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Abstract / Synopsis
The mesolimbic DA system appears to have played an important role in evolution. Natural rewards such as food, water and sexual stimulation—all essential to survival—trigger DA transmission. In limbic targets (e.g., NAcc, cortex, and BLA) DA promotes synaptic modifications of glutamatergic inputs signaling extant exteroceptive or interoceptive stimuli. Via these modifications, limbic processing of stimuli that are informative about reward consumption become capable of motivating and guiding future behavior by gaining access to motor areas downstream of the NAcc. During cocaine self-administration, the rapid entry of sufficient doses of cocaine into the brain produces exaggerated elevation of DA transmission, similarly resulting in modifications of glutamatergic signals related to interoceptive and exteroceptive stimuli. Via these processes, the subject acquires heightened sensitivity to cocaine cues which cause craving and may lead to relapse, and which potently reinstate drug seeking in animal models. One potential mechanism underlying DA-mediated synaptic change involves NMDA receptor-mediated installation of additional AMPA glutamate receptors, the most common known form of synaptic strengthening. Neurons within the NAcc play an especially prominent role in encoding drug-seeking cues and behaviors. Neurons in the NAcc shell acquire responsiveness to DSs, i.e., cues that predict cocaine's availability. Other brain regions critical for reinstatement in response to DSs include the BLA and VTA. In contrast, neurons in the NAcc core exhibit changes in firing related to CSs, i.e., cues that predict the unconditioned effects of cocaine. Core neurons exhibit larger changes in firing rate during cocaine-reinforced responses than shell neurons, suggesting the core is a common brain region involved in conditioned drug-seeking behavior. Other brain regions critical for reinstatement in response to CSs include the BLA, lateral OFC, DLS, and VP. Stress, increasingly considered a cocaine-related cue, may trigger reinstatement through sympathetic arousal as well as activation of the HPA axis and brain regions including the CeA, BNST, PFC, OFC, NAcc shell and core, VTA and VP. Accumulating empirical evidence indicates that, through cocaine’s ability to commandeer neural regions involved in natural instrumental learning (e.g., foraging), the abuser becomes abnormally sensitive to external cues (e.g., money) or internal cues (e.g., stress) previously associated with cocaine which may lead to relapse.

List of Abbreviations
List and define any abbreviations used in your article
ADX - adrenalectomized
AMPA – α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid
BNST – bed nucleus of the stria terminalis
BLA – basolateral amígdala
CeA – central nucleus of the amygdala
cort - corticosterone
CRF - corticotropin releasing factor
CR-R - cue reinforced reinstatement
CS - conditioned stimulus
CS-R - conditioned stimulus reinstatement
DA – dopamine
DLS – dorsolateral striatum
More than most other disorders, drug addiction is acquired through learning processes. Detailed knowledge gained during the past century of psychological study regarding processes underlying classical and instrumental conditioning has laid a foundation for dissecting their roles in acquiring and expressing addictive behaviours. Dissecting these roles is essential for informing the development of treatments for addiction. Cognitive/behavioural therapies, which depend on new learning by the patient, benefit from knowledge of what the patient has previously learned about predictors of cocaine use and what mechanisms are available to the clinician for behavioural change (see Chapters 63 and 68). Although there is not yet a medication approved by the U.S. Food and Drug Administration for cocaine addiction (Chapter 276), pharmacological therapies will target learning-related changes at cellular and molecular levels altered by cocaine abuse that may be vulnerable as novel drug targets to treat cocaine craving and relapse. For these reasons, the focus of this chapter is not on the array of changes induced by repeated cocaine
administration (Chapter 128). Rather, the focus is on attempting to identify what the cocaine addict learns, and the likely neurobiological sites and mechanisms involved.

