate sensitization may not be expressed [132, 133]. Lastly, and as noted in the main text, it is not fully clear how a decrease in DA could lead to an increase in motivation.

Outstanding Questions

When a given addiction-like behaviour is produced by both IntA and LgA, but effects on DA are opposite, to what extent do changes in other transmitter systems such as glutamate, contribute?

To what extent is the hyperdopaminergic state produced by intermittent cocaine intake causal in the pathological patterns of drug use characteristic of addiction?

By what mechanism(s) does intermittent cocaine intake influence the regulation of dopamine neuron activity?

The temporal pattern of drug use in humans has not been studied systematically. When individuals with addiction have control over cocaine dose and intermittency of intake, what is the pattern of use within and between bouts? Do these patterns differ between women and men?

If sensitization-like changes in DA function in humans are masked by tolerance, how long a period of abstinence is required for sensitization to become evident?

Highlights

- Repeated use of drugs of abuse induces persistent changes in brain function that promote the transition to and persistence of addiction.
- Drug self-administration procedures in laboratory animals have been refined to capture behavioural features of addiction.
- In animals, self-administration procedures that incorporate the intermittent patterns of drug use seen in humans are more effective at inducing addiction-like patterns of behaviour than procedures that use long, continuous access, and the former consistently increase dopamine function.
- Human neuroimaging studies reinforce the notion that drug-induced hyperdopaminergic states contribute to addiction.
- Therapeutic strategies to mitigate sensitized hyperdopaminergic states in addiction may be especially efficacious.

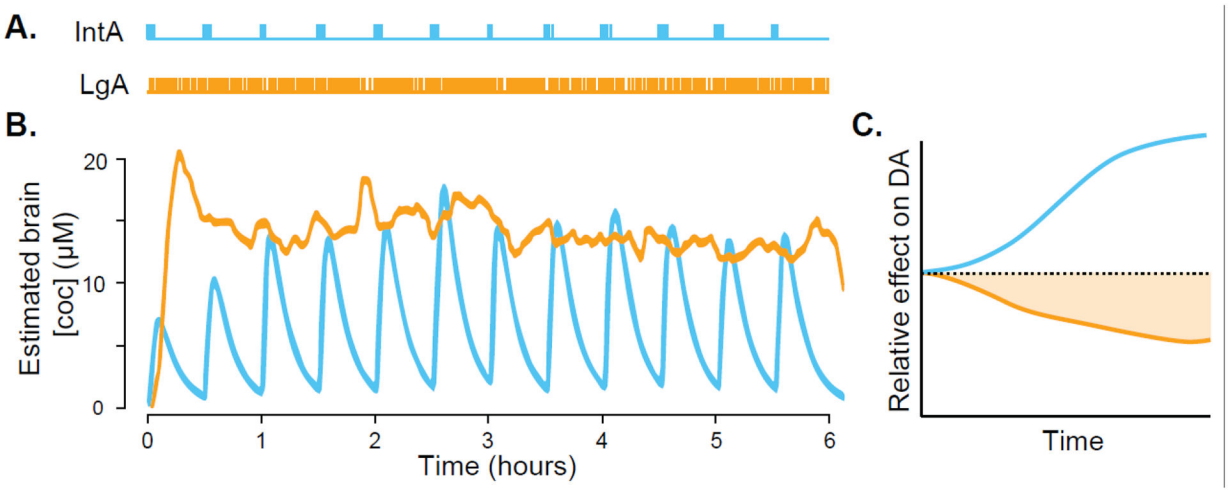

Figure 1. How intermittent- versus long-access cocaine self-administration change dopamine system function.

(A) Representative patterns of cocaine intake, and (B) estimated brain cocaine concentrations in rats self-administering the drug during a long-access (LgA) or intermittent-access (IntA) session (adapted from [13]). (C) Schematic representation of the effects of LgA and IntA cocaine experience on dopamine (DA) system function in the Nucleus Accumbens during the development of addiction. The schematics in (C) represent relative effects in relation to control levels (see below), and summarize effects as measured *ex vivo* by electrically-evoked DA release and cocaine-induced DA transporter inhibition, and *in vivo* by cocaine-induced increases in DA concentrations (see text; "Preclinical Models of Addiction: Intermittent Access (IntA)"). The dotted line illustrates control levels, as assessed either in rats with ShA cocaine experience or in cocaine-naïve rats. As shown in (A), under LgA, cocaine is continuously available throughout the session, and rats take cocaine at regular intervals. In contrast, under IntA, cocaine is only available in discrete periods, and rats take cocaine intermittently, which models the intermittency of cocaine use typical in human cocaine users. As shown in (B), LgA produces relatively steady-state brain cocaine concentrations, and IntA produces spiking brain cocaine concentrations.

As illustrated in (C), LgA promotes tolerance and a hypodopaminergic state, whereby cocaine-induced DA responses are blunted. The shading illustrates that some studies report unchanged drug-induced DA responses after LgA cocaine experience, relative to control levels. In contrast to LgA, IntA consistently produces sensitization and a hyperdopaminergic state, whereby cocaine-induced DA responses are enhanced. Of note, studies to date have assessed DA responses within the first week of abstinence, and most studies have also focused on *cocaine-induced* DA responses. In future work, DA responses to drug, cues and under baseline conditions should be examined across the abstinence period.