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REVIEW

Molecular and circuit mechanisms regulating cocaine memory

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Abstract

Risk of relapse is a major challenge in the treatment of substance use disorders. Several types of learning and memory mechanisms are involved in substance use and have implications for relapse. Associative memories form between the effects of drugs and the surrounding environmental stimuli, and exposure to these stimuli during abstinence causes stress and triggers drug craving, which can lead to relapse. Understanding the neural underpinnings of how these associations are formed and maintained will inform future advances in treatment practices. A large body of research has expanded our knowledge of how associative memories are acquired and consolidated, how they are updated through reactivation and reconsolidation, and how competing extinction memories are formed. This review will focus on the vast literature examining the mechanisms of cocaine Pavlovian associative memories with an emphasis on the molecular memory mechanisms and circuits involved in the consolidation, reconsolidation, and extinction of these memories. Additional research elucidating the specific signaling pathways, mechanisms of synaptic plasticity, and epigenetic regulation of gene expression in the circuits involved in associative learning will reveal more distinctions between consolidation, reconsolidation, and extinction learning that can be applied to the treatment of substance use disorders.

Keywords Learning · Addiction · Consolidation · Reconsolidation · Extinction

Introduction

Memories related to obtaining positive outcomes promote continued reward-seeking behavior that is important for survival. Unfortunately, when the outcome is a drug of abuse, these memories can become abnormally strong and maladaptive, thus promoting drug use over other behaviors. Even during abstinence, exposure to environmental cues associated with drug use can trigger memories that elicit craving, cause physiological stress, and initiate drug-seeking behaviors that lead to relapse [1–4]. Uncovering the mechanisms underlying the formation and retrieval of these drug memories may reveal ways to improve treatment and prevent relapse [5]. Much of the research focused on understanding the neural underpinnings of drug-associated memories has focused on memories formed during exposure to cocaine as the drug of abuse [6]. Cocaine use disorder remains a prominent burden on society, and cocaine use continues to increase [7]. Furthermore, there has been an increase in overdose deaths involving concomitant cocaine and heroin use [7]. Finally, identification of neural mechanisms relevant to cocaine memories likely can be applied to other drugs of abuse [6, 8]. Thus, in this review, we will focus on experiments specifically addressing Pavlovian associative memories between cocaine and environmental contexts and discrete cues because of the extensive literature examining the consolidation, reconsolidation, and extinction of these memories.

Types of cocaine memories

Memories about reinforcers often involve associations between the reinforcer and contextual or discrete environmental cues, information about the interoceptive effects or the value of the reinforcer, and information about behaviors that result in seeking and obtaining the reinforcer [3, 8, 9]. Drug memories can elicit cravings that promote continued use and relapse, but different types of memories may be differentially important depending on the type of drug used and

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the extent of drug use [3]. Moreover, these different types of cocaine associations may develop through different mechanisms and in different brain circuits, which is important to understand in order to optimize treatment development. With a focus on cocaine, we will briefly describe some of the types of memories that can contribute to drug-seeking behavior and relapse (Fig. 1).

Interoception and reward

Due to its direct effects on synaptic dopamine levels in brain regions associated with reward, cocaine is highly reinforcing [10]. Neurons in the ventral tegmental area (VTA) of the midbrain send dopaminergic projections to the nucleus accumbens (NAc), also referred to as the ventral striatum, which are important for reward-related prediction and learning [10]. Cocaine increases synaptic dopamine in the NAc and other brain regions, including the dorsal striatum, prefrontal cortex (PFC), and limbic regions, and dopamine's modulatory effects on neuronal activity influences both the rewarding effects of cocaine as well as reward-related learning [8, 10]. Due to its effects on the dopamine system, cocaine also produces several physiological effects, referred to as interoceptive effects, and associative memories between the use of cocaine and these rewarding/interoceptive effects are formed [11].

Pavlovian associations

In addition to interoceptive associative memories, Pavlovian associative memories can form between reinforcers and contextual or discrete environmental cues (also known as classical conditioning). Although these associations provide valuable information about the availability of natural reinforcers, environmental cues associated with cocaine use can lead to craving and relapse in individuals with substance use disorders [1]. Pavlovian associations are dependent on the basolateral amygdala (BLA), and contextual associations specifically appear to additionally rely on the hippocampus [6, 12]. These regions interact with each other, the PFC, and other sensory input regions to establish memory traces that can then promote drug using actions via outputs to the striatum when these cues and contexts are subsequently encountered [13].

Goal-directed instrumental learning (response–outcome associative learning)

When cocaine is self-administered, instrumental learning occurs alongside Pavlovian conditioning [14]. Initial learning of instrumental responses requires the formation of response–outcome associative memories that guide goal-directed behavior [15]. This process involves learning that

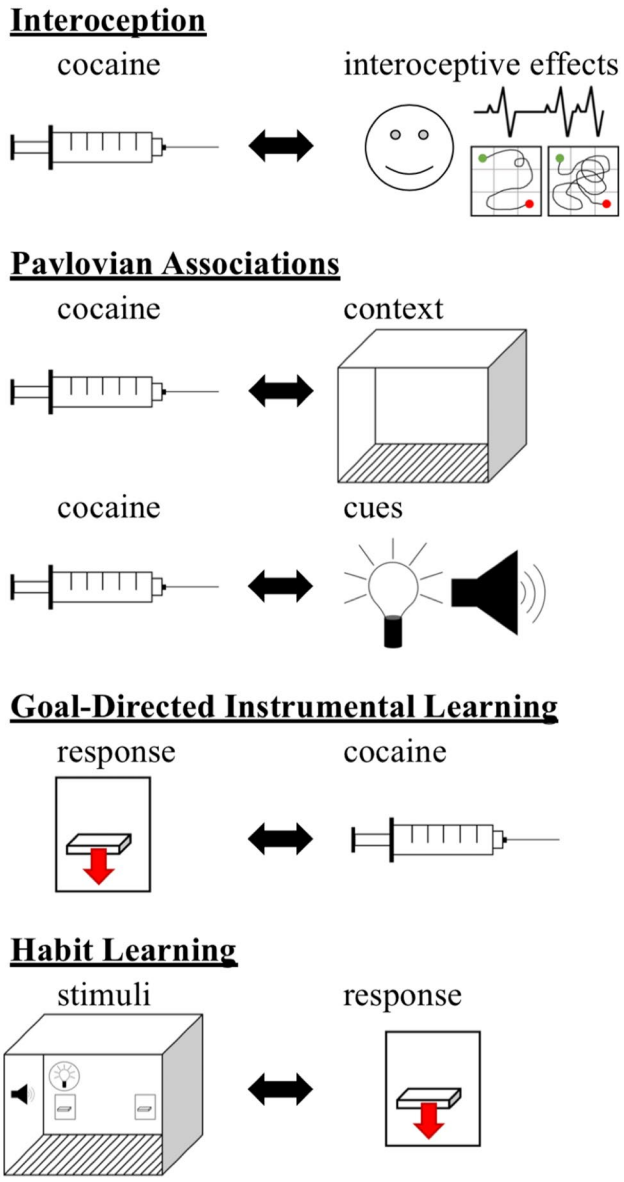

Fig. 1 Schematic illustrating the types of associative memories involved in cocaine-seeking behavior. Interoception involves associations between cocaine and its reinforcing and interoceptive effects, including increased heart rate and blood pressure, increased locomotor activity, and activation of brain regions associated with reward. Pavlovian conditioning results in associations between cocaine and discrete cues and/or the context in which cocaine is received. Goal-directed instrumental learning concerns the association between the instrumental response and cocaine, and habit learning concerns associations between contextual and discrete environmental stimuli and the instrumental response

an instrumental response or behavior results in delivery of the drug and its subsequent rewarding effects [16]. Goal-directed learning relies on cortico-striatal circuits that use contextual stimuli to detect reward availability and guide behavior [14]. The dorsomedial striatum (DMS) gets direct and indirect input from the PFC (particularly the prelimbic

region, PL) and the BLA to produce context-appropriate behavioral responses [14, 17, 18].

Habit learning (stimulus–response associative learning)

Under certain conditions, usually after significant repetition of the same action, a goal-directed behavior can shift to become a stimulus–response habit [15]. Once habits form, behavior no longer relies on the value of the outcome, but instead contextual or discriminative stimuli initiate a more automated behavioral response [19]. Acquisition of stimulus–response associative learning relies on the BLA, but the maintenance of habitual behavior depends on the central nucleus of the amygdala (CeN) [18]. Similarly to goal-directed behavior, learning habitual behavior requires changes in cortico-striatal circuitry, including a shift in the brain region mediating the behavior from the DMS to the dorsolateral striatum (DLS) [20, 21]. Although interoceptive, goal-directed, and habitual associative memory formation are important aspects of cocaine use and addiction, the most extensive knowledge about cocaine memory formation, reactivation, and extinction addresses Pavlovian associative memories, which will be the focus of this review.