Behavioural and neuroanatomical investigations of addiction have placed an emphasis on understanding relapse (Chapter 88). That is, if the behavioural, physiological, and neural mechanisms underlying relapse were understood, therapies could be created (behavioural, pharmacological, or neural (e.g., deep brain stimulation)) to prevent the phenomenon from recurring. In 1982, investigators modelled relapse using the reinstatement procedure in cocaine self-administering animals. In this behavioural paradigm, animals self-administer cocaine for a period of time, e.g., 10-14 days. Subsequently, the behavioural response (typically a lever press) is extinguished while the animal is abstinent for a variable period of time, and then a stimulus previously paired with cocaine is introduced in an attempt to “reinstate” the extinguished behaviour. This paradigm has been the dominant procedure for testing stimuli that trigger relapse episodes, for determining the learning processes that underlie the reinstatement of behaviour, and for exploring the neuronal basis of this association.

Although withdrawal is a potent motivational factor for returned drug use, cocaine induces relatively mild and short lasting withdrawal symptoms. Thus, relapse is likely triggered by cues relevant to the user he or she has learned through past drug use. Indeed, various drug-related cues induce self-reported drug cravings, and ratings of cravings increase as the user becomes temporally closer to relapse. Although drug-related cues can engender craving, craving could be induced by conditioned responses induced by the cue that are akin to those of the associated drug or opposite those of the drug. The complexity of cue-induced drug-seeking has necessitated the use of animals models investigating the potential involvement of several brain systems during relapse-related paradigms.

Neuroanatomy of cocaine addiction

Cocaine is a potent sympathomimetic drug that enhances transmission at dopaminergic, adrenergic and serotonergic synapses (Chapters 38, 251). Its potential for abuse chiefly depends on dopaminergic mechanisms in the mesolimbic DA system (Chapter 132). VTA DA neurons in the midbrain receive glutamatergic synaptic inputs from widespread areas, most prominently from dorsomedial PFC, lateral hypothalamus, central and peri-aqueductal gray and raphe nuclei. VTA DA neurons densely innervate the NAcc, which reciprocates via GABAergic projections to the VTA. The NAcc is the limbic subregion of the striatum and is the site in which DA transmission is necessary for cocaine self-administration. Mesolimbic DA neurons project less densely to other components of the limbic system. In limbic targets, DA afferents interact with convergent glutamatergic afferents that form extensive closed-loop connections between limbic structures and open loop connections with sensory association areas and premotor areas. The accumbens has been recognized as a key crossroads between the limbic and motor systems by which incentive cues or interoceptive stimuli gain access to the motor system to guide behavior. The system appears to have evolved under pressure to facilitate instrumental learning about cues associated with reward consumption. The natural rewards earned via instrumental behavior, e.g., food, water or sexual stimulation, which are all essential to survival, elevate DA transmission in limbic targets. In addition to inducing euphoria or pleasure, DA interacts with glutamatergic sensory signals converging on target neurons to strengthen the postsynaptic neurons’ responsiveness to these cues. Via common mechanisms of synaptic
plasticity, the cues become conditioned incentives that acquire the ability to activate limbic areas projecting via the accumbens to premotor areas and guide behavior when the cues are encountered in the future.

Cocaine’s elevation of DA transmission at these limbic sites is pharmacological, i.e., potentially stronger than the natural, physiological interactions involved in instrumental learning. Thus it has been hypothesized that natural mechanisms of DA-mediated plasticity are commandeered and possibly exaggerated because of the abnormally elevated DA transmission (Chapter 142). The result is that conditioned incentive cues may be especially salient or irresistible in guiding an addict’s behavior (Chapters 98, 105). Although a complete understanding has not yet emerged from imaging studies of the human brain, these studies have revealed a distributed set of regions, mainly limbic, which are altered from resting state during cue-induced cravings, including the dorsolateral PFC, orbitofrontal cortex, insula, amygdala, anterior cingulate, caudate, putamen, NAcc, VP, and cerebellum.

