OPINION

Intrinsic plasticity: an emerging player in addiction

Saïd Kourrich, Donna J. Calu and Antonello Bonci

Abstract | Exposure to drugs of abuse, such as cocaine, leads to plastic changes in the activity of brain circuits, and a prevailing view is that these changes play a part in drug addiction. Notably, there has been intense focus on drug-induced changes in synaptic excitability and much less attention on intrinsic excitability factors (that is, excitability factors that are remote from the synapse). Accumulating evidence now suggests that intrinsic factors such as K^+ channels are not only altered by cocaine but may also contribute to the shaping of the addiction phenotype.

Over the past decades, there has been a drastic shift in the societal perception of drug addiction; from a personality flaw characterized by a lack of self-control, to the classification of addiction as a chronic neuropsychiatric disorder[1]. This change has been facilitated by mounting evidence derived from neurobiological research, focused on asking questions about why and how individuals become addicted to drugs. Studies that seek to understand why people become addicted to drugs of abuse attempt to pinpoint what factors make an individual predisposed to develop addictive disorders; that is, to identify biological differences that exist before that individual was exposed to a drug of abuse. Indeed, the interaction between genetic factors and the individual's environment are thought to serve as the basis for the vulnerability to addiction. Here, we describe a subset of neurobiological modifications that are triggered by cocaine exposure that may provide insights into how individuals become addicted to drugs.

The addiction field has been influenced strongly by learning and memory research[2–4], and so it is not surprising that investigations of drug-induced changes in neuronal excitability have focused largely on synaptic alterations[5–9]; that is, on excitatory glutamate transmission (mediated by AMPA receptors (AMPARs) and NMDA receptors). However, less attention has been directed towards 'intrinsic' membrane properties: non-synaptic factors, which directly affect the probability that a neuron will fire an action potential in response to excitatory synaptic inputs (FIG. 1). Upon the generation of the action potential at the axon initial segment, the signal continues to be strongly modulated by these intrinsic factors until it reaches the axon terminals, where it triggers the release of neurotransmitters. Given the important contribution of intrinsic factors in shaping neuronal output, extrapolating from observed levels of cocaine-induced synaptic strength to global changes in neuronal excitability does not provide a complete readout of how cocaine exposure alters general neuronal activity.

To better understand how cocaine influences the firing capacity and/or the message that is conveyed from one structure to another, here we focus on the mechanisms through which cocaine induces lasting changes in intrinsic neuronal excitability. As a model, we discuss neuronal excitability adaptations that have been reported to occur in the nucleus accumbens (NAc). We also discuss how cocaine-induced intrinsic excitability changes may explain discrepancies between studies that investigate cocaine-induced synaptic adaptations. Indeed, brain circuit activity emerges from constant interactions between synaptic and intrinsic cellular excitability factors, and under specific conditions using whole-cell patch-clamp electrophysiological techniques, message alterations originating specifically from changes in intrinsic factors can be isolated (BOX 1).

Conceptually, intrinsic factors include any elements located on the soma, dendrites or axon that are 'remote' from the synapse but either passively or actively modulate membrane excitability. Exposure to cocaine and other psychostimulant drugs can also induce changes in neuronal firing capacity by altering passive intrinsic membrane properties, for example through signalling pathways that result in the activation of G-protein-gated inwardly rectifying K^+ channels[10–12] (for reviews, see REFS 13,14). However, for the sake of brevity, we refer here only to the elements contributing to the active intrinsic membrane properties: the generation of action potentials and the characteristics of repetitive firing processes that are mainly controlled by the interplay between voltage-gated Na^+, K^+ and Ca^{2+} channels[15]. Recently, there has been growing interest in examining the participation of these excitability factors, and accumulating evidence now links plasticity of intrinsic excitability to various chronic neurological and psychiatric disorders, such as schizophrenia[16], Alzheimer disease[17], depression-like phenotypes[18], neuropathic pain[19,20] and epilepsy[20].

The NAc as a model

Although it is likely that cocaine exposure leads to persistent changes in intrinsic excitability in several brain regions, such changes have been mainly characterized in the NAc[21–29] (FIG. 2a,b). One possible explanation for the focus on the NAc is that early behavioural pharmacology studies revealed that the NAc is directly involved in the development and expression of various addiction-relevant phenotypes, including incentive and psychomotor sensitization[30,31], self-administration[32], and relapse and reinstatement models[33–35]. A large body of evidence suggests that the NAc encodes the rewarding effects of food or drug outcomes, and initiates approach behaviours to obtain such rewards[36–46]. Many studies on neuronal excitability have capitalized on these key findings about

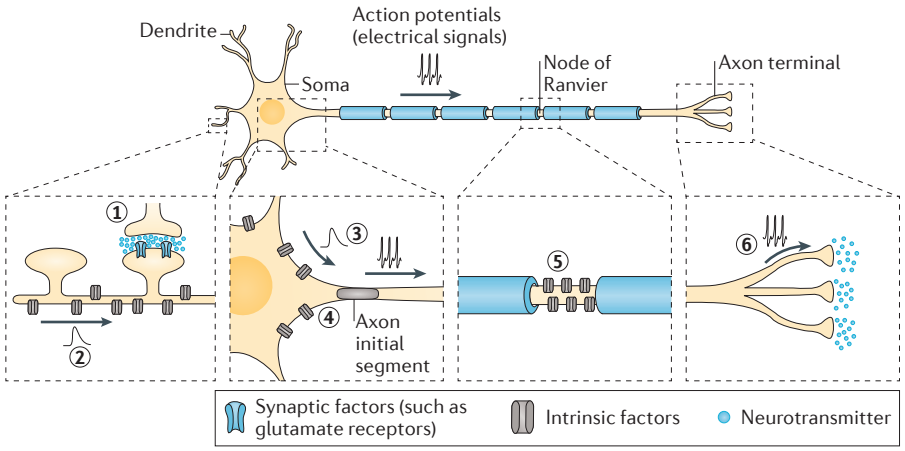


Figure 1 | **Compartmentalization of synaptic and intrinsic excitability factors within the cell.** A signal received by a neuron through presynaptic neurotransmitter release (1) travels through successive subcellular compartments before it can transmit the information to the next neuron. At the synaptic level (1), glutamate, via activation of AMPA and NMDA receptors (synaptic excitability factors), generates an excitatory postsynaptic potential (EPSP) that is influenced by intrinsic factors (such as voltage-gated ion channels; K^+, Na^+ and Ca^{2+}) as it travels along the dendrite (2), soma (3), axon hillock and the axon initial segment (4) (compartment rich in Na^+ channels). If an EPSP is strong enough to depolarize the membrane to action potential threshold, then action potentials are generated and will be further influenced by intrinsic factors, for example those located at the nodes of Ranvier (5), as they travel along the axon, until they reach the axon terminal (6), where they will trigger neurotransmitter release. Modulation of ion channel function at any of these steps can result in plasticity of intrinsic excitability, and thereby alter the generation or conduction of action potentials. Figure is modified from REF. 180; *Neurobiology of Mental Illness* by Kourrich and Bonci (2013) Fig.5.2 from Chp.5 "Synaptic and Neural Plasticity", by permission of Oxford University Press, USA.

the NAc, focusing efforts to understand the molecular and cellular changes within this region that are associated with the behavioural effects of cocaine. Therefore, although this Opinion article is not about the NAc per se, here we focus on this brain area as a model to illustrate the importance of considering alterations in intrinsic excitability factors in drug-induced neuroadaptations and behaviours; unless otherwise noted, all information presented here was observed in the NAc.