Cellular and molecular mechanisms of memory

There are several cellular and molecular processes that underlie the formation and maintenance of cocaine memories. Generally, memory traces are formed when a combination of neuronal input and activity triggers cellular events that ultimately result in changes in protein expression, including changes in the membrane expression of receptors, neuronal morphology, and the excitability of cells. All of these forms of neuroplasticity can lead to changes in the way the neuron responds to inputs, thus allowing for the formation of a memory trace and the process of learning. Drugs, including cocaine, influence these natural memory processes [22]. For example, strong evidence exists for plasticity in corticolimbic circuits during cocaine Pavlovian memory formation, and suggests that these circuits are also activated during cocaine cue-induced craving, making them important targets for the treatment of cocaine use disorder [2, 13, 23, 24].

Memory formation requires changes in how neurons communicate. Long-term potentiation (LTP) and long-term depression (LTD) are activity-dependent mechanisms by which synapses can be strengthened or weakened [25]. These processes result in altered expression and localization of glutamate receptors and their subunits at the synapse, amongst other neurophysiological adaptations [26, 27]. Although LTP and LTD can be regulated by modulatory neurotransmitters such as dopamine, these processes occur at glutamatergic excitatory synapses, and rely on glutamate release from the presynaptic neuron along with temporally related post-synaptic depolarization [24, 28–30]. LTP and LTD are induced by activation of particular kinases and phosphatases that regulate the phosphorylation and activation of signaling molecules [31]. Typically, activation of protein kinases such as calcium/calmodulin-dependent protein kinase II (CaMKII), extracellular signal-regulated kinases (ERKs), and protein kinases A and C (PKA; PKC) is associated with LTP [31, 32]. Alternatively, activation of protein phosphatases like calcineurin (CaN) and protein phosphatase 1 (PP1) is associated with LTD [31, 32]. These proteins regulate the activity of downstream proteins, signaling molecules, and transcription factors [10, 28, 31, 32].

Immediate early genes (IEGs) are a subset of genes that experience increased transcription in response to neuronal activity and plasticity [33]. These genes, including *c-fos, BDNF* and *Zif268* encode proteins that are often used as neuronal markers of plasticity because of their reliable expression in neuronal ensembles that encode memory traces [33]. Although the direct roles of each IEG in neural plasticity have not been systematically characterized, they generally encode synaptic proteins, secretory proteins, and transcription factors that have a direct impact on synaptic properties, thus contributing to the formation of long-term plasticity [33]. Synaptic plasticity is also mediated by epigenetic modifications that regulate gene expression [34, 35]. Two important epigenetic processes involved in memory include DNA methylation, regulated by DNA methyltransferases (DNMTs) and demethylases, and histone acetylation, regulated by histone acetyltransferases (HATs) and histone deacetylases (HDACs) [34, 35]. All of these learning and memory processes have been implicated in cocaine memories.

Cocaine memory acquisition, consolidation, and retrieval

The molecular and circuit mechanisms involved in the acquisition of long-term memories, including several of the mechanisms discussed above, have been extensively studied and reviewed [36]. Once memories are acquired, they can undergo consolidation, a process of stabilization that lasts for hours or days by which cellular and molecular changes create a memory trace, or a physical representation in the brain (Fig. 2) [37]. These cellular and molecular changes include gene expression, protein phosphorylation and localization, DNA methylation, and histone acetylation [10, 22, 34, 35, 38] and occur within brain circuits involved in reward, memory, and action selection [10, 39, 40]. The acquisition and consolidation of cocaine memories can differ from memories for natural reinforcers, in part because the

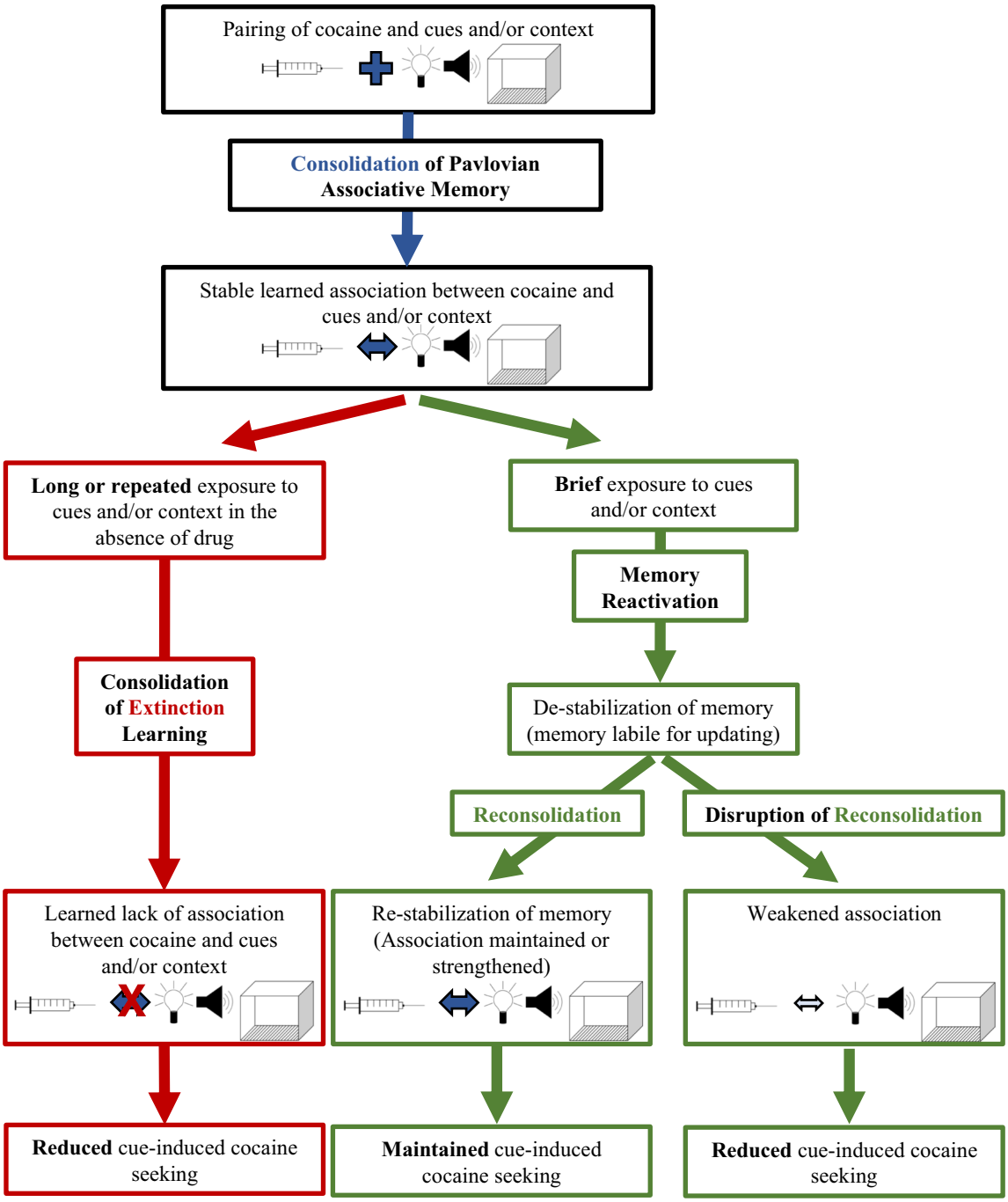

Fig. 2 Schematic demonstrating the consolidation (blue), reconsolidation (green), and extinction (red) of cocaine Pavlovian memories. The temporally paired delivery of cocaine with discrete and contextual cues results in the consolidation of the associative memory between cocaine and these cues. Once consolidated, this memory is stable. Long or repeated exposure to these cues results in extinction learning, which involves learning about the lack of association between cocaine and these cues and reduced cue-induced cocaine seeking. Alternatively, brief exposure to these cues results in reactivation of the previously consolidated associative memory, which is de-stabilized, allowing for potential updating of the memory. Under normal conditions, memory reactivation is followed by reconsolidation, and the memory is re-stabilized, resulting in maintenance of the associative memory and cue-induced cocaine seeking. If reconsolidation is disrupted, the association between the cues and cocaine is weakened, resulting in reduced cue-induced cocaine seeking

neurobiological effects of cocaine impact mechanisms of memory acquisition and consolidation, resulting in memories that can be maladaptive and hinder abstinence [9].

Memory acquisition and consolidation are separate processes that can be distinguished temporally. Experimental manipulations occurring before learning address acquisition,

while those occurring within minutes to hours after learning address consolidation [41]. However, it is important to note that experimental manipulations occurring before learning can still be in effect during the consolidation period, and may additionally affect consolidation.

Cocaine memory circuitry

Several brain regions interact to form cocaine-context and cocaine–cue associative memories because memory formation involves processing sensory information about contextual stimuli, detecting the rewarding effects of cocaine, directing attention, and forming reward-seeking behaviors. Corticolimbic circuitry is particularly involved in forming Pavlovian associations between stimuli and rewards, making these brain regions a nexus for cocaine–context and cocaine–cue associative learning [13, 42]. The dopaminergic reward circuitry and the striatum are also important for this type of associative learning [10, 39, 43, 44]. Below, we will discuss molecular mechanisms that occur in brain regions and circuits between these regions that contribute to Pavlovian associative memories between cocaine and contextual stimuli (Table 1).