Anatomical connections of the NAcc and dorsal striatum: medial-to-lateral spiraling connectivity

The subiculum, basal amygdaloid complex and prefrontal cortex send extensive, topographically arranged glutamatergic projections to NAcc medium spiny neurons. Both afferents and efferents of the NAcc are topographically organized, suggesting a topographic throughput of different kinds of information. The NAcc comprises two main subregions, core and shell. The core is largely interconnected with structures characteristic of DLS circuitry, whereas the shell exhibits a pattern of connectivity consistent with that of the extended amygdala. The rostral, magnocellular BLA projects more heavily to the core and dorsal striatum, whereas the caudal, parvicellular BLA projects more heavily to the shell and extended amygdala. Infra-limbic and pre-limbic regions of medial PFC project densely to the NAcc, and to parvicellular and magnocellular divisions of BLA, which are reciprocally connected to infralimbic and pre-limbic cortex, respectively. Dorsal pre-limbic and anterior cingulate afferents preferentially project to the core, whereas infra-limbic cortex projects most densely to the medial shell. The medial shell, but not the core, is extensively innervated by the ventral subiculum, central nucleus of the amygdala and bed nucleus of the stria terminalis. The medial shell projects, along with its primary target, ventromedial VP, to various regions of the extended amygdala, lateral hypothalamus, mesencephalic locomotor area, periaqueductal gray, and to mediodorsal thalamus, which projects to the dorsal PFC which, in turn, innervates the core. The medial shell and ventromedial VP additionally project to parts of the VTA that innervate the core. The core, and its primary target, dorsolateral VP, on the other hand, project to characteristic basal ganglia targets, i.e., GPi, and substantia nigra, both SNC and SNR, ultimately reaching ventromedial and mediodorsal thalamic nuclei and their targets in premotor and lateral PFC, respectively. These regions send corticostriatal projections to the DLS. Core projections to SNC also ultimately target the entire dorsal striatum. The lateral, or sensorimotor, striatum, often referred to as the “dorsal striatum”, but here referred to as DLS, receives convergent and topographic projections from S1, M1 and PMC. DLS MSNs project via the GPi and/or SNr to VA and VL (“motor” thalamic nuclei), which in turn project to PMC and M1, completing the cortical-subcortical re-entrant motor loop. Thus, limbic signals projected to the medial shell are projected, via laterally “spiraling” mesencephalic and thalamocortical connections, to core, which continues the spiraling projections to mesencephalic and thalamocortical
regions that innervate the DLS, which connects via VA and VL thalamus to PMC and M1, enabling motivationally significant cues to guide behavior. Much evidence has demonstrated the involvement of the ventral striatopallidal system including the ventral tegmental area and nucleus accumbens in drug-seeking behavior. Recent evidence suggests that the dorsal striatopallidal system including the substantia nigra and DLS gains importance in drug-seeking behavior following extended drug use.

**Mechanisms of synaptic plasticity involving cocaine’s actions in the mesolimbic system**

The most studied and possibly most common form of experience-dependent synaptic plasticity observed in widespread neural systems involves enhanced glutamate transmission via NMDA receptor-mediated installation of additional post-synaptic AMPA receptors, resulting in LTP (other mechanisms, including LTD, are discussed in Chapters 127, 128, 131). Cocaine exposure leads to upregulation of AMPA glutamate receptors in the VTA and NAcc. Increases in AMPAR/NMDAR ratio (suggesting LTP) and mEPSC frequencies (suggesting an enhancement in glutamate release) support the idea that self-administration of cocaine causes long-term enhancement of glutamate transmission onto VTA DA neurons. Cocaine self-administration induces long-lasting upregulation in the expression of glutamate receptor subunits, including GluR1 and GluR2 in the accumbens, and NMDA1 in the VTA and accumbens (further study is needed to clarify the role(s) of NMDA receptors in the NAcc). After prolonged withdrawal from cocaine, increased numbers of synaptic AMPA receptors combined with the higher conductance of GluR2-lacking AMPA receptors may increase the reactivity of NAcc neurons to cocaine-related cues, leading to an intensification of drug craving and relapse. Consistent with these findings, reinstatement of cocaine seeking is reduced, or stimulated, respectively, by microinjecting AMPA/kainate receptor antagonists or agonists into the NAcc core or shell. Together, these data indicate that increased glutamate transmission through AMPA/kainate receptors in both the core and shell of the nucleus accumbens promotes the reinstatement of cocaine-seeking behavior. Indeed, during tests of cue-induced relapse following abstinence from cocaine self-administration, neurons in the NAcc shell selectively respond to the discriminative cue while core neurons selectively respond during the drug seeking response evoked by the cue, each of which is likely driven by enhanced glutamatergic, limbic afferents to the NAcc. A better understanding of the neuronal bases underlying what is generally termed “cue-induced” relapse or reinstatement will require consideration of subtle differences in the types of cocaine-related cues that are present during self-administration and relapse-related paradigms. The following sections describe some pertinent behavioral differences among different kinds of cues associated with drug self-administration that differentiate how and where they are processed in the brain.

