Published in final edited form as:
Drug Discov Today Dis Models. 2008 ; 5(4): 251–258. doi:10.1016/j.ddmod.2009.03.001.

Relapse to drug seeking following prolonged abstinence: the role of environmental stimuli

R.A. Fuchs, **H.C. Lasseter**, **D.R. Ramirez**, and **X. Xie**
Department of Psychology, University of North Carolina, NC 27599-3270

Abstract

Successful treatment of drug addiction must involve relapse prevention informed by our understanding of the neurobiological bases of drug relapse. In humans, exposure to drug-associated environmental stimuli can elicit drug craving and relapse. Because exposure to drug-paired stimuli similarly induces drug-seeking behavior in laboratory animals, several animal models of drug relapse have been developed. Here, we review animal models of cue-induced drug relapse and critically evaluate their validity and utility in addressing human relapse behaviors.

Introduction

Relapse (see italicized terms in Box 1. *Glossary of Terms*) is the primary impediment in the treatment of drug addiction. Even after extended periods of *abstinence*, exposure to drug-associated stimuli, periods of stress, or small amounts of drug can produce robust drug craving and increase the probability of relapse to drug use [1]. To explore the neurobiological mechanisms of this complex behavioral phenomenon, *in vivo* models have been utilized in combination with functional neuroanatomical, pharmacological, neurochemical, and electrophysiological techniques. These efforts have significantly increased our understanding of the mechanisms of relapse produced by environmental stimuli, an achievement critical for the systematic development of effective anti-relapse pharmacotherapies. These efforts have also provided information about the efficacy and limitations of the models themselves. In this brief review, we compare the theoretical and technical utility of frequently employed cue-induced drug relapse models and summarize recent preclinical findings to demonstrate their applications.

Box 1

Glossary of Terms

Corresponding Author: Rita A. Fuchs, Ph.D., Department of Psychology, University of North Carolina, CB#3270, Chapel Hill, NC 27599-3270, http://psychology.unc.edu.
Editors-in-Chief: Jan Törnell and Andrew McCulloch
Series Editors: Nigel Maidment, Niall Murphy, Foster Olive

Conflict of Interest
The authors do not have any conflict of interest to declare.

Abstinence	A self-imposed (humans) or experimenter-imposed (laboratory animals) drug-free period. In the preclinical literature, the terms abstinence, forced abstinence, and withdrawal are used interchangeably.
Conditioned reinforcement	Reinforcement elicited by a conditioned reinforcer
Conditioned reinforcer	A stimulus that acquires reinforcing properties through repeated pairing with the primary reinforcing effects of an unconditioned stimulus (e.g. drug)
Conditioned reward	Conditioned appetitive state elicited by the presentation of an appetitive conditioned stimulus in the absence of the unconditioned stimulus
Conditioned stimulus	A unimodal or bimodal stimulus that acquires conditioned properties through repeated pairing with an unconditioned stimulus (e.g., the euphoric effects of a psychoactive drug). Consequently, it gains the ability to signal imminent unconditioned stimulus (e.g., drug) effects. In the drug addiction literature, CS^+ refers to a CS that signals imminent unconditioned stimulus