To better understand the manner through which alterations in NAc activity modulate behaviours, one must consider both of the major NAc subregions, the shell and core, and their respective afferent and efferent projections, which define the distinct neuroanatomical circuits that they are a part of[47] (FIG. 2a,b). The NAc core and shell are implicated in distinct aspects of appetitive behaviour[36–41] and drug seeking[42–46], and so cocaine-induced changes in intrinsic excitability in the NAc core versus shell could differentially affect the behavioural effects of cocaine. Specifically, although increases in NAc core activity promote approach behaviour[41,48], increases in NAc shell activity inhibit consummatory and/or reward-related behaviour[49,50]. Another important consideration is that NAc shell activity indirectly influences the NAc core through two pathways that have received little attention, namely the ventral pallido–thalamo–cortical and mesencephalic pathways[51] (FIG. 2b).

Another level of complexity is that medium spiny neurons (MSNs) of the NAc are strongly influenced by neuronal microcircuits composed of interneurons, including fast-spiking and cholinergic interneurons. However, our understanding of the effects of cocaine on synaptic or intrinsic excitability of NAc interneurons is limited[52], and therefore we focus on drug-induced changes in excitability of MSNs.

We first summarize initial studies that led to the conclusion that non-contingent cocaine injections or self-administered cocaine decrease intrinsic excitability (firing capacity) in NAc shell MSNs measured *ex vivo*[21,23,24,26,27]. Then, we discuss the identified cellular mechanisms and molecular substrates of this adaptation and how they relate to *in vivo* physiology and behavioural findings. Next, we attempt to integrate key cocaine-induced synaptic adaptations[5–7] with the observed changes in intrinsic excitability and discuss how changes in these two factors influence one another to shape final neuronal output. We then briefly revisit some of the prominent hypotheses and suggest new possibilities. Last, we discuss how complementary approaches and current technologies may contribute to further assess causal relationships between drug-induced changes in intrinsic excitability and cocaine behavioural effects.

Although much of the research investigating cocaine-induced changes in intrinsic excitability has used passive drug exposure regimens (FIG. 3), one aim of our Opinion article is to speculate on how such changes may contribute to patterns of voluntary drug use and abuse observed in addicts, which are approximated by various animal models of addiction (FIG. 3a). Further studies are needed to examine whether the drug-induced neuroadaptations identified using non-contingent drug exposure procedures also play a part in driving drug-seeking behaviour in drug self-administration and relapse models.

Cocaine-induced intrinsic plasticity

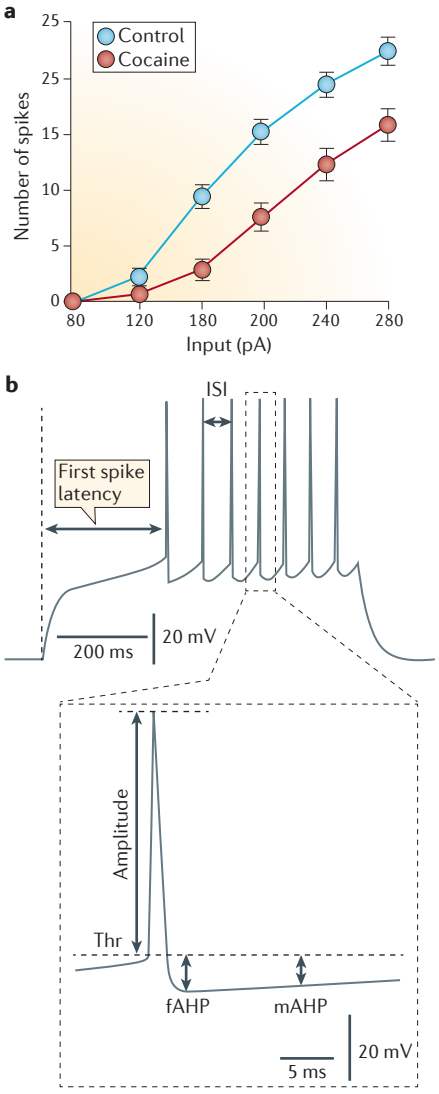
In contrast to high concentrations of cocaine, which can directly block Na^+ (REFS 53–55) and K^+ (REFS 56,57) channels, low brain concentrations of cocaine achieved by standard chronic regimens (<3 μM)[58] can indirectly alter the functions of these channels through mechanisms that we discuss below. Although not directly tested, this process seems to require repeated exposure to cocaine and results in enduring modifications in neuronal firing. Here, we focus on these persistent cocaine-induced changes in neuronal intrinsic excitability.

Francis J. White's laboratory provided early evidence that repeated *in vivo* cocaine administration leads to changes in several ionic conductances in NAc MSNs (shell and core subregions were undistinguished), including Na^+, Ca^{2+} and K^+ currents[22,28,29]. They found that repeated non-contingent cocaine injections in rats (for 5 consecutive days), which induces psychomotor sensitization, increased various K^+ currents[22] and decreased both basal Na^+ conductance (I_{Na})[29], and N- and R-type Ca^{2+} currents[28]. Such changes in ion conductances after *in vivo* cocaine administration were later shown to translate into depressed NAc shell MSN firing capacity in brain slices, an adaptation that can last up to 3 weeks after cocaine exposure [21,23,26] (FIG. 3c). However, there are differences in the duration of this effect after non-contingent cocaine exposure[23,26] or intravenous cocaine self-administration[27].

Box 1 | **Investigative approaches to studying intrinsic excitability**

Electrophysiological whole-cell patch-clamp recordings carried out under specific pharmacological conditions are routinely used to distinguish between factors that control synaptic versus intrinsic excitability. Intrinsic excitability is usually assessed in *ex vivo* preparations (brain slices) by measuring the number of action potentials elicited by incremental depolarizing current steps. The figure, part **a**, shows cocaine-induced depression of firing rate in medium spiny neurons (MSNs) of the nucleus accumbens (NAc) shell, recorded using this method at an early withdrawal time point (1–3 days post-treatment) following 5 days of sensitizing cocaine treatment.

The figure, part **b**, shows how the firing pattern and action potential waveform can be dissected in several components (for example, latency to spike after current injection; the interspike interval (ISI); action potential threshold (Thr); fast and medium after-hyperpolarization (fAHP and mAHP); and amplitude). These components are shaped by a timed and coordinated opening and closing of specific voltage-gated ion channels (Na^+, Ca^{2+} and K^+). To generate hypotheses regarding which ion channels or group of channels have changed following drug exposure, investigators quantify the differences in spiking patterns and the precise details of the action potential waveform between drug and control conditions. Using this method, they have found, among other alterations, that cocaine exposure increases the latency to the first spike and the ISI, which suggests that the activity of some members of the K_v1 and SK (Ca^{2+}-activated) K^+ channel subfamilies is enhanced. As described in many studies[25–27,62], subsequent pharmacological approaches allow further identification and/or confirmation of the participation of the hypothesized channels.



The figure, part **a**, is reprinted from *Cell* **152** (1-2), Kourrich, S., Hayashi, T., Chuang, J. J., Tsai, S. Y., Su, T. P. and Bonci, A. Dynamic interaction between Sigma-1R and $K_v1.2$ shapes neuronal and behavioral responses to cocaine. 236–247, Copyright (2013), with permission from Elsevier.