**Discriminative stimuli**

Cocaine-related cues are conditioned in various ways. Cues that precede self-administration are learned as SDs. They signal drug availability, but require a drug-seeking response. Some may no longer be present when the drug effects are experienced, such as a pay check or drug pusher. In the laboratory, SDs model the signalling of drug availability. Presented non-contingently during testing (as during training), SDs efficaciously and persistently reinstate responding. We have observed in animals that self-administered
cocaine under control of an SD, following a month of abstinence, that SD presentation leads to a 13 fold increase in responding above that during a period when the SD was not presented. Even when an SD is associated with cocaine availability once, the SD can engender enhanced responding up to one year later. Enhanced responding is dopamine-dependent and is associated with increased extracellular dopamine in NAcc and amygdala. Indeed, the interplay of the BLA, NAcc, and VTA appear to be integral to SD-induced responding.

During natural-reward seeking, GABA agonism within the VTA or dopamine antagonism within the NAcc blocks SD-induced responding. Furthermore, VTA GABA agonism disrupts SD-induced firing of single NAcc neurons. During cocaine-reward seeking (reinstatement), prior BLA lesions block SD-induced responding. Moreover, during reinstatement single neurons of the NAcc shell and, to a lesser extent, NAcc core increase firing rates in response to the SD when none did so prior to cocaine self-administration training, suggesting the accumbal signal towards the SD was learned. However, in contrast to NAcc core neurons, NAcc shell neurons did not change firing rates in response to a neutral cue, indicating that the NAcc shell discriminated the drug-availability cue whereas core did not.

Additional insight was provided in an experiment using a tastant as an SD, to which a subset of NAcc neurons are unconditionally sensitive. Interestingly, a tastant SD paired with the opportunity to self-administer cocaine selectively produced "aversive" orofacial reactions while a different tastant paired with the opportunity to self-administer saline did not. The number of aversive orofacial reactions in response to the cocaine-related SD positively correlated with the consumption of cocaine. Given that animals produced "aversive" orofacial reactions to the cocaine-related cue, but not to the saline-related cue, the experimenters hypothesized that the CS-induced conditioned withdrawal motivated self-administration behaviour. Neuronally, prior to self-administration training, a subset of NAcc neurons unconditionally decreased firing rates in response to both tastant SDS. However, after learning the SD-cocaine relationship, a subset of NAcc neurons shifted the direction of firing rate changes to increases in firing rate. In contrast, firing to the tastant SD paired with saline self-administration remained a decrease in firing rate. Taken together with the previously mentioned electrophysiological data, increases in firing rate in response to SD cues by accumbal neurons may be a mechanism that promotes drug-seeking behaviors.

Conditioned stimuli

Cues that predict or are experienced with the unconditioned effects of cocaine are considered conditioned stimuli (CS). An example may be drug-related paraphernalia. Such cues may be modelled preclinically in a variety of ways such as pairing a cue with noncontingent injections of cocaine or presenting a cue during infusion after completion of the operant response. At test, the CS could be presented to the animal noncontingently or contingently upon responding, to measure cue-induced drug-seeking versus cue-reinforced drug-seeking, respectively. In spite of the greater face-validity of the cue-induced paradigm, little research has been performed using non-contingent presentations of the CS. Instead, the cue-reinforced approach, i.e., presenting the CS contingent upon (after) each operant response, despite requiring prolonged extinction sessions (over weeks) prior to testing, is by far the most researched CS-related reinstatement paradigm, and thus will be the focus of
this section. This approach will be referred to as the conditioned reinforcement reinstatement (CR-R) method. In one effective method, the animal self-administers cocaine without a particular cue, and in a separate session, that cue (CS) is paired with noncontingent infusions of cocaine (US). Since presenting the CS contingent upon responding reinstates drug seeking behaviour but randomized CS presentations during training or presenting a novel cue during test do not reinstate, the CR-R method requires learning of the cue-cocaine relationship.