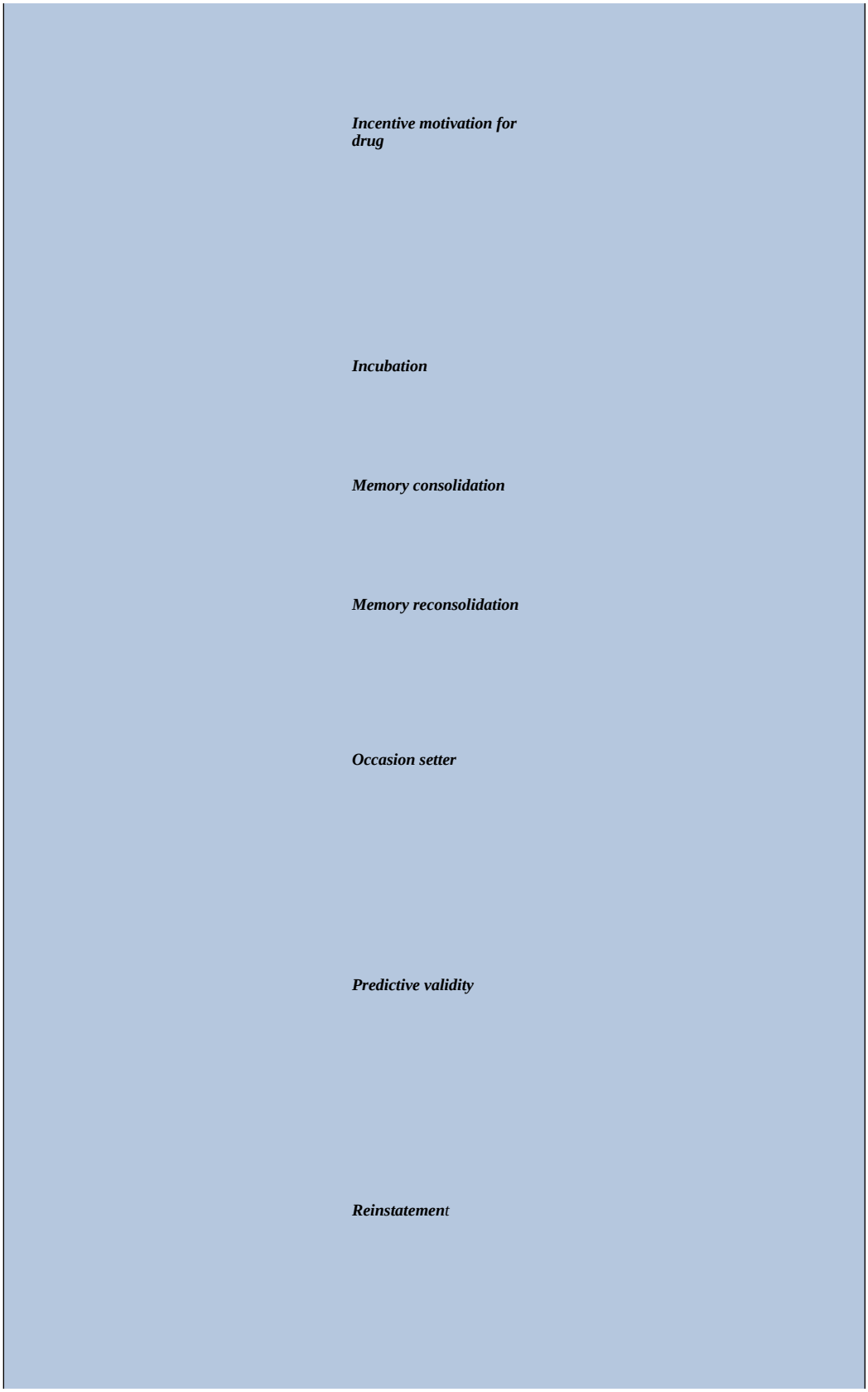
presentation, whereas CS^- to a CS that signals the absence of imminent unconditioned stimulus presentation after stimulus discrimination training.

Static multimodal background stimuli which constitute a setting where CS-unconditioned stimulus and/or response-unconditioned stimulus associations can form. Contextual stimuli are presented throughout an experimental session, independent of the subject's behavior.

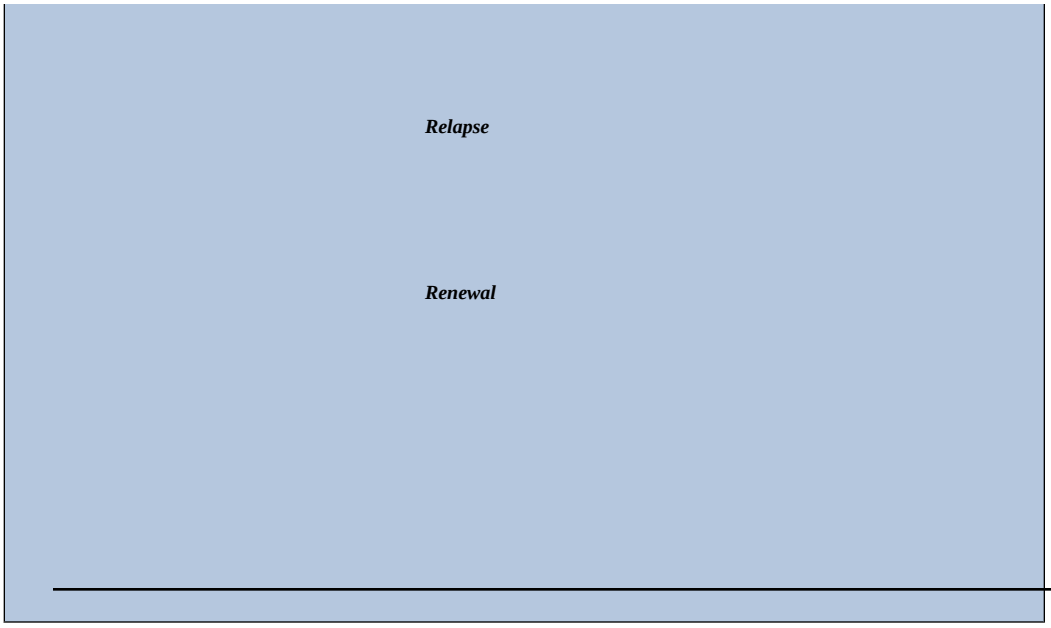
A unimodal or bimodal stimulus that gains the ability to signal a particular reinforcement contingency in the course of discrimination training. It is presented independent of the subject's behavior. In the drug addiction literature, S^+ typically refers to a S_D that signals drug availability, whereas S^- to a S_D that signals drug unavailability