Moreover, the observation that amphetamine, another psychostimulant drug but with a different mechanism of action[59,60], also leads to depression of NAc shell MSN firing rate[26] suggests that depressed NAc shell MSN firing may be a more general physiological mechanism that contributes to psychostimulant behavioural effects.

Although several voltage-gated ion channels are altered after termination of repeated non-contingent cocaine injections[22,28,29] (<3 days after the last cocaine injection), recent studies indicate that K^+ conductances may have a key role in MSN firing rate depression. For instance, a sensitizing regimen of cocaine in mice was shown to trigger an early and long-lasting upregulation of a transient voltage-gated A_s current (a subtype of A-type K^+ current, also called D-type)[26], later identified as being mediated by $K_v1.2$ channels[25]. A separate study[23] using the same cocaine exposure regimen in rats observed an upregulation of small-conductance Ca^{2+}-activated K^+ currents (SK currents).

The cellular mechanism that results in cocaine-induced enhancement of K^+ currents is still under investigation, but several candidate mechanisms have been suggested. One prominent proposed mechanism is that cocaine, a dopamine re-uptake inhibitor, increases the levels of extracellular dopamine and thereby dopamine receptor (DAR) activation[61]. Whether this mechanism of action contributes to the development of plastic changes in intrinsic excitability is still unknown. Another candidate that does not exclude a role for DAR-activated kinases[28] is the α-isoform of calcium/calmodulin-dependent protein kinase II (αCaMKII)[62], which can directly regulate surface K^+ channel density and currents[63–65] (as well as regulating AMPAR trafficking). Indeed, overexpression of a constitutively active form of striatal neuron-specific αCaMKII (in which Thr286 is mutated to Asp) decreases MSN firing capacity in the NAc shell, a mechanism that involves an increase in A-type K^+ currents[62] and that is consistent with the regulatory role of A-type K^+ currents by αCaMKII[63–65]. Nonetheless, because these targets were either exogenously manipulated[62] prior to cocaine exposure, or indirectly assessed in *ex vivo* NAc shell slices after *in vivo* cocaine treatment[28], they have not been causally linked to cocaine-induced plasticity of intrinsic excitability.

A recent study identified an additional candidate mechanism, showing that cocaine leads to firing rate depression of NAc shell MSNs through the activation of sigma 1 receptor (SIG1R) following the same cocaine exposure regimen and in the absence of any prior exogenous manipulation[25]. SIG1R is an endoplasmic reticulum (ER) chaperone protein[66] that is known to be associated with several neuropsychiatric disorders[67–69], including addiction, and to have a role in the regulation of many voltage-gated ion channels[68]. Upon ligand activation, SIG1R dissociates from an anchor protein (binding immunoglobulin protein (BiP)) and translocates from the mitochondrion-associated ER membrane (MAM) to other subcellular compartments[66,70,71], where it can carry out various functions; for example, protein trafficking and ion channel regulation. A recent study[25] showed that both repeated non-contingent cocaine injection and *in vitro* cocaine bath application (applied on NG108-15 and neuro-2A cell culture preparations) upregulate SIG1R-dependent trafficking of $K_v1.2$ channel subunits (A_s K^+ current) from intracellular compartments (ER or MAM) to the plasma membrane, a mechanism that leads to lasting depression of NAc shell MSN firing rate (10–14 days).

This study shed new light on the endogenous cellular mechanism through which cocaine can alter neuronal functions and thereby behaviour, but many questions remain. For example, do the DAR-triggered, CaMKII-mediated and SIG1R-dependent pathways operate in parallel or do they belong to a common cellular mechanism?

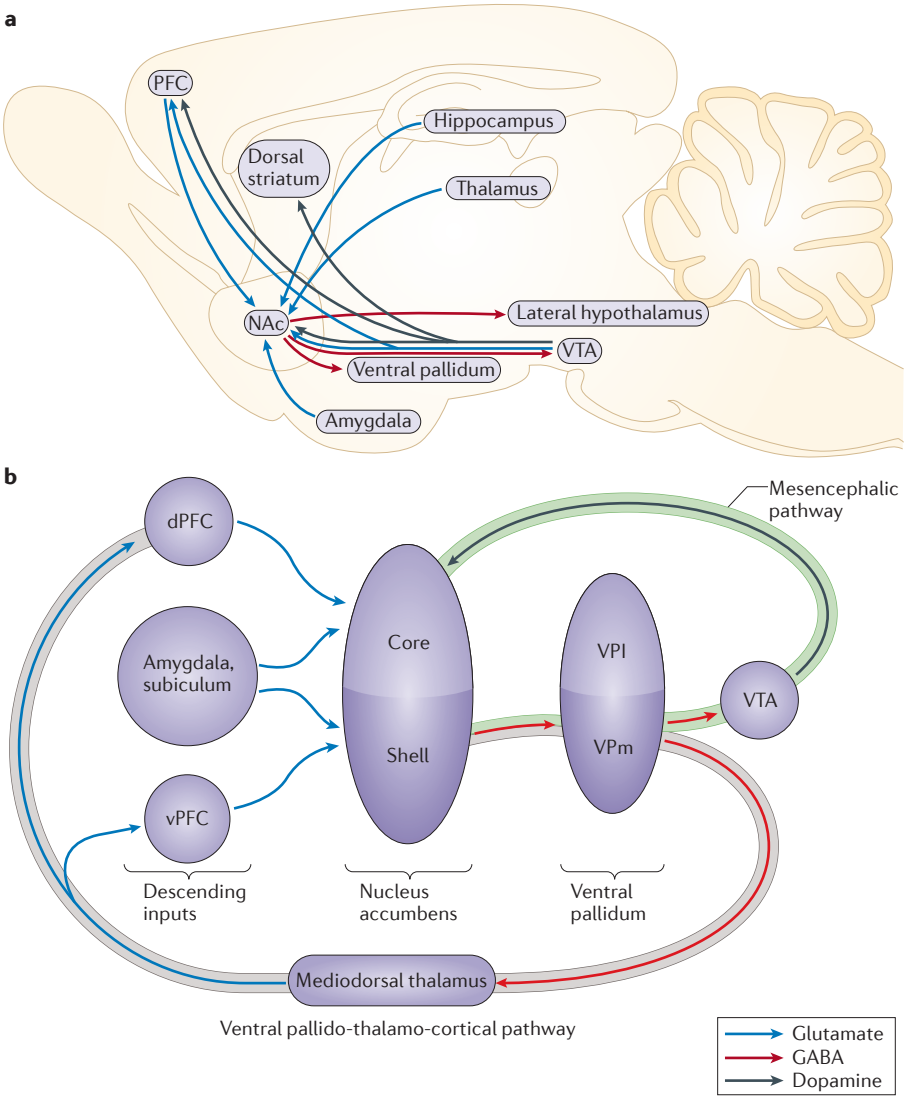


Figure 2 | **Key reward-related neural circuits. a** | The reward system, or dopaminergic system, originates from the ventral tegmental area (VTA) and sends dopaminergic projections to corticolimbic structures, including the nucleus accumbens (NAc), the prefrontal cortex (PFC) and the dorsal striatum. The NAc, a brain region that is mainly (>90%) composed of medium spiny neurons (MSNs), receives excitatory glutamatergic inputs from structures such as the PFC, hippocampus, thalamus, amygdala and VTA[181–183], and sends GABAergic projections to structures such as the ventral pallidum, the VTA and lateral hypothalamus. **b** | The NAc is subdivided into two substructures, the shell and the core. NAc shell activity can influence the core through two pathways: the ventral pallido–thalamo–cortical pathway, which involves signals from the NAc shell to the ventro-medial ventral pallidum (VPm), mediodorsal thalamus, dorsal PFC (dPFC) and NAc core (shaded in grey); and the mesencephalic pathway, which involves signals from the NAc shell to the VPm, VTA and NAc core (shaded in green)[51]. vPFC, ventral PFC; vPl, ventrolateral pallidum. Part **b** is reprinted from Neurosci. *Biobehav. Rev.* **24**, Zahm, D. S. An integrative neuroanatomical perspective on some subcortical substrates of adaptive responding with emphasis on the nucleus accumbens. 85–105, Copyright (2000), with permission from Elsevier.