Hippocampus

It is widely accepted that the hippocampus plays a major role in memory acquisition, and particularly the dorsal hippocampus (DHC) in contextual Pavlovian conditioning for drug memories [12]. Local inhibition of the DHC with muscimol prior to cocaine conditioned place preference (CPP) conditioning disrupts learning, affirming that the DHC is also important for the acquisition of contextual conditioning for cocaine [41]. Additionally, inhibition of the DHC impairs retrieval of a cocaine CPP memory [45]. The role of the DHC in cocaine memory consolidation is less clear. Although evidence suggests that the DHC is necessary for the consolidation of aversive contextual conditioning, inhibition of the DHC immediately or 6 h after cocaine CPP training does not disrupt learning, providing evidence that the DHC is not immediately essential for the consolidation of cocaine-context associations [41]. In contrast, inhibition of the DHC with muscimol 12 h after cocaine CPP conditioning impairs memory retention, indicating that neuronal activity in the DHC may be important for other memory storage processes or late-stage consolidation [46].

Epigenetic mechanisms in the DHC are also important for cocaine–context associative memory. Systemic administration of the HDAC inhibitor sodium butyrate prior to cocaine CPP conditioning leads to increased histone acetylation in the hippocampus, but not the amygdala, and improves later recall of cocaine–context associative memory [47]. These results suggest that histone acetylation plays a role in the acquisition or consolidation of these memories in the hippocampus. Additionally, injection of a DNMT inhibitor into the CA1 area of the hippocampus hindered acquisition of the cocaine–context associative memory, indicating that DNA methylation in the hippocampus is also important for acquisition [48].

Amygdala

Research involving fear-related associative learning suggests that whereas the DHC is particularly important for contextual associations, the BLA is important for both contextual and cue associations [12]. Evidence supports this dichotomy in the cocaine literature as well [47, 49]. Expression of a cocaine CPP memory is impaired by inhibition of protein synthesis or PKC in the BLA, indicating that both protein synthesis and PKC-mediated protein phosphorylation in the amygdala are necessary for cocaine-context memory retrieval [49]. Similarly, the consolidation and expression of cocaine CPP memory is impaired by inhibition of the protein kinase cyclin-dependent kinase 5 (cdk5) in the BLA [50]. Additionally, the BLA plays a critical role in the acquisition and consolidation of cocaine-cue (or cocaine-conditioned stimuli) associative memories. NMDA receptor antagonism in the BLA immediately before or after a cocaine-cue classical conditioning session inhibits the acquisition and consolidation of the cocaine–cue associative memory, respectively [51]. Pairing an audiovisual cue with cocaine infusions during self-administration compared to saline also leads to potentiation of projections from the MGN of the thalamus to the lateral amygdala, indicating that potentiation of synapses carrying auditory information about conditioned stimuli to the amygdala during drug use plays an important role in acquiring these associations [52]. Further investigation is required to determine if cocaine associative memory formation depends on intracellular signaling pathways and epigenetic mechanisms in the amygdala similar to those required for other associative memories [53, 54].

Prefrontal cortex

Cocaine memory acquisition, consolidation, and retrieval also rely heavily on the PFC and its corticolimbic circuit connections to the hippocampus and amygdala [13]. The PFC is thought to be important for action selection based on the value of goals, which is an essential aspect of drug-seeking behavior [10]. Chemogenetic inhibition of glutamatergic, but not GABAergic, neurons in the medial prefrontal cortex (mPFC) suppresses both the acquisition and expression of cocaine CPP, without affecting lithium chloride-induced conditioned place aversion, suggesting a unique role of excitatory transmission in the mPFC in reward–context associative memory acquisition and retrieval

Table 1 Summary of experiments addressing mechanisms of cocaine Pavlovian memory acquisition, consolidation, and expression

Paradigm	Brain region	Manipulation	Results	Species, age, sex	Citations
CPP	DHC	Inhibition with muscimol	Impaired acquisition, expression, and late-stage consolidation, but not early consolidation	Rat, adult, M; mouse, adult, M; rat, adult, M	Meyers et al. [41]; Hitchcock and Lattal [45]; Kramar et al. [46]
CPP	DHC	HDAC inhibitor	Enhanced acquisition and/or consolidation	Mouse, adult, M	Itzhak et al. [47]
CPP	DHC and PL	DNA methyltransferase inhibitor	Inhibition in the DHC restrained acquisition, inhibition in the PL blocked expression	Mouse, adult, M	Han et al. [48]
CPP	DHC	D1/D5 dopamine receptor antagonist	Impaired acquisition and expression, but not consolidation	Rat, adult, M	Kramar et al. [46]
CPP	DHC	D1 dopamine receptor agonist or antagonist	Agonist impaired and antagonist enhanced consolidation	Rat, adult, M	Kramar et al. [73]
CPP	DHC	β-adrenergic receptor antagonist	Impaired expression	Rat, adult, M	Otis and Mueller [76]
CPP	BLA	Protein synthesis, PKA, PKC, and MEK inhibitors	Inhibition of protein synthesis and PKC, but not PKA or MEK, blocked expression	Mouse, adult, M	Lai et al. [49]
CPP	Amygdala	Cdk5 inhibitor	Cdk5 inhibition in the BLA, but not CeA, inhibited consolidation and expression	Rat, adult, M	Li et al. [50]
Classical conditioning after self-administration	BLA	NMDA receptor antagonist	Inhibited acquisition and consolidation	Rat, adult, M	Feltenstein and See [51]
Self-admin	MGN-LA	n/a	Potentiation of projections from the MGN to the LA as associations form	Rat, adult, M	Rich et al. [52]
CPP	mPFC	Chemogenetic inhibition	Inhibition of glutamatergic, but not GABAergic, mPFC neurons suppressed acquisition and expression	Mouse, adult, M	Zhang et al. [55]
CPP	PL	Removal of perineuronal nets from interneurons	Impaired acquisition	Rat, adult, M	Slaker et al. [56]
CPP	mPFC	CB1 receptor antagonist	Consolidation of memory induced by high cocaine dose impaired, by low cocaine dose facilitated	Mouse, adult, M	Hu et al. [57]
CPP	NAc core	Rac inhibitor	Inhibited consolidation	Rat, adult, M	Ding et al. [58]
Self-admin	NAc	mTOR inhibitor	mTOR inhibition in the core, but not shell, impaired consolidation	Rat, adult, M	Wang et al. [59]
CPP	NAc	knockout of the histone acetyltransferase CBP	Prevented acquisition	Mouse, adult, M + F	Malvaez et al. [63]
CPP	NAc	Dephosphorylation of HDAC5 at S279	Impaired acquisition	Mouse, adult, M	Taniguchi et al. [62]
CPP	NAc	HDAC3 knockout	Enhanced acquisition	Mouse; adult, M + F	Rogge et al. [61]
CPP	NAc	Baf53B knockout (inhibits nucleosome remodeling)	Reduced acquisition and LTP	Mouse, adult, M + F	White et al. [64]

Table 1 (continued)

Paradigm	Brain region	Manipulation	Results	Species, age, sex	Citations
CPP	NAc	Chemogenetic inhibition	Inhibition of GABAergic neurons inhibited expression	Mouse, adult, M	Zhang et al. [65]
CPP	VTA	NMDA receptor antagonist	Impaired acquisition and expression	Rat, adult, M	Zhou et al. [72]
CPP	Systemic	Stress-induced noradrenergic activity leading to increased dopamine release in the mPFC	Attenuated acquisition and expression	Rat, adult, M	Shinohara et al. [74]
CPP	Systemic	β1-adrenergic receptor antagonist	Impaired expression	Rat, adult, M	Fitzgerald et al. [75]
CPP	Systemic	M1 receptor antagonist	Impaired consolidation	Mouse, adult, M	Zacarias et al. [77]

[55]. Although chemogenetic inhibition of GABAergic neurons in the mPFC does not affect cocaine CPP learning, these GABAergic neurons still play an important modulatory role [56]. Specifically, the removal of perineuronal nets, which are important for neural plasticity, from parvalbumin-containing, fast-spiking GABAergic interneurons in the PL impairs the acquisition of cocaine CPP [56]. Additionally, activity at CB1 receptors in the mPFC can bidirectionally modulate consolidation of cocaine CPP learning, with CB1 antagonism in the mPFC impairing CPP memory consolidation induced by higher doses of cocaine, but facilitating consolidation induced by lower doses [57]. Finally, inhibition of DNMTs in the mPFC impairs the expression, but not acquisition, of cocaine CPP, demonstrating a role of DNA methylation in the mPFC in the retrieval of cocaine–context associative memories [48].