Experimental contingency during which instrumental responses have no programmed consequences

A desirable quality of animal models. It indicates the extent of overt similarity between the model and the



Incentive motivation for drug	natural (human) phenomenon under study Externally- or internally-elicited (i.e., interoceptive stimulus-induced) motivation to experience the effects of a drug (humans) or to self-administer a drug (laboratory animals)
Incubation	Increase in the magnitude of drug seeking after a prolonged abstinence period
Memory consolidation	Stabilization of a memory trace in long-term memory stores after initial acquisition
Memory reconsolidation	Re-stabilization of a memory trace into long-term memory stores after retrieval-induced destabilization
Occasion setter	Discriminative stimulus or context that can disambiguate a CS or response, signaling whether it will be reinforced or not. It does not have a direct effect on behavior
Predictive validity	A desirable quality of animal models. It indicates the extent to which a model responds to manipulations in a similar way as the natural (human) phenomenon under study.
Reinstatement	Recovery of a previously extinguished instrumental or Pavlovian conditioned response upon exposure to un-extinguished CS or context, small



amount of drug, or stress.

Resumption of drug seeking and/or drug taking following a period of abstinence in humans

Recovery of a previously extinguished instrumental or Pavlovian conditioned response upon re-exposure to the CS in the training context after the CS is extinguished in an alternate context

In vivo models of cue-induced drug relapse

Several animal models have been developed to assess cue-induced *incentive motivation for drug*, including the explicit *conditioned stimulus*-induced (CS), contextual, and *discriminative stimulus* (S_D)-induced reinstatement models, the renewal model, the abstinence model, and related paradigms (see Table 1). Before critically assessing the specific strengths and weaknesses of these animal models, it is important to point out the theoretical considerations and procedural factors that guide our evaluation.

Theoretical Considerations

In the course of chronic drug use, environmental stimuli are repeatedly paired with the effects of the drug. Depending on the temporal relationship and contingency between these stimuli and drug effects, the stimuli can acquire conditioned rewarding, conditioned reinforcing, and/or incentive motivational properties through associative learning processes. *Conditioned reward* and *conditioned reinforcement* are demonstrated by (a) attraction to drug-paired stimuli in humans and acquired preference for drug-paired contexts in laboratory animals and (b) instrumental responding maintained by CS presentations, respectively [2]. Conversely, incentive motivation for drug is evident in humans as desire to experience the effects of the drug itself and in laboratory animals as drug seeking manifested as non-reinforced instrumental responding with drug delivery as the end goal [3,[4]]. Because the latter phenomenon more closely mirrors drug craving and relapse in humans [4], cue-induced drug relapse models that attempt to assess the incentive motivational effects of drug-associated stimuli are preferred.