Learning of the cue-cocaine relationship depends on the BLA, as does conditioned reinforcement in general. Tetrodotoxin infusions into the BLA prior to CS-US learning blocked later CR-R whereas the same manipulation in the central amygdala (CeA) had no effect. Instead, BLA or CeA tetrodotoxin each blocked the expression of CR-R when infused prior to test. Further research identified a dopaminergic involvement. D1 antagonism of the BLA during CS-US learning also reduced CR-R whereas D2 antagonism potentiated CR-R. Furthermore, acute dopamine blockade in BLA reduces CR-R whereas injection of D-amphetamine potentiated CR-R. Acetylcholine also plays a role given that scopolamine, an acetylcholine muscarinic antagonist, injected into BLA prior to CS-US pairing blocked CR-R.

Expression of CR-R appears to also involve circuitry connecting the BLA and prelimbic cortex, anterior cingulate cortex, lateral orbitofrontal cortex, dorsolateral striatum, NAcc core, and ventral pallidum. In contrast, knowledge of the mechanisms of CS-induced reinstatement (CS-R; noncontingent presentations) is lacking. Systemic NMDA antagonism reduces CS-R, suggesting a central mechanism. Indeed, single NAcc neurons exhibit phasic changes in firing rate in response to noncontingent (CS-R) or contingent (CR-R) CS presentations. Interestingly, NAcc core neurons were activated by the CS more than NAcc shell neurons suggesting that the core’s CS firing correlates may signal anticipation of the drug’s effects at the onset of each self-infusion. Whereas shell, with its SD firing correlates, may signal the anticipation of emitting the response required for self-administration.

Context

The self-administration context alone can reinstate responding (CX-R), although it has received less attention than CS-R. Such an event may be akin to entering a neighbourhood in which the drug has been used. In light of the observed serially connected dorsolaterally spiralling loop from the medial NAcc shell to the DLS, it has been suggested that a shift in neuronal processing occurs away from the ventral striatopallidal system toward the dorsal striatopallidal system with extensive drug experience. In support of this, NAcc core or lateral shell manipulations had no effect on CX-R whereas manipulations of DLS did. However, it appears that a number of other structures in both systems are involved in CX-R including the dorsal hippocampus, dorsomedial prefrontal cortex, BLA, infralimbic cortex, substantia nigra, and ventral tegmental area. The reader is referred to Chapter 72.

Stress

Stress is believed to cause relapse. In the laboratory, it has been observed that imagined stress can increase drug “craving”. Subjects were interviewed by experimenters and described situations in which relapse occurred after entering certain situations (drug cues) and also described situations of heightened stress (i.e., firing or divorce). The experimenters then created “scripts” from the self-report of the users and used an “imagery
procedure” for the drug cue, stress situation, and neutral (relaxation) imagery. The users were instructed to close their eyes and imagine the situations “as if” they were occurring. Stress imagery increased heart rate, self-reported “drug craving” and “anxiety”. Although stressors differ between humans and animals, some of the physiological mechanisms underlying stress-induced, drug-related responding have been determined using animal research.

One study in rats utilized a stressor to produce reinstatement. Animals self-administered cocaine for 10-14 days and then responding was extinguished over weeks to a small response criterion per day. After roughly a week of abstinence, footshock (FS) was able to reinitiate responding in these animals. The mild footshock parameters used in this study (variable time 40 sec schedule, ~.5 sec duration, ~.75 mA current, and ~15 min in duration) have been utilized in nearly every subsequent report. Interestingly, the reinstatement (lever pressing in extinction) was as strong as cocaine induced reinstatement, although both lasted only ~1 hour following stimulus (cocaine or FS) exposure. Furthermore, following 2 months of abstinence away from the self-administration environment, animals displayed footshock-induced reinstatement (FS-R) again. This time, FS-R was higher than cocaine induced reinstatement. Thus, FS-R potently reinstates responding, even after long periods of abstinence and prior experience with the same stressor.