With regard to SIG1R specifically, what is the sequence of molecular events from cocaine exposure to SIG1R activation? One possibility is the dopamine transporter (DAT) blockade and consequently DAR activation. However, an alternative hypothesis is that cocaine in its neutral (membrane permeant) form can freely diffuse through the plasma membrane and directly bind to the SIG1R, triggering its activation and chaperoning activity. Although direct evidence is still lacking, binding assays carried out on cell homogenates — a preparation that nevertheless does not preserve plasma membrane integrity — showed that cocaine, at doses found to be rewarding in rodents, can bind SIG1R[72,73]. Another question is whether cocaine-induced changes in Na^+, Ca^{2+} and K^+ channels[22,28,29] are also mediated by the activation of and binding to SIG1R, given that SIG1R can modulate all classes of voltage-gated ion channels.

Investigating these questions may have broad implications for human health and diseases. Indeed, from a pathoaetiological viewpoint, the discovery that the SIG1R can form complexes with $K_v1.2$ channels and that it can undergo enduring experience-dependent maladaptive plasticity suggests new mechanistic hypotheses for other chronic neuropsychiatric disorders that are associated with alterations in SIG1R and K^+ channel functions.

NAc firing and behaviour

Differential role of NAc subregions. Dong *et al.*[21] observed that, decreasing NAc MSN excitability by viral enhancement of the K+ channel Kir2.1, an inward-rectifying K+ channel that reliably depresses neuronal intrinsic excitability[74], results in an enhanced locomotor response to an acute cocaine injection[21]. Conversely, Benavides *et al.*[75] found that increasing NAc MSN firing through genetic manipulation (a conditional knockout of cyclin-dependent kinase 5) also enhances cocaine psychomotor sensitization and conditioned place preference. How do opposite exogenous manipulations of NAc intrinsic excitability produce similar cocaine-associated behavioural effects?

A study from Kourrich and Thomas[26] provided results that may reconcile this apparent discrepancy. Specifically, although repeated *in vivo* cocaine injections depressed firing rate in the NAc shell, they potentiated the firing rate of neurons in the NAc core (recording between 1–3 days after last cocaine injection). Recordings in the study by Benavides *et al.*[75] were performed in the NAc core (J. Bibb, personal communication); the recorded subregion was not mentioned in the study by Dong *et al.*[21]. These observations suggest that decreases in the excitability of the NAc shell or increases in the excitability of the NAc core both lead to enhanced locomotor responses to cocaine. Consistent with the hypothetical role of the NAc shell, Kourrich *et al.*[62] established a causal link between A-type-driven depression of NAc shell firing rate and cocaine-induced psychomotor sensitization. In particular, mice in which a constitutively active form of αCaMKII was overexpressed selectively in striatal neurons[62] exhibited NAc shell firing

rate depression in the absence of any detectable changes in NAc synaptic glutamate transmission. These mice exhibited a presensitized phenotype, a behaviour that was characterized by enhanced cocaine-induced locomotion to a level that was comparable to that observed following repeated cocaine injections, and an enhanced conditioned place preference to cocaine at a dose that was subthreshold for wild-type mice. When NAc firing capability was restored, the locomotor response to cocaine was similar to that observed in drug-naive mice, suggesting that depressed firing capacity of NAc shell neurons may predispose individuals to express rewarding and psychomotor activating effects of cocaine[62]. Taken together, we speculate that a decrease in NAc shell intrinsic excitability[62] or an increase in NAc core excitability[75], two subsets of early cocaine-induced neuroadaptations[26], recapitulate early physiological and behavioural effects exhibited by mice after repeated exposure to non-contingent cocaine injections.

Interestingly, *in vivo* electrophysiological studies in rats during or after chronic self-administration of cocaine parallel the *ex vivo* findings. However, this comparison must be taken with caution because under *in vivo* conditions, firing can be either tonic (constant) or phasic (in bursts), whereas in *ex vivo* studies firing is elicited by positive current injections (see BOX 1); we also cannot dissociate intrinsic from synaptic influences on neuronal firing in *in vivo* studies. Nevertheless, striking similarities between *in vivo* and *ex vivo* studies encourage us to speculate. For example, during long-access (6 hours daily for 12–18 days prior to recording) cocaine self-administration, decreases in tonic firing are more prevalent in NAc shell than NAc core neurons, whereas increases in tonic firing are more common in NAc core than in NAc shell neurons[76]. Furthermore, during a similar cocaine self-administration paradigm (6 hours daily for 2–3 weeks prior to recording), increases in the magnitude or incidence of phasic firing is greater in NAc core than in shell neurons during presentation of a cue that an animal has learned to associate with cocaine[48,77] and when a cocaine-associated cue is randomly presented after one month of drug abstinence from short-access cocaine self-administration (2 hours per day for 2–3 weeks)[78,79]. These cocaine-associated cues are used in animal models to better understand the physiological correlates of cue-driven cocaine seeking that have also been observed in humans[80]. *Ex vivo* observations of reduced NAc shell excitability