Nucleus accumbens (NAc)

Dopaminergic activity in the NAc, particularly the shell region, has also been implicated in the consolidation of Pavlovian learning [8]. Moreover, numerous intracellular signaling processes in the NAc have also been implicated in cocaine-associative memory. For example, Rac, a regulator of actin dynamics and neural plasticity, is essential for the consolidation of cocaine CPP conditioning, and the kinase activity of mammalian target of rapamycin (mTOR) in the NAc core regulates the expression of cocaine–cue associations in a self-administration paradigm [58, 59]. In addition, epigenetic mechanisms play a role in cocaine memory formation [60]. Local knockout of the histone acetyltransferase CREB-binding protein inhibits cocaine CPP learning, and increased activity of HDAC5 in the NAc suppresses the acquisition of cocaine CPP, while local knockout of HDAC3 in the NAc enhances CPP acquisition, providing evidence that histone acetylation in the NAc is an important mechanism for cocaine–context associative learning [61–63]. In addition to histone acetylation, nucleosome remodeling in the NAc also appears to be essential, demonstrated by reduced LTP and cocaine CPP acquisition when nucleosome remodeling is inhibited [64]. Finally, chemogenetic inhibition of GABAergic neurons in the NAc prior to CPP testing reduces place preference, suggesting that the activity of GABAergic neurons in the NAc is also important, though this experiment did not differentiate between GABAergic interneurons and medium spiny neurons (MSNs) [65].

Dorsal striatum

When Pavlovian associations between cocaine and environmental stimuli form in a paradigm where the drug is obtained by operant self-administration, these associations guide the acquisition of the drug-seeking and drug-taking behavior [44, 66, 67]. Evidence suggests that while Pavlovian conditioning relies on the ventral striatum (NAc), as drug-seeking progresses, Pavlovian associations guide the formation of goal-directed and eventually habitual instrumental response strategies aimed at obtaining the drug [44, 66, 67]. Goal-directed drug-seeking depends on input to the DMS as well as corticolimbic circuits described above [20, 44, 66]. Under certain conditions, drug-seeking can become habitual, where the behavior is initiated by environmental stimuli without relying on the value of the outcome, and this behavior is dependent on dopaminergic input to the DLS [20, 66, 68]. Goal-directed cocaine-seeking and the acquisition of habitual cocaine-seeking are also reliant on functional connectivity between the BLA and DMS, and the performance of habitual cocaine-seeking behavior relies on multisynaptic functional connectivity between the CeN and the DLS [18]. Cue-controlled goal-directed and habitual drug seeking additionally continue to rely on corticolimbic circuits described above [18, 67, 69].

Modulatory systems

Modulatory neurotransmitter systems, such as the dopaminergic, noradrenergic, and cholinergic systems, affect neural plasticity and influence memory acquisition, consolidation, and expression [70, 71]. Drugs of abuse, including cocaine, increase dopamine concentrations at the synapse, which then alters memory formation processes throughout the reward circuitry, including the PFC, striatum, and limbic system [10]. The role of dopaminergic projections from the midbrain in reward-related learning and memory has been extensively reviewed previously, so a few representative studies are included here [10]. For example, one study showed that NMDA receptor activity in the VTA, which contains dopaminergic cell bodies, is necessary for both cocaine CPP memory acquisition and retrieval [72]. Furthermore, several studies suggest that VTA dopaminergic projections to the DHC are particularly critical for contextual learning related to drugs of abuse [10]. For instance, infusion of a D1/D5 dopamine receptor antagonist into the DHC before cocaine CPP conditioning impairs memory acquisition, and infusion before testing impairs retrieval, suggesting that dopaminergic input to the DHC is important for both the acquisition and retrieval of cocaine–context associative memories [46]. Alternatively, this input may be less important for consolidation, because D1/D5 antagonism immediately and 12 h after cocaine CPP conditioning did not impair learning [46]. Interestingly, administering a D1 receptor antagonist in the DHC 12 h after cocaine CPP conditioning actually extends the persistence of the cocaine–context associative memory, while administering a D1 agonist at this timepoint impairs later recall [73]. Together, these experiments suggest that dopaminergic input to the DHC is initially important for cocaine–context associative memory acquisition and for later retrieval and memory expression, but may actually hinder late-stage consolidation [46, 73].

In addition to dopamine, noradrenergic projections from the locus coeruleus regulate attention and vigilance, and therefore have a role in memory acquisition and retrieval [10]. Recent evidence suggests that stress-induced noradrenergic activity interacts with the VTA reward circuitry to increase dopamine release in the mPFC, augmenting cocaine CPP memory retrieval [74]. Systemic inhibition of β1-adrenergic receptors impairs the retrieval of cocaine-CPP memory, demonstrating an influence of adrenergic activity on memory expression [75]. More specifically, adrenergic input to the DHC also plays a role, as inhibition of β-adrenergic receptors in the DHC impairs the retrieval of cocaine CPP memories [76]. Finally, the neuromodulator acetylcholine is also implicated in the regulation of appetitive contextual memories, as systemic antagonism of M1 type muscarinic receptors disrupts cocaine CPP memory consolidation [77].

Effects of cocaine on memory systems

The circuitry described above is important for memory acquisition, consolidation, and expression, and has been particularly implicated in Pavlovian associative memories between cocaine and environmental cues and contexts. Because cocaine's effects on dopamine release influence the reward circuitry involved in endogenous reward learning and Pavlovian conditioning, it can enhance the formation of these memories and lead to aberrant learning that promotes behaviors characteristic of addiction [9]. Drugs of abuse, including cocaine, have behavioral, physiological, and molecular effects on learning and memory that have been extensively reviewed elsewhere [3, 9, 10, 22, 66]. Briefly, exposure to cocaine and other stimulants leads to persistent plastic changes in the circuits involved in reward and memory formation, and can also promote the formation of habits, which are thought to contribute to the development of the compulsive drug use characteristic of addiction [9, 78–81].

Cocaine memory reactivation and reconsolidation

After memories are acquired and undergo consolidation, they are believed to be stable and are resistant to amnestic agents [82]. However, memory retrieval, or reactivation, triggers a reconsolidation process during which memories are again labile and susceptible to manipulation (Fig. 2) [82, 83]. This reconsolidation process may serve the evolutionary purpose of allowing memories to be updated with new information, but it may also allow for the disruption of maladaptive drug-related memories [84–88]. There is considerable overlap between the molecular and circuit mechanisms that underlie original consolidation and subsequent reconsolidation, with processes including protein synthesis, transcription factors, protein kinases and phosphorylation, NMDA-receptor-mediated synaptic plasticity, and modulatory receptor activity [28, 83, 89]. However, there are distinctions between the consolidation and reconsolidation of memories, both in the molecular processes and brain regions involved [83, 90].

Disrupting reconsolidation

The period of lability a memory enters during reconsolidation has become a target for intervention in substance use disorders [91]. Because cocaine memories often promote drug craving and seeking, disrupting these memories could provide relief for people trying to maintain abstinence [87]. Much of the research about the reconsolidation of cocaine memories has investigated methods of reactivating cocaine memories, what processes are required for reconsolidation,

and how to then interfere with these processes in order to develop potential clinical treatments (Table 2).

Context reactivation

One method of preclinically investigating the reconsolidation of cocaine–context associative memories is by briefly re-exposing an animal to a cocaine-associated context [92]. This re-exposure can occur after either cocaine CPP conditioning or conditioned activity (CA), a paradigm in which Pavlovian associations between a psychostimulant and an environment produce increased locomotion when the animal is re-exposed to the environment without drug [92]. Although these methods can model subsequent retrieval of the cocaine-context associative memory through preference for the drug-paired chamber or presence of conditioned reactivity, they cannot evaluate subsequent drug-seeking behavior. Therefore, re-exposure to the context of drug self-administration after cocaine self-administration training has been used to evaluate both subsequent memory retrieval and drug-seeking behavior [52, 93–95]. Brief re-exposure to a cocaine-associated context triggers reactivation and reconsolidation (Fig. 2). Reconsolidation of a CPP and CA memories after context exposure are inhibited by systemic administration of NMDA receptor antagonists, β-adrenergic receptor antagonists, a muscarinic acetylcholine receptor antagonist, protein synthesis inhibitors, and kinase inhibitors, suggesting several of the processes involved in cocaine memory consolidation are also required for reconsolidation [92, 96–103]. The re-exposure to a context associated with cocaine self-administration also increases serum corticosterone concentrations, and this activation of the HPA axis may also play a role in memory reactivation and reconsolidation [104]. In addition, a role for dopamine modulation of the reward circuitry on reconsolidation is demonstrated by the observation that antagonism of dopamine D3 receptors, which are preferentially expressed in mesocortioclimbic regions, impaired reconsolidation of CPP memory [105]. Further, nitric oxide signaling, a retrograde messenger involved in the formation of memories through facilitation of synaptic plasticity, as well as NMDA receptor activity, is also important for reconsolidation after reactivation of cocaine contextual memory in the CPP paradigm [99, 106, 107].