Procedural Factors Influencing Model Validity

To evaluate the *face* and *predictive validity* of cue-induced drug relapse models, several procedural factors must be considered. First, whether drug exposure is passive or self-initiated critically influences neural responses [5]. Therefore, models are favored that a) allow experimental subjects control over drug delivery, b) reflect the human condition in that drug exposure is at least sub-chronic rather than acute, and c) utilize routes of drug administration employed by humans. Second, diverging neural systems mediate cue-induced versus drug priming-induced incentive motivation for drug and drug reinforcement [6]. Consequently, relapse testing must occur in the absence of drug reinforcement. Third, cue-induced drug

relapse is rarely preceded by explicit extinction therapy in clinical settings. Thus, models that assess drug seeking after a drug-free abstinence period as opposed to instrumental *extinction training* may better capture the neural mechanisms of cue-induced relapse in humans. Fourth, as noted above, cue-induced relapse after prolonged abstinence is typically precipitated by inadvertent stimulus exposure. It has been theorized that passive exposure to stimuli that predict drug availability initiates, whereas response-contingent CSs maintain, drug seeking [7]. Accordingly, models in which passive cue manipulations can induce drug seeking are strongly preferred not only for their face validity but also for their predictive validity. Another measure of predictive validity is the response of drug seeking in the model to pharmacological manipulations that alleviate craving and relapse propensity in clinical populations. Unfortunately, scarcity of available literature precludes extensive discussion of this topic. This stems in part from the limited availability of effective anti-craving medications.

CS-induced Reinstatement Model

In this model, subjects are trained to perform an instrumental response for drug reinforcement in an operant conditioning chamber where drug delivery is explicitly paired with presentation of a discrete stimulus complex (e.g., light-tone). After self-administration training, subjects undergo extinction training in the same chamber. During extinction training, responses no longer result in drug reinforcement or CS presentations. After an arbitrary extinction criterion is reached within a single session, or across several daily extinction sessions, non-reinforced responding is assessed in the response-contingent presence of the CS [8]. The resulting robust and reliable *reinstatement* in responding is the index of motivation for drug in this model. One important advantage of this model is that CS-drug associations can develop during a single session, making the model suitable to investigate associative learning and *memory consolidation* mechanisms that promote cue-induced drug seeking. Contrary to inadvertent cue exposure in the human condition, CS presentation is response-contingent because passive CS presentation elicits weak reinstatement [9]. Under these conditions, the CS can serve as a *conditioned reinforcer*. As a result, reinstatement may reflect motivation for the CS or the drug. Additionally, while extinction training isolates the influence of the CS on reinstatement from that of the *context*, response habit, or stress, it unfortunately reduces the face validity of the model given that humans rarely undergo explicit extinction training. Furthermore, extinction learning elicits neuroplasticity in the brain relapse circuitry, including the nucleus accumbens core (NACc), basolateral amygdala (BLA), and dorsomedial prefrontal cortex (dmPFC), altering the recruitment of these brain regions in subsequent drug seeking [10,[11]]. Hence, distinguishing neuroplasticity that occurs during self-administration training, extinction training, and reinstatement testing will be important for understanding the distinct contributions of these learning experiences to drug seeking.

Utilizing the CS-induced reinstatement model, recent studies have revealed a role for the BLA in the acquisition of CS-drug associations that underlie cocaine seeking [12,[13]] and in the consolidation and *reconsolidation* of these associations in long-term memory [13–[15]]. Furthermore, pharmacological and electrophysiological studies have demonstrated that expression of CS-induced cocaine seeking is mediated by a corticolimbic circuitry, which includes the BLA, dmPFC, NACc, and dorsolateral caudate-putamen (dlCPu) [11,[16]–[18]]. Most recently, studies have begun to investigate the influence of cocaine-induced and experience-based neuroplasticity on propensity for CS-induced reinstatement [5,[19]].

Contextual Reinstatement Model

This model utilizes an ABA experimental design. Subjects are trained to perform an instrumental response for drug reinforcement in a distinct environmental context (context A), in which explicit CS presentations are not programmed to occur [20]. After self-administration

training, subjects' responding is extinguished in a distinctly different context (context B). On the reinstatement test day, the subjects are re-exposed to the previously drug-paired context (context A), which results in reinstatement of responding. Reinstatement does not reflect dishabituation, or an increase in behavioral output elicited by an unexpected shift in the testing context, given that the exposure of AAB control subjects to a novel, non-drug-associated context fails to reinstate responding [20]. The contextual model possesses some advantages over the CS-induced reinstatement model. Namely, context exposure is passive, which produces uniform context exposure across subjects during training and testing. This also mirrors the human condition wherein inadvertent stimulus exposure precipitates drug relapse. The model provides an index of drug context-induced incentive motivation for drug *per se* due to the absence of a response-contingent CS, or conditioned reinforcer. However, it is not clear whether the context acts as an *occasion setter*, which predicts the reinforcement of instrumental responses, or as a weakly associated Pavlovian CS. A limitation of this model is greater attrition due to inadequate response acquisition when self-administration training occurs in the absence of a CS. Furthermore, the context must be salient and multi-modal in order to elicit substantial reinstatement and to permit repeated reinstatement testing. While extinction isolates the influence of the context on reinstatement, it unfortunately reduces the face validity of the model.