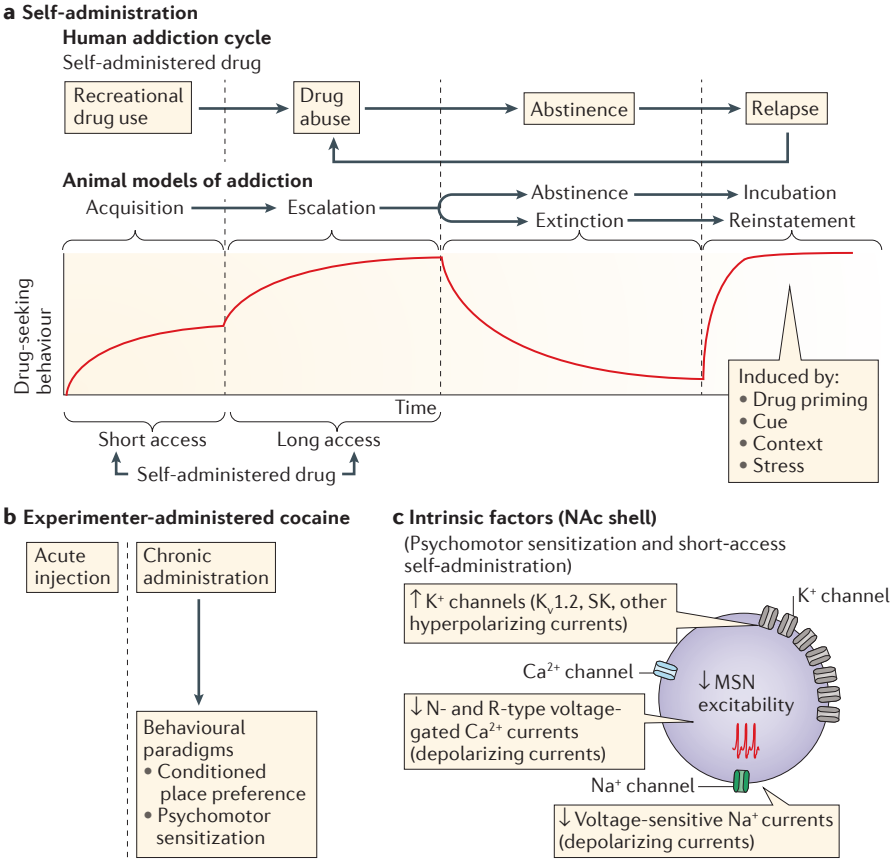


Figure 3 | **Drug-exposure procedures and animal behavioural models used to approximate human addiction. a** | The human addiction cycle is characterized by initial recreational drug use, followed in some individuals by a period of drug abuse (increased dose and/or frequency of drug intake). A period of abstinence from drug use is often followed by a relapse to drug use or abuse; relapse can be triggered by several environmental factors. Animal models attempt to recapitulate these phases of the human addiction cycle by first training animals to self-administer intravenous contingent cocaine injections. Over a few days (short access) of this training, drug intake initially increases and then stabilizes as animals learn the behavioural response required to self-administer the drug (the acquisition phase). Short-access procedures are thought to approximate voluntary recreational drug use. Long-access procedures involve extended periods of daily access to self-administrable cocaine, and drug intake in some individuals can escalate under these conditions (thought to approximate the beginnings of the drug abuse stage in humans). The abstinence phase of human addiction is modelled in animals either by extinction (where the learnt behaviour no longer results in drug delivery) or forced abstinence without extinction (when the animals do not have access to cocaine), which can lead to incubation, a time-dependent increase in cue-induced drug seeking after abstinence. Reinstatement (resumption of drug-seeking) induced either by a priming injection of cocaine itself, cocaine-associated cues, cocaine-associated contexts, or stress can be used to model the impact of various environmental factors on relapse to drug use. **b** | Animal models of cocaine-induced behavioural changes usually involve either an acute injection of the drug (used to study the acute locomotor-activating effects of cocaine), or repeated intraperitoneal cocaine injections (used to study the effects of chronic cocaine use). These approaches are often referred to as experimenter-administered or non-contingent to distinguish them from voluntary self-administration. Two frequently used behavioural paradigms are conditioned place preference (whereby repeated cocaine administration is associated with a later preference for the cocaine-paired environment) and psychomotor sensitization (whereby repeated intraperitoneal cocaine injections are associated with an incremental increase in the locomotor-activating effects of cocaine). **c** | Intrinsic factors that change following cocaine treatment. A non-contingent cocaine regimen that induces psychomotor sensitization in rats reduces depolarizing currents and increases hyperpolarizing currents, resulting in a reduced excitability of medium spiny neurons (MSNs) in the nucleus accumbens (NAc). These changes result from alterations in various intrinsic excitability factors, such as increases in hyperpolarizing K^+ currents[22], and decreases in both N- and R-type Ca^{2+} currents[28] and depolarizing basal Na^+ conductance (I_{Na})[29]. Recent studies have identified key K^+ conductances, including a transient voltage-gated K^+ current (slowly inactivating A_s current), which is now known to be mediated by $K_v1.2$ subunits[25], and the small conductance Ca^{2+}-activated K^+ currents (SK currents)[23], which has also been shown to be upregulated following cocaine self-administration[27].

Glossary

Abstinence
A period of no drug use usually occurring after a period of repeated drug use. This term is used to describe both human abstinence, in which subjects voluntarily (rehabilitation) or involuntarily (incarceration) abstain from drug use, and also in animal models of drug relapse, in which abstinence is experimentally imposed (forced) by removing the animals from the drug self-administration environment.

A-type K^+ current
A transient K^+ current that is activated at subthreshold voltage and therefore plays an important part in the generation of the first action potential. A-type K^+ currents were originally subdivided in two subtypes: A_s (also known as I_D), which are mediated by K_v1 channels; and A_f (also known as I_A), which can be mediated by members from K_v1, K_v3 and K_v4 subfamilies. A_s currents are slowly inactivating (hundreds of milliseconds) K^+ currents, whereas A_f are fast-inactivating (tens of milliseconds) K^+ currents.

Conditioned place preference
A Pavlovian (classical) conditioning model in which one distinct context is paired with drug injections, whereas another context is paired with vehicle injections during the training phase. In 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 rewarding effects.

Contingent cocaine injections
Intravenous cocaine injections that are delivered as a consequence of the animal's conditioned responding (commonly a lever press or nose poke) during self-administration procedures. These injections are frequently paired with cues (such as a tone or light) that become associated with drug injections.

Incubation of cocaine craving
A hypothetical process of time-dependent increases in cue-induced cocaine seeking after withdrawal from cocaine self-administration in rats.

Non-contingent cocaine injections
Cocaine injections that are delivered independently of the animal's conditioned response; that is, non-voluntary cocaine injections. In psychomotor sensitization, non-contingent intraperitoneal cocaine injections are commonly administered by the experimenter. Self-administration procedures sometimes use control animals that receive non-contingent intravenous injections that equivalent to linked to the conditioned responding of an actively self-administering animal.

Psychomotor sensitization
A progressive increase in locomotor activity or other activity-related measure (stereotypy) that occurs after repeated injections of cocaine and related drugs.

Reinstatement
The recovery of a learned response (for example, lever-pressing) that occurs when a subject is exposed non-contingently to the unconditioned stimulus (for example, food) after extinction. In studies of reinstatement of drug seeking, reinstatement typically refers to the resumption of drug seeking after extinction following exposure to drugs, drug cues or stressors.

Self-administration
In the context of animal models of drug use and addiction, self-administration refers to a behavioural procedure in which animals perform an operant conditioned response (lever press or nose poke) to receive intravenous drug (that is, cocaine) injections. This procedure allows the animal to control its own drug intake voluntarily and thus more closely models the human condition.

after both non-contingent[23,26] and short-access (2 hours per day for 5 days) self-administered[27] cocaine are also consistent with the predominant tonic inhibition in NAc shell during short-access cocaine self-administration sessions (~1 hour per day for 2 weeks prior to recording)[81–83] and the role of the NAc hypoactivity in cocaine behavioural effects[84].

A recent study[85] may provide additional insights, identifying distinct roles for changes in NAc core and shell neuronal firing in post-abstinence cocaine seeking and drug taking, respectively. In this case, the normalization of cocaine-induced NAc shell (tonic) hypoactivity after 30 days of abstinence from long-access cocaine self-administration (6 hours per day for 16 days) correlated with reduced drug-taking behaviour, whereas an increased prevalence of NAc core neurons that phasically fire during cocaine seeking after abstinence was correlated with the time-dependent increases in cue-induced cocaine seeking after withdrawal or incubation of cocaine craving[85,86].