Experiments involving region-specific interventions have revealed, unsurprisingly, that several of the brain regions important for cocaine-context memory consolidation are also involved in reconsolidation. Whereas the DHC is particularly important for the acquisition of these memories, its role in consolidation is somewhat ambiguous [41, 46–48]. However, the DHC plays a clear role in the reconsolidation of cocaine–context associative memories. Inhibition of excitatory pyramidal neurons in the DHC after cocaine-context memory reactivation impairs the reconsolidation of a cocaine CPP memory, and DNA demethylation by the methylcytosine dioxygenase tet3 plays an essential role in the epigenetic control of the post-retrieval activity of these neurons [108]. Additionally, inactivation of the DHC with tetrodotoxin after re-exposure to the context of cocaine self-administration reduced subsequent reinstatement in this context, suggesting the disruption of reconsolidation [95]. NMDA receptor-mediated plasticity in the DHC appears to be particularly important, as inhibition of SFK, a tyrosine kinase that regulates the phosphorylation of NMDA receptor subunits disrupts reconsolidation of a cocaine-self-administration contextual memory [109]. However, inhibition of protein synthesis in the hippocampus had no effect, indicating that regions other than DHC are responsible for the effects of broad protein synthesis-dependent reconsolidation events [95].

Indeed, inhibition of protein synthesis in the BLA after reactivation of the cocaine context memory blunted context-induced reinstatement of self-administration, suggesting that the BLA may be at least one region that requires protein synthesis for reconsolidation of these memories [110]. Additionally, activity of the protein kinase Cdk5 in the BLA is required for the reconsolidation of cocaine CPP memories just as it is required for consolidation, and PKA, but not CaMKII, activity is also required for the reconsolidation of the associative memory between cocaine and the context of self-administration [50, 93]. Other kinase activity in the BLA, including ERK and glycogen synthase kinase 3β (GSK-3β), are important for cocaine–context associative memory reconsolidation for self-administration and CPP, respectively, indicating that the mechanisms of plasticity regulated by these kinases play a role in reconsolidation in the BLA [111, 112]. Modulatory input to the BLA also influences reconsolidation, demonstrated by the ability of β-adrenergic receptor blockade to disrupt reconsolidation, but not retrieval, of cocaine CPP memories [113]. Interestingly, reconsolidations of cocaine–context associative memories for self-administration not only relies on the DHC and BLA individually, but functional disconnection of the two regions disrupts reconsolidation, indicating that interaction between the two regions is essential for cocaine–context associative memory reconsolidation [114].

Kinase activity in the NAc is also required for reconsolidation of cocaine–context associative memories. Inhibition of ERK in the NAc core region interferes with both the retrieval and reconsolidation of cocaine CPP memory by preventing the activation of several downstream transcription factors that regulate the expression of IEG-regulated proteins important for synaptic plasticity [115]. Additionally, expression of the IEG-regulated proteins Zif268 and Fos B is increased by cocaine CPP reactivation in several brain regions, including the NAc, amygdala, hippocampus,

Table 2 Summary of experiments addressing mechanisms of cocaine Pavlovian reconsolidation

Paradigm	Brain region	Manipulation	Results	Species, age, sex	Citations
CPP or CA, context reactivation	Systemic	NMDA receptor antagonist	Impaired reconsolidation	Rat, adult, M	Alaghband et al. [92] and Brown et al. [107]; Alaghband et al. [96]
CA, context reactivation	Systemic	Protein synthesis inhibitor	Impaired reconsolidation	Rat, adult, M	Bernardi et al. [101]
CPP, context reactivation	Systemic	β-adrenergic receptor antagonist; protein synthesis inhibitor; nNOS inhibitor; GSK3 inhibitor; D3 dopamine receptor antagonist	Impaired reconsolidation	Rat, adult, M; mouse, adult, M; mouse, adult, M; mouse, adult, M; mouse, adult, M + F	Fricks-Gleason et al. [97] and Bernardi et al. [102]; Fan et al. [98]; Itzhak et al. [99]; Shi et al. [103]; Yan et al. [105]
CPP, context reactivation	Systemic	muscarinic receptor antagonist, NMDAR antagonist, or NMDAR partial agonist	Impaired reconsolidation (or enhanced extinction)	Mouse, adult, M	Kelley et al. [100]
CPP, context reactivation	DHC	Chemogenetic inhibition or Tet3 knockdown in pyramidal neurons	Impaired reconsolidation	Mouse, adult, M	Liu et al. [108]
Self-admin, context reactivation	DHC	Inactivation with tetrodotoxin or protein synthesis inhibitor; SFK inhibitor	Only inactivation with tetrodotoxin impaired reconsolidation; impaired reconsolidation	Rat, adult, M	Ramirez et al. [95]; Wells et al. [109]
Self-admin, context reactivation	DHC	SFK inhibitor	Impaired reconsolidation	Rat, adult, M	Wells et al. [109]
Self-admin, context reactivation	BLA	Protein synthesis inhibitor	Impaired reconsolidation	Rat, adult, M	Fuchs et al. [110]
CPP, context reactivation	Amygdala	Cdk5 inhibitor	Inhibition in BLA, but not CeA, impaired reconsolidation	Rat, adult, M	Li et al. [50]
Self-admin, context reactivation	BLA	PKA or CaMKII inhibitor; ERK inhibitor	PKA and ERK, but not CaMKII inhibition impaired reconsolidation;	Rat, adult, M	Arguello et al. [93]; Wells el. al [111]
CPP, context reactivation	BLA	GSK-3β inhibitor	Impaired reconsolidation	Rat, adult, M	Wu et al. [112]
CPP, context reactivation	BLA	β-adrenergic receptor antagonist	Impaired reconsolidation, not expression	Rat, adult, M	Otis et al. [113]
Self-admin, context reactivation	BLA/DHC	Unilateral protein synthesis inhibitor in BLA and contralateral inhibitor on DHC	BLA-DHC disconnection impaired reconsolidation	Rat, adult, M	Wells et al. [114]
CPP, context reactivation	NAc core	MEK (ERK kinase) inhibitor	Impaired reconsolidation	Rat, adult, M	Miller and Marshall [115]
CPP, context reactivation	NAc shell	NMDA receptor antagonist or D1 dopamine receptor antagonist	Impaired reconsolidation	Rat, adult, M	Li et al. [116]
CPP, context reactivation	PL	cAMP pathway inhibitors	Impaired reconsolidation	Rat, adult, M	Otis et al. [118]
CPP, context reactivation	mPFC	histone lysine demethylase inhibitor	Impaired reconsolidation	Mouse, adult, M	Zhang et al. [119]

Table 2 (continued)

Paradigm	Brain region	Manipulation	Results	Species, age, sex	Citations
Self-admin, cue reactivation	Systemic	HAT inhibitor; β-adrenergic receptor antagonist or protein synthesis inhibitor	Impaired reconsolidation; only protein synthesis inhibitor impaired reconsolidation	Rat, adult, M	Monsey et al. [120]; Dunbar and Taylor [121]
Self-admin, cue reactivation	BLA	Zif268 knockdown; DNMT inhibitor; PKA inhibitor; Epac activator; CaMKII inhibitor	Impaired reconsolidation	Rat, adult, M	Lee et al. [94, 125]; Shi et al. [122]; Sanchez et al. [123]; Wan et al. [124]; Rich et al. [126]
Self-admin, response-contingent cue reactivation	Systemic	β-adrenergic receptor antagonist	Impaired reconsolidation	Rat, adult, M	Milton et al. [130]
Self-admin, response-contingent cue reactivation	Systemic, IL, or NAc	NMDA receptor antagonists	Impaired reconsolidation	Rat, adult, M	Hafenbreidel et al. [128]
Self-admin, response-contingent cue reactivation	Systemic or BLA	NMDA receptor antagonist	Impaired reconsolidation	Rat, adult, M	Milton et al. [129]
Self-admin, response-contingent cue reactivation	Systemic	D1 or D3 dopamine receptor antagonist	Impaired reconsolidation	Mouse, adult, M + F	Yan et al. [132]
Self-admin, US reactivation	Systemic	HAT inhibitor	Impaired reconsolidation	Rat, adult, M	Dunbar and Taylor [135]

PFC, and VTA [116]. This upregulated expression in the NAc shell in response to contextual memory reactivation was reduced by the infusion of NMDA or dopamine D1 receptor antagonists, which also disrupted reconsolidation, suggesting the activation of these receptors and subsequent IEG protein expression in the NAc is a necessary mechanism for reconsolidation [116]. Finally, reconsolidation of CPP memories is also dependent on protein degradation in the NAc [117].

Other mechanisms appear to regulate the reconsolidation of cocaine–context associative memories in the PFC. Particularly in the PL, cocaine CPP training increases the intrinsic excitability of pyramidal neurons [118]. This plasticity is positively correlated with memory retrieval, and prevention of this plasticity interferes with the reconsolidation of these memories [118]. Additionally, reconsolidation of CPP memories involves histone methylation-mediated regulation of synaptic plasticity in the mPFC [119].