Context-induced and CS-induced motivation for drug reinforcement is mediated by distinct, yet partially overlapping, neural circuitries. Reinstatement of cocaine or heroin seeking produced by either of these stimuli involves the dlCPu, BLA, mPFC, and NACc [11,[16]–[18],[20],[21]]. However, context-induced drug seeking uniquely recruits the dorsal hippocampus (DH) and nucleus accumbens shell (NACs) as well as functionally significant interactions between the BLA and DH [21,[22]].

Drug-predictive Discriminative Stimulus (S^+)-induced Reinstatement Model

In this model, subjects receive extensive stimulus discrimination training, during which drug reinforced and non-reinforced training sessions alternate [23]. During the reinforced sessions, drug is available contingent upon instrumental responding in the presence of a passively presented S_D (S^+) and a response-contingent "time-out" stimulus, which likely functions as a CS^+. During non-reinforced sessions, drug reinforcement is withheld in the presence of a different S_D (S^-) and time-out stimulus (CS^-). After the acquisition for stimulus discrimination is verified, subjects receive additional extinction training in the absence of the discriminative and time-out stimuli, or undergo a drug-free abstinence period. On the reinstatement test days, drug seeking is assessed in the presence of the S^+/CS^+ and the S^-/CS^- using a repeated testing design. A strength of this testing procedure is that the stimulus selectivity of drug seeking is evaluated. However, behavioral training is lengthy and tedious. It is unclear whether responding is elicited by the drug-predictive S^+ or the CS^+, since the CS^+ is a better predictor of drug effects. This is important because the response-contingent CS^+ may act as a conditioned reinforcer. Furthermore, explicit extinction training decreases the face validity of the model. While reinstatement of responding is generally modest, the feasibility of repeated testing designs makes this model valuable for studying the dose-dependent effects of pharmacological manipulations on drug seeking.

Acamprosate and naltrexone, FDA-approved medications that promote abstinence in alcohol abusers [24,[25]], dose-dependently attenuate ethanol seeking in response to the S^+/CS^+ without altering responding to the S^-/CS^- [23,[26]]. These findings support the predictive validity of this paradigm, as a model of cue-induced ethanol relapse.

Renewal Model

In the renewal model, subjects are trained to exhibit an instrumental response for drug reinforcement in a distinct environmental context where drug delivery is paired explicitly with

CS presentations [27–29]. After self-administration training, subjects' responding is extinguished in a distinctly different context but in the presence of the previously drug-paired CS. On the test day, subjects are given response-contingent access to the CS in the previously drug-paired context, according to an ABA design. As in the contextual reinstatement model, exposure to a novel context fails to renew drug seeking after extinction training in the drug-paired context (AAB). However, studies using natural reinforcers suggest that it may produce weak renewal after extinction training in a novel context (ABC; as reviewed in [28]). Unlike in the S^+-induced reinstatement procedure, the context acquires greater predictive value and influence over drug seeking than the CS in the renewal model, because the CS is extinguished or made ambiguous in the course of extinction training. *Renewal* of drug seeking is argued to reflect the context's ability to act as an occasion setter, a stimulus that predicts drug availability contingent upon responding and thus elicits incentive motivation for drug. Alternatively, the context may disambiguate the CS, restoring its conditioned reinforcing property. Consequently, the extent to which renewal reflects context-induced incentive motivation versus CS-induced conditioned reinforcement remains somewhat unclear. Furthermore, explicit extinction training prior to renewal testing reduces the face validity of the model. Despite these limitations, the renewal model is well-accepted because subjects easily acquire instrumental responding for drug reinforcement in the presence of the context and the CS, and renewal responding is robust and reliable.