At the circuit-level. How do cocaine-induced firing rate adaptations in the NAc alter the functions of downstream brain regions and thereby behavioural outputs? One of the main problems in answering this question is that it is difficult to make predictions for cocaine-induced changes in neuronal activity *in vivo* (which result from a combination of changes to the intrinsic properties of the cell and to both excitatory[5–7] and inhibitory[87] synaptic transmission). As discussed above, alterations in NAc shell and core excitability could differentially affect the behavioural effects of cocaine.

Given this neuroanatomical and functional framework for NAc core- and shell-associated circuitry, we draw on observations from *ex vivo* studies to suggest that increases in NAc core intrinsic excitability[26,75] may facilitate the initiation of approach behaviour to obtain rewards[41,48]. By contrast, decreases in NAc shell excitability[21,23,26,27,62] could release the inhibitory influence on the subcortical limbic structures and promote consummatory and/or reward-related behaviours.

Consistent with the proposed role for reduced NAc shell activity in promoting reward seeking, evidence suggests that NAc shell neurons inhibit consummatory behaviours[88–92], an effect that has apparent downstream implications in the lateral hypothalamus[93,94]. Interestingly, activation of the lateral hypothalamus (presumably the same functional effect as NAc 'disinhibition'), reinstates a previously extinguished morphine-conditioned place preference[95], and inactivation of the lateral hypothalamus blocks context-induced reinstatement of alcohol and sucrose seeking[96]. Together, these observations suggest a potential role for this circuit in mediating reward seeking. NAc shell activity also influences the NAc core via the ventral pallido–thalamo–cortical and mesencephalic pathways[51] (FIG. 2b). As a result, decreased NAc shell activity may also contribute to increased NAc core neuronal activity and influence operant behaviour to obtain rewards or seek drugs.

Intrinsic-to-synaptic interactions

Repeated non-contingent cocaine exposure and self-administration of the drug lead to an early and rapid decrease in intrinsic excitability in NAc shell MSNs[21,23,26,27], which is opposed by a slowly developing and lasting postsynaptic AMPAR-mediated synaptic potentiation[5–7,97–99]. However, differences have been reported: for example, the type of AMPAR subunits that are altered[7,100], input specificity (hippocampus[100,101] or prefrontal cortex[100,102–104]) and site of alterations (presynaptic[103] versus postsynaptic[100,102]). Below, we first revisit two influential hypotheses that could explain the functional relationship between cocaine-induced changes in intrinsic excitability and synaptic excitability: the homeostatic and signal-to-noise ratio hypotheses (FIG. 4a). We then present a new hypothesis, the permissive function hypothesis, which links cocaine-induced transient increases in NAc core firing to delayed increases in NAc core synaptic strength (FIG. 4b).

Homeostatic hypothesis. Because decreased intrinsic excitability of NAc shell neurons precedes increased NAc synaptic strength, it is reasonable to hypothesize that increased synaptic strength is a cell-autonomous form of homeostatic adaptation that is programmed to renormalize global neuronal excitability (see reviews in REFS 6,7) (FIG. 4a). It has been shown that blocking postsynaptic firing in dissociated cultured cortical neurons can autonomously trigger synaptic scaling to renormalize neuronal activity[105,106], a mechanism that has also been recently

reported *in vivo*[107]. There is increasing evidence that this is a general mechanism for stabilizing neuronal function, and thus is also likely to operate in the NAc, although there is no direct evidence.

Reconciling the homeostatic hypothesis with results from behavioural studies is an intriguing but challenging task. Homeostatic neuroadaptations are likely to develop to compensate for a disrupted neuronal function that causes maladaptive behaviour. Following this reasoning, NAc shell synaptic potentiation may mediate a form of compensation, whereby enhanced glutamate transmission inhibits the response to cocaine and cocaine cues. Although several pieces of evidence support this prediction[104,108,109], other studies suggest otherwise[100,102,110,111]; that is, that AMPAR-mediated synaptic potentiation in NAc shell neurons causes, rather than protects from, an enhanced behavioural response to cocaine. These discrepancies are difficult to reconcile in light of old and recent evidence. For example, considering psychomotor sensitization only, an aspect all studies agree on is the temporal dissociation between the NAc shell AMPAR-mediated synaptic potentiation that develops a week after the last cocaine exposure and locomotor sensitization, which is already present at the end of the 5-day injection procedure. In other words, it is unclear how early locomotor sensitization can be mediated by a neuronal adaptation that has not yet occurred (delayed increase in AMPAR signalling (>1 week)), unless early withdrawal sensitization is mediated by different cellular mechanisms. Another limiting aspect to consider is the dissociation between increased AMPAR function and enhanced behavioural responses to cocaine, both locomotor-activating[62,112,113] and incentive motivational effects[62].

Among other factors that may explain these discrepancies, such as the type of glutamate receptor subunits that are enhanced (GluA1 versus GluA2)[104,109] and type of cocaine reinstatement model (cue- versus stress-induced)[114], we should also consider the behavioural phenotype that is under investigation and the neuroanatomical location of enhanced AMPAR-mediated transmission (NAc shell versus NAc core)[104]. For example, in contrast to what occurs in the NAc shell, repeated cocaine non-contingent exposure increases the firing rate of MSNs in the NAc core[26]; therefore, the cell-autonomous homeostatic adaptation hypothesis cannot be applied in this subregion. Thus, it is plausible that cocaine-induced increases in AMPAR transmission in the NAc core,