Cue reactivation

Associative memories between cocaine and discrete cues, such as an audiovisual cue presented during infusion of cocaine in a self-administration paradigm, undergo similar consolidation and reconsolidation processes as contextual cues, though in some instances the brain regions and molecular mechanisms regulating cocaine-cue memories do differ from cocaine–context memories. Cocaine cue memories can also be reactivated with brief re-exposure to the cues, and disrupting the reconsolidation of these cocaine–cue associations learned during self-administration leads to reduced cue-induced cocaine-seeking behavior, which is thought to model a reduction in cue-induced drug craving [5, 28, 120]. The reconsolidation of these cocaine-cue associative memories is disrupted by both inhibition of protein synthesis or inhibition of HATs, but contrary to consolidation, reconsolidation does not appear to rely on the activity of β-adrenergic receptors [120, 121]. Just as in cocaine-cue associative memory consolidation, the BLA is the main site of reconsolidation of these memories. Several molecular substrates of plasticity are required in the BLA for reconsolidation of cocaine–cue associative memories, including protein synthesis, DNA methyltransferase, calcium-calmodulin dependent kinase II (CaMKII), and cAMP signaling that regulates downstream PKA and exchange protein activated by cAMP (Epac) activity [94, 122–126]. Additionally, reactivation of cocaine-cue associative memories results in increased phosphorylation of several proteins in the BLA and NAc, providing further evidence that mechanisms of plasticity involving phosphorylation cascades are required [127].

In addition to simply using brief cue re-exposure to reactivate cocaine–cue associative memories, some experiments have used response-contingent cue presentations in

the context of self-administration, in which cues, but no drug, are presented in response to active lever presses in the self-administration context [128–132]. Although it is difficult to differentiate between effects of cocaine–context memory reactivation, cocaine-cue memory reactivation, and instrumental responding in these experiments, they still provide additional information about the molecular mechanisms and circuits involved in reconsolidation of reactivated cocaine memories. When cocaine memories are reactivated in this way, β-adrenergic receptor blockade disrupts reconsolidation [130]. This effect is likely primarily due to disruption of the cocaine–context associative memory, because evidence suggests that β-adrenergic receptor blockade effectively disrupts reconsolidation of cocaine-context, but not cocaine-cue, associative memories [97, 102, 121]. In addition, NMDA receptor blockade in the infralimbic region of the mPFC or in the BLA disrupts reconsolidation after memory reactivation by this brief, response-contingent cue exposure paradigm, further implicating these regions in cocaine memory reconsolidation [128, 129]. Furthermore, both dopamine D1 and D3 receptor blockade can disrupt reconsolidation and reduce subsequent cue-induced reinstatement, supporting a role of the dopamine modulatory system in the reconsolidation of cocaine-cue memories [132].

Unconditioned stimulus (US) reactivation

Due to the fact that brief exposure to a CS selectively destabilizes the memory of the association between the US and that CS, disruption of reconsolidation only affects the reactivated cue [120, 133]. Thus, cue reactivation may have limited clinical potential because of the vast number of cocaine-associated cues and contexts that likely exist for human substance users [120, 134, 135]. However, evidence from both the fear conditioning and the drug self-administration literature suggest that reactivation of the unconditioned stimulus, or US, can destabilize multiple US–CS associations, making this a potentially more effective target for disrupting a sufficient number of cocaine-associated memories to reduce relapse [134–137]. As previously described, inhibition of HATs after reactivation of cocaine-cue associative memory by brief cue presentation selectively reduces subsequent reinstatement mediated by the reactivated cue [120, 135]. Alternatively, systemic HAT inhibition after cocaine memory reactivation with a priming dose of cocaine disrupts the reconsolidation of cocaine's association to multiple cues, resulting in reduced cue-induced reinstatement to non-reactivated cues [135]. To date, little other research has investigated mechanisms for disrupting cocaine memories after US reactivation, leaving this as an important for future studies.

Reconsolidation and distinctions from consolidation

Overall, several of the molecular mechanisms and neural circuits involved in memory consolidation are also important for the reconsolidation of cocaine–context Pavlovian associative memories, including kinase activity, NMDA-receptor mediated plasticity, expression of IEG proteins, neuromodulation, and epigenetic modifications [92–94, 102, 135]. However, there are some distinctions in the mechanisms of plasticity involved between the two processes and in their reliance on different brain regions. For example, although the role of DHC activity is not immediately necessary for consolidation of cocaine–context associations, DHC inhibition does impair reconsolidation of cocaine–context associations [41, 108]. Although there are few direct comparisons between consolidation and reconsolidation of cocaine associative memories, evidence from literature examining the consolidation and reconsolidation of other associative memories suggests that older memories are more resistant to disruption of reconsolidation than disruption of consolidation and that memories being consolidated may take longer to stabilize than memories being reconsolidated [83]. Additionally, evidence suggests that in the hippocampus, BDNF is required for consolidation, but not reconsolidation, of fear conditioning [90]. Alternatively, Zif268 is required for reconsolidation, but not consolidation [90]. Taken together, these results support dissociable mechanisms regulating consolidation and reconsolidation.

Clinical applications of reconsolidation disruption

Many of the studies investigating reactivation of cocaine memories and the disruption of their reconsolidation have identified several plasticity mechanisms, signaling cascades, and neurotransmitter systems that may be potential targets for use in the treatment of substance use disorders, which have been extensively reviewed [91, 138–141]. For example, a study showing that systemic inhibition of β-adrenergic receptors with propranolol could somewhat disrupt reconsolidation following reactivation of cocaine-cue associative memory provides evidence that this may be an effective treatment option [142]. Additionally, a meta-analysis of the few clinical experiments examining the disruption of memory reconsolidation to treat substance use disorders produced moderately encouraging results [91]. In these experiments, participants dependent on or currently using substances of abuse including alcohol, cocaine, heroin, or nicotine underwent memory reactivation by exposure to drug-associated cues [91, 142]. Following reactivation, pharmacological, and behavioral interventions were performed, such as delivery of NMDA receptor antagonists, counter-conditioning, or extinction [91]. Findings from these clinical experiments are

modest, indicating that these methods may need to be improved upon to effectively treat substance use disorders in humans [91, 142]. Preclinical evidence suggests that during reconsolidation of reactivated cocaine–context associative memories, these memories may additionally be more susceptible to counter-conditioning, providing another avenue for improving clinical treatments [138]. Still, several reasonable concerns have been raised about the ethical challenges posed by these types of treatments, which could cause stress, harm, or increased risk of relapse if treatment is not effective, and these concerns will need to be carefully considered as knowledge is gained from preclinical examination of reconsolidation and is translated into clinical practice [141].

Cocaine memory extinction

Memory retrieval can not only initiate reconsolidation of that memory, but can also initiate a process known as extinction. Extinction learning occurs when a memory is repeatedly retrieved in the absence of the expected outcome. After extinction learning, the previously formed associative memories are less likely to guide behavior [143]. Although extinction was initially interpreted as erasure of learning, ample memory phenomena contradict this idea, including spontaneous recovery (the recovery of an extinguished memory with time), renewal (the re-expression of the original memory outside of the extinction context, and reinstatement (the re-expression of the original memory when the outcome is experienced again) [143]. Therefore, extinction of associative memories is generally accepted as a process that involves new learning about a lack of association, and these new memories compete with previously learned associative memories to guide behavior (Fig. 2) [5, 87, 143]. Because extinction involves the formation of new memories, it is not surprising that many of the mechanisms involved in initial memory consolidation and reconsolidation are also required for extinction learning [144], but there are also several distinctions between these processes [145, 146].

Extinction can involve several types of learning. The molecular mechanisms of instrumental extinction, which describes the learning of a lack of association between a behavioral response and its outcome, have been thoroughly investigated in preclinical models of drug self-administration [3, 39]. Although it is a valuable tool for investigating subsequent cue-induced and cocaine-primed reinstatement of drug-seeking behavior, it is outside the scope of this review's focus on Pavlovian cocaine memories. Therefore, we will focus on the molecular and circuit mechanisms of the extinction of Pavlovian associations (Table 3).

Pavlovian extinction

Although brief re-exposure to a cocaine-paired context or discrete cue reactivates a memory and triggers reconsolidation, extended or repeated exposure to these stimuli without cocaine reinforcement initiates extinction learning [5, 87]. The cocaine–context association can be extinguished in a cocaine CPP model by extended exposure to the cocaine-paired compartment without cocaine, which reduces preference for the cocaine-paired chamber [45, 87, 147]. Similarly, for cocaine self-administration, extended exposure to the context of self-administration can extinguish the cocaine–context association and lead to subsequently reduced drug-seeking behavior [148]. Additionally, in self-administration paradigms, repeated exposure to the cocaine-paired discrete cue results in a learned lack of association between cocaine and the cue [52, 87, 149]. Subsequently, reinstatement of drug-seeking behavior in response to cue exposure is attenuated [52, 149, 150]. Investigation of extinction learning has revealed several molecular mechanisms necessary for this memory process.

Context extinction

Because of the divergent mechanisms involved in Pavlovian cocaine–context and cocaine–cue associations, we will separately discuss the processes involved in the extinction learning of these associative memories. Given the DHC's well-established role in cocaine-context associations, it is not surprising that inactivation of the DHC inhibits both CPP extinction learning and retrieval of a previously learned extinction memory [45]. Glutamate-dependent neuroplasticity also plays a clear role, as evidenced by the ability of systemically administered D-serine and DCS, which both facilitate NMDA receptor signaling through activation of the glycine modulatory site [151–154], to facilitate the extinction of cocaine-context associative memories in both CPP and self-administration paradigms [147, 152–154]. Additionally, the mGluR5 receptor (which is coupled to NMDA receptors) plays a role in extinction of cocaine–context associations in both a CPP and self-administration paradigm [148, 155].