While FS-R occurs in animals with cocaine self-administration experience, for animals that self-administered food, FS did not reinitiate responding. Since cocaine is a sympathomimetic, these experimenters put forward the hypothesis that FS is a cue that mimics the sympathomimetic effects of cocaine itself. Thus reinstatement occurs because the cue activates some of the same physiological mechanisms that the drug does (a proponent process).

This hypothesis requires that animals learn during self-administration to discriminate the sympathomimetic effects of cocaine. There is evidence to support this notion in humans. During laboratory self-administration of cocaine and in the presence of a CS+, users self-reported “wanting cocaine” and “anxiety”, exhibited decreased skin temperature, and increased heart rate. When these users were presented the CS+ during abstinence, the CS+ similarly increased heart rate, self-reported “wanting cocaine”, “anxiety”, and decreased skin temperature, supporting a proponent process of the CS with the sympathomimetic effects of cocaine. In contrast, these effects did not occur to the CS-, which was paired with placebo self-administration.

If stress acts as an interoceptive cue activating a proponent process, the cue must be learned during self-administration. The duration of training plays a role in learning about this interoceptive cue. Animals that self-administered for 2 hours per day exhibited greater FS-R than animals that self-administered 12 hours per day. Perhaps the ability of the sympathomimetic effects of cocaine to be discriminated when presented with FS became diminished with the overexposure to cocaine during training. However, animals self-administering for 1 week exhibited similar FS-R rates as animals self-administering for 3 weeks. Thus, it appears that animals learn to discriminate the sympathomimetic effects of cocaine rather quickly during training.

Preclinical studies have corroborated the idea that stress reinstates cocaine seeking by mimicking some of the drug’s interoceptive (sympathomimetic) effects. That is, because perceived sympathetic effects during stress are similar to many of those produced by cocaine, the latter of which are associated with cocaine’s reinforcing effects, sympathetic
activation during stress may be learned as a conditioned stimulus predicting cocaine’s reinforcing effects. In a novel therapeutic approach, rats with a history of chronic cocaine self-administration were repeatedly primed with cocaine in the absence of drug reinforcement, in order to extinguish the conditioned interoceptive effects of cocaine. Indeed, results showed that both cocaine-primed and FS stress-induced reinstatement of cocaine seeking strongly decreased, suggesting that the interoceptive effects of a priming dose of cocaine or of FS had lost their conditioned predictive value, i.e., less strongly predicted the reinforcing effects of cocaine. Conversely, in a study using a pharmacologic stressor (i.e., yohimbine, a sympathomimetic drug with strong anxiogenic properties) in rats that had self-administered cocaine, repeated exposure to yohimbine during extinction training subsequently attenuated stress-induced reinstatement of cocaine seeking. Preclinical demonstrations that FS- or yohimbine-induced reinstatement of cocaine seeking can be blocked by clonidine (which reduces noradrenergic activity in the brain) have recently been extended in a translational study to humans, suggesting that such an agent may help prevent relapse in drug abusers experiencing stress or situations that remind them of drug use.

**HPA mechanisms.** Glucocorticoids, such as corticosterone (in the rat; cortisol in the human) play a significant role in self-administration behaviour and reinstatement. Experimentally adrenalectomizing (ADX) rats disrupts the end result of the HPA axis (the adrenal’s production of cort). ADX severely impairs cocaine self-administration. The animals still self-administer but the dose response curve, which is typically an inverted U, is flattened. Injections of cort dose-dependently reversed the dose-response curve flattening in ADX animals, demonstrating the importance of cort in self-administration. Furthermore, in normal rats, injection of cort was able to dose dependently reinstate responding. Thus, one potential physiological mechanism of FS-R is a rise in cort induced by FS.

Indeed, ADX animals do not show FS-R, but cort replacement in ADX animals restores it. Further, unlike normal animals, in ADX animals (with or without cort replacement), FS does not increase cort. Thus, FS-R depends on the presence of cort (a necessary condition) but was not a sufficient condition for FS-R to occur. Instead, systemic injection of a CRF receptor antagonist was able to attenuate FS-R in ADX animals on cort replacement. In normal animals, systemic CRF antagonists have been shown to block FS-R for cocaine. Thus, CRF appears to be an important modulator of FS-R.