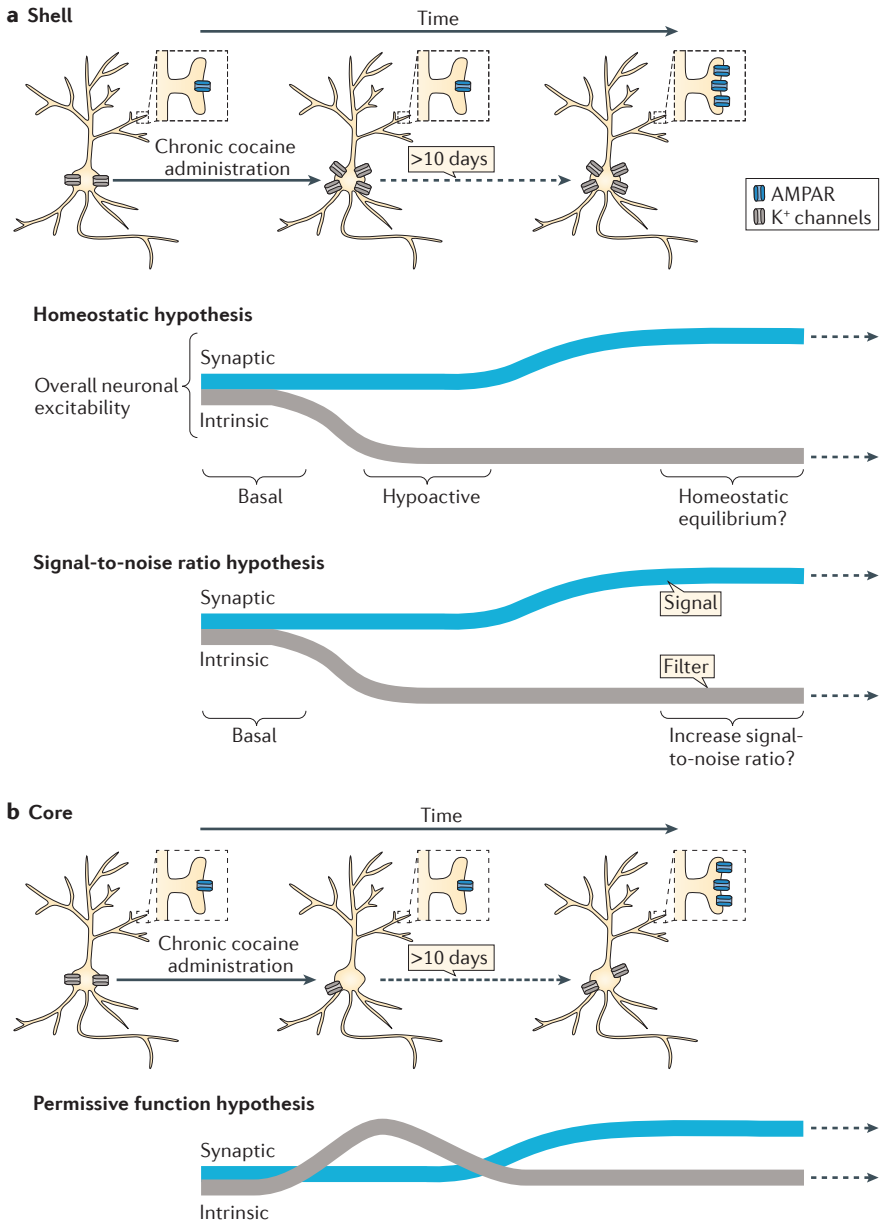


Figure 4 | **Intrinsic-to-synaptic interaction hypotheses. a** | In nucleus accumbens (NAc) shell neurons, repeated cocaine administration results in an initial increase in K^+ channel expression at the soma, followed by increased AMPA receptor (AMPAR) expression at synapses. This results in a decrease in intrinsic excitability and AMPAR-mediated synaptic potentiation. Two hypotheses have been proposed to explain these changes. First is the homeostatic hypothesis, derived from the observation that cocaine-induced decreases in NAc shell intrinsic excitability, which are produced partly through increases in K^+ channel expression[25–27], precede increased AMPAR-mediated synaptic strength[97–99]. This would suggest that this reduction in intrinsic excitability triggers a cell-autonomous homeostatic increase in synaptic strength that is programmed to renormalize global neuronal excitability. An alternative explanation is the signal-to-noise ratio hypothesis, whereby cocaine-induced decreases in intrinsic excitability may act as a noise filter that allows only strong and behaviourally relevant synaptic inputs, which represent the signal, to reach action potential threshold, activate the neuron and trigger the behaviour that is conveyed by the activated potentiated circuit. **b** | Chronic cocaine administration also produces changes in the NAc core, notably an initial increase in intrinsic excitability[26], followed by an increase in synaptic AMPAR expression[118] (and therefore an increase in synaptic excitability). We propose the permissive function hypothesis, whereby increases in intrinsic excitability, through decreases in K^+ currents[26], may provide a permissive function for synaptic potentiation to develop (that is, they lower the threshold at which synaptic potentiation can develop). This may facilitate the initiation of approach behaviour, which is directed at obtaining natural or drug rewards.

in contrast to the NAc shell, does mediate some behavioural effects of cocaine, such as the incentive motivational properties of cocaine[115] and susceptibility to relapse[104].

Signal-to-noise ratio hypothesis. How can opposite adaptations in the NAc shell, an increased synaptic[102] and a decreased intrinsic excitability[25,62] all lead to enhanced psychomotor sensitization to cocaine? Kalivas and Hu[116] posited a theory that may reconcile this apparent paradox, whereby decreased intrinsic excitability may act as a noise filter that allows only strong and behaviourally relevant synaptic inputs, which represent the signal, to reach action potential threshold and activate the neuron, enhancing the signal-to-noise ratio (FIG. 4b). This theory was originally proposed to explain data obtained in the NAc core, as it assumes that cocaine also decreases firing in NAc core neurons.

Although firing in NAc core neurons was later shown to be transiently potentiated[26] instead of persistently depressed[23,24,26], the theory is still appealing and has a great explanatory power for both NAc core and shell cocaine-induced neuroadaptations. Regarding NAc core neurons, after a period of withdrawal (>10 days), potentiated intrinsic excitability returned to basal levels[26], whereas synaptic transmission increased[5–7], which together suggest an increased signal-to-noise ratio in this region. Regarding NAc shell neurons, after a similar period of withdrawal, intrinsic excitability remained depressed[23,24,26], whereas synaptic transmission increased[5–7,97–99], which together also support an enhanced signal-to-noise ratio. Increased signal-to-noise ratio may predispose MSNs to fire only in highly salient situations. For example, this could favour stronger inputs (from the hippocampus[100,101], prefrontal cortex[100,102–104] and amygdala[117]) that may increase the response to cocaine-associated cues to readily trigger action potentials in NAc neurons and initiate cocaine-seeking behaviours. This idea is consistent with AMPAR-mediated incubation of cue-induced cocaine craving[118].

Permissive function hypothesis. In contrast to what is seen in NAc shell neurons, passive repeated non-contingent cocaine injections induce an early and transient firing potentiation in core NAc MSNs that quickly dissipates (measured 1–3 days after the last cocaine injection)[26]. Another study showed that during a period of abstinence from cocaine self-administration, a synaptic potentiation slowly develops in the NAc core[118] (FIG. 4b). Therefore, an intrinsic-to-synaptic homeostatic relationship between these two factors of excitability is unlikely. However, this does not exclude the possibility that these two neuroadaptations are sequentially related; the delayed synaptic potentiation may be a consequence of the transient firing potentiation. An idea that originates from learning and memory research proposes that increases in intrinsic excitability may provide a permissive function for synaptic potentiation to develop, which may be one possible mechanism that underlies the memory trace. For example, rabbits subjected to eyeblink conditioning exhibited enhanced hippocampal intrinsic excitability that was evidenced by a decreased spike after hyperpolarization (mostly mediated by SK current). This increased intrinsic excitability appeared before eyeblink conditioning was acquired and was no longer present when the rabbits, still showing a strong memory, were tested a few weeks later[119–122]. The authors of this study suggested that increased hippocampal intrinsic excitability was not a part of the engram (that is, the memory trace), but may have provided a permissive function for the memory trace to be formed. We speculate that NAc core hyperexcitability may predispose the neural network to generate long-term neuronal changes, such as delayed synaptic potentiation[123].

The permissive function hypothesis suggests that although both the NAc shell and the NAc core develop a similar delayed synaptic potentiation, they may be differentially induced and can facilitate different physiological and behavioural functions. This idea is consistent with the fact that the NAc shell and core have different roles in behaviour directed towards natural and drug reward seeking[36–45]. Synaptic potentiation may encode highly salient rewards in the NAc shell, and the motor programme needed to obtain those rewards in the NAc core. Support for this idea comes from neuroanatomical studies suggesting that the NAc shell can influence the behavioural output of the NAc core[51,124]. Increased synaptic strength in the NAc shell may be ideally positioned to allow highly salient drug-associated cues to further amplify the NAc core behavioural output.