More specifically, NMDA receptor activity in the PFC appears to play an important role in the extinction of cocaine–context associative memories. Systemic or mPFC-specific activation of NMDA receptors enhances extinction [156], and inhibition of vmPFC pyramidal neurons inhibits CPP extinction learning [157]. In the infralimbic (IL) region of the PFC, enhancement of GluN2B NMDA receptor activity by brain-derived neurotrophic factor (BDNF) activation of the tropomyosin-related kinase B (TrkB) signaling cascade facilitates extinction learning [158]. Furthermore, IL activation of β-adrenergic signaling and the β-arrestin

Table 3 Summary of experiments addressing mechanisms of cocaine Pavlovian extinction

Paradigm	Brain region	Manipulation	Results	Species, age, sex	Citations
CPP, context extinction	Systemic	Partial NMDA receptor agonist	Enhanced extinction	Rat, adult, M; mouse, adolescent, M	Hammond et al. [151]; Paolone et al. [153]; Thanos et al. [147]
Self-admin, context extinction	Systemic	Partial NMDA receptor agonist	Enhanced extinction	Mouse, adolescent, M	Thanos et al. [154]
Self-admin, context extinction	Systemic	mGlu5 glutamate receptor negative allosteric modulator	Impaired extinction	Rat, adult, M	Kim et al. [148]
CPP, context extinction	Systemic	mGlu5 glutamate receptor positive allosteric modulator	Enhanced extinction	Rat, adult, M	Gass and Olive [155]
CPP, context extinction	DHC	Inactivation with muscimol	Impaired extinction and expression of extinction	Mouse, adult, M	Hitchcock and Lattal [45]
CPP, context extinction	Systemic or BLA	Partial NMDA receptor agonist	Enhanced extinction	Rat, adult, M	Botreau et al. [152]
CPP, context extinction	Systemic or mPFC	NMDA receptor activation	Enhanced extinction	Mouse, adult, M	Tsai et al. [156]
CPP, context extinction	vmPFC	Optogenetic inhibition	Impaired extinction	Mouse, adult, M	Van den Oever et al. [157]
CPP, context extinction	IL	TrkB agonist	Enhanced extinction	Rat, adult, M	Otis et al. [158]
CPP or self-admin, context extinction	IL	β-adrenergic receptor antagonist	Impaired extinction	Mouse, adult, M	Huang et al. [159]
CPP, context extinction	PL	D1 dopamine receptor overexpression	Enhanced extinction	Rat, juvenile, M + F	Brenhouse et al. [160]
CPP, context extinction	Systemic	D3 dopamine receptor antagonist	Enhanced extinction	Mouse, adult, M	Ashby et al. [161]; Galaj et al. [162]
CPP, context extinction	Global	D4 dopamine receptor antagonist	Impaired extinction in females	Mouse, adult, M + F	Ananth et al. [163]
CPP, context extinction	NAc	Optogenetic stimulation or inhibition of ChAT interneurons	Activation enhanced extinction, inhibition suppressed extinction	Mouse	Lee et al. [165]
CPP, context extinction	Systemic	NPY inhibitor	Enhanced extinction	Mouse, M	Sørensen et al. [166]
CPP, context extinction	Systemic	HDAC or HDAC3 inhibitor; HDAC inhibitor	HDAC3 and HDAC inhibition at a low dose enhanced extinction; HDAC inhibition at a high dose impaired extinction	Mouse, adult, M	Malvaez et al. [167, 168]; Raybuck et al. [169]
Self-admin, cue extinction	n/a	n/a	Cue extinction reduces cue-induced reinstatement	Rat, adolescent and adult, M	Madsen et al. [149]
Self-admin, cue extinction	Systemic; NAc	mGluR5 antagonist; NMDA receptor antagonist	Impaired extinction	Rat, adult, M	Perry et al. [172]; Torregrossa et al. [171]
Self-admin, cue extinction	MGN-LA	n/a	Cue extinction induces LTD	Rat, adult, M	Rich et al. [52]
Self-admin, contingent extinction	rBLA, dSUB, or IL	Protein synthesis inhibitor	rBLA and dSUB, but not IL, inhibition impaired extinction	Rat, adult, M	Szalay et al. [174]

Table 3 (continued)

Paradigm	Brain region	Manipulation	Results	Species, age, sex	Citations
Self-admin, contingent extinction	rBLA and dSUB	Disconnection (unilateral, contralateral inhibition with lidocaine)	Impaired extinction	Rat, adult, M	Szalay et al. [175]
Self-admin, contingent extinction	BLA and PL	n/a	Increased c-Fos expression after contingent extinction	Rat, M	Dhonnchadha et al. [176]
Self-admin, contingent extinction	Systemic	Partial NMDA agonist	Enhanced extinction	Mouse, adult, M; rat, adult, M; rat and squirrel monkey, adult, M	Thanos et al. [154]; Thanos et al. [178]; Dhonnchadha et al. [177]
Self-admin, contingent extinction	vmPFC, BLA, NAc, DHC	n/a	Total expression of GluA1 increased in the vmPFC and decreased in the BLA, and GluA1 phosphorylation increased in the vmPFC and NAc	Rat, adult, M	Dhonnchadha et al. [179]
Self-admin, contingent extinction	NAc shell, core, and DLS	n/a	Altered synaptosomal GluR1, NMDAR1, PICK1, and PSD95; altered synaptosomal mGluR5	Rat, adult, M; Rat	Ghasemzadeh et al. [180]; Ghasemzadeh et al. [181]

cascade, which facilitates ERK activation, promotes extinction learning [159].

In addition to the IL, the dorsally located prelimbic (PL) PFC has also been shown to regulate the extinction of cocaine–context memories. For example, overexpression of dopamine D1 receptors in the PL in juvenile male rats facilitates CPP extinction learning, and because the D1 receptor increases neuronal activity through the activation of PKA, these results suggest that increased excitability of PL neurons promotes extinction learning [160]. However, the dopamine system may regulate extinction differentially based on brain region, as systemic selective D3 antagonism can also enhance CPP extinction [161, 162]. Moreover, there may be sex differences in how the dopamine system regulates extinction, as knockout of the D4 receptor in females inhibits extinction learning, while knockout in males reduces cocaine-primed reinstatement of CPP memory [163]. These results indicate subtleties in the effects of dopamine on extinction learning and suggest that dopamine receptors positively coupled to adenylyl cyclase (i.e., D1) promote extinction, while receptors negatively coupled to adenylyl cylcase (i.e., D3 and D4) generally oppose extinction learning [164].

In addition to dopamine, other modulatory neurotransmitters are involved in extinction of cocaine–context associations. First, cholinergic interneurons regulate the plasticity of excitatory synapses onto NAc MSNs that occurs during CPP extinction learning [165]. Additionally, systemic inhibition of neuropeptide Y (NPY) facilitates extinction learning and protects against cocaine-priming induced reinstatement without affecting CPP learning [166]. Finally, epigenetic mechanisms of cocaine–context extinction learning have been identified. For example, nonspecific HDAC and specific HDAC3 inhibition enhance extinction [167, 168]. However, higher doses of HDAC inhibitors may inhibit extinction, suggesting possible dose-dependent effects of histone acetylation or off target effects of the inhibitors [169].

Cue extinction

Cue extinction involves repeated exposure to drug-associated discrete cues in order to extinguish drug–cue associations. This procedure allows for the subsequent evaluation of cue-induced drug-seeking behavior in self-administration paradigms. Interestingly, compound cue extinction, or the presentation of multiple cocaine-associated discrete cues simultaneously, leads to reduced spontaneous recovery of cocaine seeking, suggesting there may be an advantage of simultaneously extinguishing multiple drug–cue associations [170]. In both adolescent and adult rats, cue extinction after cocaine self-administration or 1 week into abstinence reduces cue-induced reinstatement for up to 30 days of abstinence [149].

Several studies have shown that glutamate receptor activity-dependent plasticity is necessary for cue extinction learning. Inhibition of NMDA receptors in the NAc inhibits cue extinction learning [171]. Additionally, systemic inhibition of the mGlu5 receptor inhibits cue extinction learning [172]. Furthermore, plasticity in the lateral amygdala, which has been repeatedly implicated in Pavlovian cue associations, appears to be a critical locus for cue extinction learning [52]. Specifically, cue extinction induces LTD at thalamo-lateral amygdala synapses, and this LTD accompanies reduced cue-induced reinstatement of cocaine-seeking behavior [52]. To further support the role of thalamo-amygdala synaptic plasticity in cue extinction, optogenetic induction of depotentiation of synapses in the LA receiving inputs from the MGN of the thalamus was found to mimic the physiological and behavioral effects of cue extinction [52].

Response-contingent cue extinction

In several experiments, extinction sessions occur in which cues are presented contingently in response to lever presses without the delivery of cocaine. Although it is difficult to disentangle the effects of cue extinction learning and instrumental extinction learning in these experiments, they may provide additional insights into the extinction of cocaine–cue associations. Not surprisingly, evidence suggests that response-contingent cue extinction may be more effective than cue extinction alone [173].