The role of glucocorticoids (such as cort) in FS-R could play a still bigger role. Similar to ADX, knockout mice with the central glucocorticoid receptor nullified show a flattened dose response curve during self-administration, demonstrating that central glucocorticoid signalling is required for normal self-administration. Further, in normal animals, systemic glucocorticoid antagonism dose dependently decreases the progressive ratio break points for self-administering cocaine. The break point procedure is a schedule of reinforcement in which the ratio requirement of animals to receive cocaine is progressively increased at each earned reward, determining the amount of effort the animal will put forth to earn drug. Thus, it appears that glucocorticoid signalling in the brain may be important for the motivation to self-administer cocaine. Glucocorticoids could influence the reinforcing effects of cocaine and thus reduce the motivation to self-administer as well as flatten the dose response curve. Further research will be needed to determine within which brain areas glucocorticoid signaling is affecting which of these behavioural processes.
As discussed above, CRF is important for FS-R. However, CRF is linked with glucocorticoid production. The paraventricular nucleus of the hypothalamus produces and secretes CRF into the median eminence where it enters the portal system. CRF activates the POMC gene in the anterior pituitary and POMC is cleaved to ACTH. ACTH then facilitates the production of cort in the adrenal cortex. This is the normal process of the stress response, typified by the flight or fight response. Glucocorticoids play an important role in that they facilitate protein and lipid storage as carbohydrates, which is important to replenish after just escaping a predator (an allostatic response). However, glucocorticoid signaling also has a cost. While it can facilitate the production of memories for aversive events, too much glucocorticoid signaling has been shown to produce dendritic atrophy in the hippocampus (an allostatic load). If cocaine self-administration and FS-R depend on glucocorticoid signaling, each day self-administering cocaine as well as each stressful event may cost in terms of dendritic atrophy. Such a result may bias users toward relapse due to less effective hippocampal plasticity during clinical therapy. In other words, users may be less amenable to learning the strategies taught in traditional treatment programs.

Human research has supported the notion that elevated glucocorticoid signaling occurs in abstinent cocaine users during craving episodes. Utilizing the imagery procedure described earlier, it was found that, compared with neutral imagery, stress imagery increased heart rate, “anxiety”, “craving”, cort, noradrenalin, epinephrine, and ACTH. The involvement of noradrenalin will be discussed in the next section. However, in addition to these stress-related interoceptive signals, stress induced by noradrenalin manipulation affects incentive cue-related reinstatement. Yohimbine, an anxiogenic α2-noradrenergic antagonist, potentiates CR-R. Furthermore, plasma cort levels are increased during CR-R alone and cort synthesis inhibition by ketoconazole as well as CRF1 antagonism by CP-154,256 blocked CR-R. Thus, it seems clear that glucocorticoids are part of the process of FS-R, self-administration, and human recall of stressful events that elicit cravings.

Neural mechanisms. Since systemic CRF antagonists were shown to decrease FS-R, brain regions that are involved in CRF signaling have been investigated. CRF antagonism in the bed nucleus of the BNST but not CeA blocks FS-R. Furthermore, local injection of a CRF agonist was able to reinstate responding in the BNST but not the CeA. Although this suggests the CeA is not involved in FS-R, the disconnection procedure was utilized to discover a role for a serial pathway from CeA to BNST in FS-R. A sodium channel blocker was injected into the CeA in one hemisphere of rats and a CRF antagonist into the other hemisphere’s BNST. The logic is that if these areas are linked to control the behaviour, unilateral injection alone (either one) should not be sufficient to decrease the behaviour because the other hemisphere is available to control the behaviour. However, when both hemispheres are injected and if there is a serial pathway controlling the behaviour, i.e., the pathway from CeA to BNST, then the pathway in both hemispheres is blocked, decreasing the behaviour. This is exactly what was observed. Specifically, unilateral injection of tetrodotoxin in CeA or CRF antagonism in BNST did not change FS-R. However, infusion of both attenuated FS-R, implicating the pathway from CeA to BNST in the behaviour. Since this attenuated but did not block FS-R, other mechanisms are likely also involved. Indeed, bilateral noradrenergic antagonism (β1 and β2) in either the CeA alone or the BNST alone was able to block FS-R.