Challenges and future perspectives

Cocaine experience affects both intrinsic and synaptic NAc MSN excitability. One of the challenges for the field is to demonstrate a causal role for any given drug-induced neuronal excitability mechanism for driving specific cocaine-associated behaviours that are related to drug addiction in humans. Another challenge is to understand how drug-induced changes in synaptic and intrinsic excitability interact to shape final NAc MSN output, as well as its consequences on neural circuit activity and thereby on cocaine-seeking behaviour. An area that has received little attention is the identification of mood states that are associated with increased synaptic or decreased intrinsic excitability in the NAc. More specifically, if the decreased firing capacity of the NAc shell predisposes individuals to a positive drug experience[62,125], then what are the mood states associated with NAc firing rate depression? Is the early and rapidly appearing decrease in NAc shell intrinsic excitability an electrophysiological marker of withdrawal? Indeed, the negative symptoms associated with drug withdrawal will promote addicted individuals to engage in drug-seeking and drug-taking behaviours to relieve these symptoms[126]. Are these unidentified drug-induced emotional states a factor of vulnerability to relapse in drug addicts? As mentioned at the beginning of this Opinion article, pre-existing biological conditions (for example, epigenetic variations) may also contribute to the development of addictive disorders in some individuals. So, it is possible that there are epigenetic variations in NAc excitability (for example, owing to innate or developmentally acquired differential expression of specific ion channels) that render some individuals predisposed to experience enhanced rewarding properties of the drug and make them prone to develop cocaine addiction.

Moreover, as discussed earlier, synaptic and intrinsic excitability are constantly working in concert to shape global neuronal activity to control information transmission within the nervous system. There is currently a strong focus on understanding how manipulating synaptic factors affects reward-related behaviours at various stages of the addiction cycle (FIG. 3a). One must extend these experimental manipulations to discrete intrinsic excitability factors (for example, K^+ channels), to draw a more accurate picture of the functional relationships that may exist between intrinsic membrane properties, neural network activity and, ultimately, behavioural phenotypes. Old and recent data from learning and memory research support this idea. In particular, learning and drug addiction processes seem to share many common molecular mechanisms[127]. A newly identified potentially common mechanism may be the participation of specific K^+ currents in both learning[119,122,128] and addiction, as discussed here. Regarding learning mechanisms, pharmacological blockade and genetic knock-down of specific K^+ channel subtypes, presumably altering different

firing characteristics, have been shown to differentially modulate learning and memory performance in both memory-type- and stage-specific manners[129–132], some of which exhibit direct correlation between learning capabilities and K^+ channel functions, protein or transcript expression[119–121,133,134]. Therefore, it would be plausible to relate specific K^+ conductances with the development or expression of specific aspects of addiction-related behaviours, or perhaps with stages of the addiction cycle.

More insights into addiction behaviour may be obtained using newly developed techniques and computational models. One such example is optogenetics, which allows researchers to manipulate neural activity in a temporally precise and relatively cell-specific manner, and can be used to demonstrate a causal link between neuronal activity at the circuit level and behavioural responses that are relevant to addiction and other psychiatric disorders, such as depression[135,136]. However, the specificity of information transmitted within neural circuits arises from a finely tuned firing frequency-modulated code, a mechanism that is made possible by the well-orchestrated activation and inactivation of specific K^+ channels[15]. Moreover, the high diversity of K^+ channels, which are heterogeneously distributed throughout both the neuron[137] and the brain, will also strongly affect spatial and temporal intracellular Ca^{2+} dynamics, and therefore neuronal signalling and plasticity[138]. In contrast to the fine-tuning of neuronal excitability provided by K^+ channels, optogenetic manipulations uniformly increase or decrease neuronal firing through the expression of exogenous light-activated proteins. This could result in a loss of information specificity that may be encoded by a combination of various K^+ channel-dependent neuronal excitability features (for example, action potential threshold, spike waveforms and frequency adaptation) and their effects on dynamics of cellular Ca^{2+} signalling.

Conferring molecular specificity to optogenetic techniques may help to overcome this issue, providing causal links between specific native ion channel functions and behaviour. Efforts to develop and use photoswitchable molecules that modulate gating of relatively specific indigenous K^+ channels with light are currently underway[139–146]. This method consists of either manipulating K^+ channels with specific light-controlled ligands[142] or expressing engineered photoswitch-ready channels with built-in pharmacological specificity[139]. The advantages of using experimenter-controlled native K^+ channels are self-explanatory: these are non-foreign proteins that are not likely to trigger compensatory mechanisms, which are usually observed in classic genetic knock-in or knockout models[147–150]. A next step would be to make highly specific photochemical ligands or neuron-specific photoswitchable channel subtypes that have the same biophysical properties and trafficking patterns as the target channels. Reaching such molecular specificity and such a degree of regional and temporal control will allow us to finely tune particular aspects of neuronal excitability, and thus to reprogramme the activity of specific neural networks in real-time as we assess changes in behaviour.

The mechanism by which NAc intrinsic excitability alters behavioural output remains an open question. As discussed previously, there is a high diversity of K^+ channels, heterogeneously expressed across different subcellular compartments within neurons[137,151,152]. However, it remains unclear how changes in specific types of K^+ channels, within specific subcellular compartments, might differentially shape the complex features of neuronal excitability (for example, action potential threshold, spike waveforms and frequency adaptation), which ultimately shape the specificity of the information communicated to downstream targets. Neurocomputational models that predict how upregulation or downregulation of a particular type of K^+ channel within a given subcellular compartment would impact neuronal excitability have tremendous power, as they provide insights into unanswered questions about how the neuron works, how it shapes information and how it conveys the information to downstream targets. Such computational models of NAc MSNs have emerged[153–156], and the development of more comprehensive computational models that include a broader representation of existing conductances within NAc MSNs will further enhance our understanding of how subcellular- and cellular-level alterations in ion channel make-up can affect the complex features of neuronal excitability.

A critical next step would be to understand how cocaine-induced changes in NAc neuronal excitability may drive drug-seeking behaviour. One possibility is to integrate the resulting excitability changes from the cellular-level model proposed above, into existing associative learning[157], reinforcement learning and striatal-based actor-critic neurocomputational models[158–162] that generate direct and testable predictions for natural[163–168] and drug-reward learning and seeking behaviours[169–175]. Considering the well-established role of the NAc core and shell in natural and drug reward seeking[36–46], as well as mounting evidence suggesting that cocaine exposure alters the landscape of information encoding in these regions[48,76–79,85,176–179], there would be tremendous utility in pursuing a neurocomputational approach that bridges the gap between NAc neuroadaptations observed after drug exposure and NAc-dependent drug-seeking behaviours.

Altogether, the development of neurocomputational models, in parallel with the *in vivo* manipulation of cell-specific photoswitchable target channels, could significantly advance our understanding of how drug-induced changes in specific intrinsic factors shape neuronal activity and circuit dynamics, and how they lead to the behavioural adaptations that characterize drug addiction. These theoretical and technological advancements may also contribute to the understanding of the functional relationships between alterations in a given ion channel and neuronal dysfunctions that are associated with a number of psychiatric and neurological disorders (channelopathies).

Saïd Kourrich is at the Department of Psychiatry, The University of Texas Southwestern Medical Center, Dallas, Texas 75390–9011, USA.

Donna J. Calu and Antonello Bonci are at the National Institute on Drug Abuse, Intramural Research Program, Baltimore, Maryland 21224, USA.

Antonello Bonci is also at the Solomon H. Snyder Neuroscience Institute, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205, USA.

Correspondence to S.K. and A.B:
e-mails: Said.Kourrich@UTSouthwestern.edu; antonello.bonci@nih.gov

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