Inhibition of protein synthesis in the rostral BLA and dorsal subiculum (dSUB) of the hippocampus immediately after contingent cue extinction reduces extinction learning [174]. Additionally, functional disconnection of these regions by contralateral unilateral inhibition also reduces extinction learning, suggesting a role of protein synthesis in and interaction between the BLA and hippocampus during extinction learning [174, 175]. Additionally, response-contingent cue extinction increases c-Fos expression in the BLA and PL, suggesting increased neuronal activity in these areas during extinction learning [176]. NMDA receptor partial agonism with DCS augments consolidation of response-contingent cue extinction learning in mice, rats, and squirrel monkeys [154, 177, 178]. Contingent cue extinction also causes changes in the expression of the GluA1 AMPA receptor in the BLA and ventromedial PFC (vmPFC) and changes in phosphorylation in the vmPFC and NAc, but no changes in the DHC [179]. Contingent cue extinction leads to altered synaptic localization of glutamate receptor subunits and scaffolding proteins in the NAc and DLS [180, 181]. Overall, these results implicate the BLA, hippocampus, PFC, and NAc in response-contingent cue extinction. Particularly, glutamate-related neural plasticity in several of these regions appears to be important for response-contingent cue extinction learning [179].

Clinical applications of Pavlovian extinction

There are multiple challenges in the application of Pavlovian extinction to clinical practice [182]. Despite strong preclinical support for the use of Pavlovian extinction to reduce cue-induced reinstatement, cue exposure therapy has shown mixed results for reducing relapse to cocaine and other drug use [182, 183]. In these experiments, participants with histories of drug use were exposed to drug-associated cues repeatedly, often in multiple sessions, in an attempt to replicate preclinical findings that these exposures can extinguish drug–cue associations [182, 183]. Meta-analyses indicate that cue exposure treatments have only been modestly successful and point to potential areas of improvement [182, 183]. One prominent challenge is that its affects appear to be context specific, limiting the efficacy of cue extinction outside the clinic [150, 184, 185]. Systemic and intra-NAc core partial NMDA receptor agonism with DCS after cue extinction reduces the context specificity of cue extinction for cocaine-associated cues in rodents [150]. This is likely due to enhanced extinction, and indicates a possible avenue for overcoming the context specificity of cue extinction [150, 171]. Still, the use of DCS to enhance the effects of cue exposure therapy has not yielded promising results, suggesting other or additional strategies may be necessary [186–188].

Several other obstacles exist, including targeting extinction without inducing and enhancing reconsolidation, particularly because the two processes rely on very similar mechanisms [87]. Evidence from preclinical research suggests that compounding a cocaine-associated cue with a food-associated cue in cue extinction may interfere with cue extinction, so care should be taken to prevent this effect in clinical studies [189]. Finally, sex differences in these mechanisms are largely understudied. 17β-estradiol is important for extinction learning in females, suggesting sex differences and hormone levels may be important considerations for clinical application [190].

Conclusions and future directions

Memory mechanisms that allow for natural reward-related learning can become maladaptive in the formation of substance use disorders [3, 9]. Not only do drugs affect normal memory processes, but drug-associated memories can contribute to craving and relapse [6, 9, 22]. A large body of research has focused on the molecular and circuit mechanisms involved in cocaine-related Pavlovian associations. This research has uncovered memory mechanisms involving activity-dependent neural plasticity, phosphorylation and signaling molecules, expression of IEGs, and epigenetics that occur in various brain regions associated with

reward-related learning, particularly corticostriatolimbic circuitry. These findings have contributed toward advances in the clinical treatment of substance use disorders, but many challenges still impede the efficacy and development of treatment options.

Age and sex considerations

Almost all of the preclinical experiments reviewed above were conducted exclusively in adult, male rodents. Therefore, little is known about how consolidation, reconsolidation, and extinction of drug–cue associative memories changes throughout development and differs between sexes. Evidence suggests that adolescents are more sensitive to cocaine reward and less susceptible to extinction [191–193]. Adolescent rats are quicker to acquire, take more, and have more inelastic economic demand for cocaine during self-administration than adults [191, 194]. Additionally, adolescent rats are less sensitive to negative consequences when self-administering cocaine compared to adults [192]. In both adolescents and adults, females acquire self-administration more quickly and show a higher demand for cocaine under progressive ratios [194, 195].

These differences in the rewarding effects of cocaine may result in altered formation of Pavlovian associations between cocaine and cues. Age and sex have a clear effect on cocaine–context associations formed in CPP learning, where females and adolescents tend to be more sensitive to CPP than males and adults, and adolescents are more resistant to extinction and adolescents and females are more susceptible to reinstatement [193, 196–198]. There are also established sex differences in cocaine-cue-induced fos expression and cue-induced reinstatement of cocaine-seeking, and some of these sex differences may be attributed at least in part to differential effects of gonadal hormones [199, 200]. Despite extensive knowledge of sex and age effects on the reinforcing properties of cocaine and the formation and persistence of cocaine-context associations, little is known about their impact on the cellular and molecular mechanisms of Pavlovian memory consolidation and reconsolidation, making this an important avenue for future research.

Combining strategies for treatment

As discussed above, there are several similarities between the molecular mechanisms and neural circuits involved in the consolidation, reconsolidation, and extinction of cocaine memories. Targeting these processes may provide novel strategies for the treatment of cocaine use disorders as well as other substance use disorders. Particularly, both the disruption of reconsolidation and facilitation of extinction learning have shown promising results preclinically. However, applying these concepts to clinical practice has been more challenging. As with treatments for other psychiatric disorders, it is likely that the most effective treatments for substance use disorders will involve a combination of strategies.

One interesting proposal is the combination of extinction learning with reconsolidation disruption in a paradigm termed retrieval-extinction. The effects of performing extinction during the reconsolidation window after retrieval of drug–cue and other associative memories have been extensively reviewed [201–203]. Preclinical evidence shows that cocaine CPP context extinction following reactivation of the cocaine–context associative memory further inhibits cocaine-primed CPP reinstatement, and retrieval-extinction can also decrease reinstatement, spontaneous recovery, and renewal in animals that self-administered cocaine or methamphetamine [204–206]. However, some preclinical evidence indicates that retrieval-extinction does not enhance extinction for cocaine, and may even inhibit extinction for nicotine [207]. Although these discrepancies could be due to methodological differences, there is significant evidence against extinction-retrieval for other types of memory as well [201, 208]. However, clinical applications of retrieval-extinction for substance use disorders have yielded moderately promising results [91, 205]. Overall, retrieval-extinction should be further investigated as a potential strategy to improve treatment outcomes.

Additionally, combining pharmacological manipulations with behavioral interventions could further enhance effects. The possibility of pharmacologically enhancing extinction learning while simultaneously disrupting reconsolidation of the original drug memory has been proposed [28]. Because of the mechanistic overlap between reconsolidation and extinction, many pharmacological interventions, such as the partial NMDA receptor agonist DCS, would simultaneously enhance extinction and reconsolidation, producing potentially deleterious effects [28, 146, 209]. However, there are distinctions between reconsolidation and extinction [145, 146]. Proteomic analysis of protein phosphorylation has been used to identify a phosphorylation site on calcium-calmodulin-dependent kinase II α (CaMKIIα) that is bidirectionally regulated by reconsolidation and extinction [126]. Furthermore, inhibition of CaMKII in the BLA facilitates extinction and disrupts reconsolidation, providing evidence that these processes can be inversely regulated by a single intervention [126]. Further investigation into regulators of reconsolidation and extinction learning would likely provide a basis for enhancing the combination of these strategies when applied clinically.

Expansion of animal models to model more cocaine memories

Along with the challenges of context specificity of extinction and the difficulty in identifying biological differences

between reconsolidation and extinction, other factors may complicate the treatment of cocaine use disorders. Extensive cocaine use can result in weakened executive control, impaired working memory, and the development of habitual behavior [210–213]. Unlike human cocaine use disorder, much of the preclinical research described involves experimenter-administered cocaine or short-term drug self-administration that facilitates goal-directed drug-seeking behavior, which cannot fully encompass the long-term effects of cocaine on memory functions and behavior [212]. Therefore, continued research should evaluate how Pavlovian associations may guide the development of increasingly habitual or compulsive drug use. Additionally, the formation and extinction of cocaine-associated Pavlovian memories should be examined in animal models that focus on under-studied aspects of addiction, such as extended drug self-administration and habitual and compulsive drug use.

Manipulation of cocaine memories

The finding that optogenetic induction of depotentiation in thalamo-amygdala synapses mimics the effects of cue extinction provides evidence that more specific interventions may be possible [52]. Although optogenetic and chemogenetic tools are currently only suitable for answering preclinical questions, expansion in the fields of genetics and medical technology suggests that similar tools may eventually be suitable for clinical applications. Continued preclinical research expanding our understanding of the circuits underlying how cocaine memories are consolidated, reactivated, and extinguished will allow for the continued application of this knowledge to clinical practice.

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