Although the CeA and BNST are among brain regions that can control FS-R, other brain regions were also found to affect stress-induced relapse including the prelimbic
cortex, OFC, NAcc medial shell, core, and VP. Moreover, the field has been narrowed by showing that GABA a+b infusions into BLA, mediodorsal thalamus, or infralimbic cortex do not affect FS-R. Cortical regions in humans, such as the dorsolateral PFC, have exhibited a correlation between fMRI activation and self-reported craving induced by stress imagery, suggesting PFC in human and rat may both be important for stress induced relapse.

Given the aforementioned brain regions involved in FS-R, the chemical analysis of FS-R has recently been explored. First, inactivation of the shell, which blocked FS-R, also blocked increased extracellular DA levels in the prelimbic cortex induced by FS. Second, DA (D1/D2) blockade in the prelimbic cortex blocked FS-R. Third, inactivation of the prelimbic cortex (which blocked FS-R) blocked a rise in extracellular Glu in the NAcc core, which is normally induced by FS. Because the NAcc core projects to VP and inactivation of either region blocked FS-R, the authors of these studies proposed that the extended amygdala (including CeA, BNST, and NAcc shell) affects DA levels in the prelimbic cortex, which in turn activates the NAcc core through a glutamatergic projection, and subsequently affects the VP and downstream premotor areas (as per the aforementioned spiral circuitry through the VTA) to carry out reinstatement. Given that the mediodorsal thalamus is not involved in FS-R, downstream mesencephalic projections from PFC, amygdala, and other regions (e.g., VP) appear to be important sites mediating FS-R.

FS-R increases extracellular DA, Glu, and CRF in the VTA of rats. Furthermore, CRF antagonism of the VTA blocks FS-R. Reverse microdialysis of Glu into the VTA increases CRF and DA concentrations suggesting glutamatergic innervation of the VTA is a neuronal trigger for FS-R. As already mentioned, the prelimbic cortex plays a role in FS-R by projecting Glu to the core. However, one of the largest glutamatergic projections in the rat brain to the VTA is from the prelimbic cortex. Such a projection would presumably increase local CRF and DA concentrations. Furthermore, increased DA would likely be projected to all VTA targets, including prelimbic cortex, OFC, and NAcc, in any of which DA antagonism blocks FS-R.

As noted, Glu alone projected to the VTA can cause FS-R. However, it is possible that the BNST, CeA, and hypothalamic paraventricular nucleus projection of CRF to the VTA may be responsible for FS-R. Nevertheless, abstinence alone from cocaine self-administration increases glutamatergic receptor expression in the VTA and NAcc. Given that Glu in the NAcc is a factor of FS-R, it appears that cocaine self-administration primes both the NAcc and VTA for glutamatergic throughput to cause reinstatement. Such mechanisms may be the underpinnings by which various types of stressors and their interoceptive effects, or exteroceptive cues, could cause a human to relapse. If so, one possible therapeutic target may be the desensitization of the conditioned effects of stressors or other drug-related cues through the teaching of coping mechanisms or systematic desensitization, possibly in conjunction with medications that alter glutamatergic throughput of the VTA and NAcc.

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**Relevant Websites**

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West laboratory website
National Institute on Drug Abuse
Author Biography and Photograph

Please provide a brief biography (a maximum of 200 words) plus a colour photograph of yourself (likewise any co-authors).

Mark O. West:
Mark West received his B.S. from the University of California, Irvine in 1976, and his Ph.D. from Wake Forest University School of Medicine in 1982 using electrophysiological study of the hippocampus during behavior. He is Professor of Psychology at Rutgers, the State University of New Jersey, and has studied the neural basis of psychostimulant drug self-administration for 25 years.

David H. Root:
David received a B.S. from Western New England College in 2004 investigating the learning deficits induced by prenatal marijuana exposure and a M.S. from Seton Hall University investigating the role of the dorsolateral striatum in natural reward and alcohol self-administration. David is currently a Ph.D. candidate in Dr. Mark O. West’s lab investigating the electrophysiological mechanisms of natural reward and cocaine self-administration within the dorsal and ventral striatopallidal systems.

Tables
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