Empirical evidence suggests that, at least in part, context-induced renewal utilizes neural circuitry involved in contextual reinstatement. Consistent with this, context-induced renewal of ethanol seeking is associated with c-fos mRNA expression in the DH [30]. Immunohistochemical studies also reveal neuronal activation in the lateral hypothalamus (lH) and infralimbic cortex upon renewal responding in ethanol-trained and cocaine-trained rats, respectively [31,32]. The functional involvement of the lH remains to be verified. However, the infralimbic cortex likely promotes extinction learning because neural inactivation of this area is sufficient to reinstate cocaine seeking in an extinguished drug-paired context [33]. After self-administration training in the presence of a distinct context and a response-contingent CS, different brain regions may acquire dissociable roles in context- versus CS-induced components of drug seeking. In support of this, in rats trained to self-administer heroin in the presence of both a distinct context and an explicit CS, there is a double dissociation in the involvement of NACs and NACc dopamine receptors in drug seeking elicited by the drug context versus the CS alone [34].

Abstinence Model

Similar to the reinstatement procedures, subjects in the abstinence model are first trained to perform an instrumental response for drug reinforcement ideally in the absence of a CS. After training, subjects remain in their home cages or an alternate context, which contains no instrumental operanda. This experimenter-imposed drug-free period (abstinence) can range in duration from days to months [6,35]. On the test day, subjects are re-exposed to the drug-paired context, ideally in the absence of a CS, which results in robust drug seeking. This response is not considered reinstatement per se since it is not preceded by extinction training. The fact that subjects do not undergo explicit extinction training prior to testing grants strong face validity to this model, but restricts data interpretation. Thus, drug seeking may reflect a number of exogenous, albeit arguably relapse-relevant, factors, including response habit, novelty-induced stress, exploratory behavior, and innate motivation, in addition to context-induced incentive motivation for drug. This is a disadvantage in situations wherein a research study aims to identify distinct neural processes associated with context-induced incentive motivation *per se*. Furthermore, given that abstinence is forced, it can be assumed that drug seeking likely reflects the interplay of a slightly different set of factors than those that contribute to relapse

following self-imposed abstinence in drug users. Nevertheless, given its complexity, the abstinence model can serve as a stringent screen for novel anti-relapse therapies.

Post-abstinence cocaine-seeking behavior is dependent on the functional integrity of the dlCPu, a brain region involved in habit learning [11]. In contrast, the functional integrity of brain regions involved in associative learning processes (e.g., BLA, dmPFC, NACc) is not critical for this behavior [11,[36]]. Nevertheless, post-abstinence exposure to a cocaine-associated context increases activity-related gene expression (e.g., arc, zif/268, and c-fos) in the dlCPu, as well as in the NACc and dmPFC [6,[37]], and the functional significance of these molecular events will be important to explore. Studies have also demonstrated that the robustness of drug seeking increases, or "incubates," during the first two months of experimenter-enforced abstinence [6,[35]]. This *incubation* phenomenon has been intensely researched as it has been theorized to reflect the development of neuroadaptations that promote relapse propensity in addicts [37–[39]].

Related Models

Additional models employed to assess the effects of drug-associated environmental stimuli on addictive behavior include the second-order schedule, runway, and place conditioning paradigms. While these procedures have not been employed routinely to study the neurobiology of cue-induced drug relapse after an extended drug-free period *per se*, their contribution to the drug addiction research field has been well recognized. We review the fundamental procedural features of these models in Table 1. However, due to space limitations, the interested reader is referred to other works for an in-depth evaluation of these models and the corresponding research literature [40–[42]].

Model Comparison

The five most frequently employed *in vivo* cue-induced drug relapse models (see Table 2) reviewed here possess strong face validity, since they involve extensive cue-drug conditioning established in the course of instrumental drug self-administration training and entail testing for cue-induced motivation in the absence of drug reinforcement. These models complement one another in that they can be used to identify neural substrates and neuroadaptations that promote or inhibit incentive motivation for drug triggered by different stimulus types and stimulus combinations. A limitation of these models is that they do not provide a selective index of incentive motivation for drug in the sense that reward seeking can also be elicited by natural reinforcers (e.g., food) [5]. Thus, differences in the neurobiology of drug cue- versus natural reward cue-induced incentive motivation will need to be explored to identify drug addiction-specific neural substrates and neuroplasticity. Each of these models can be used to evaluate experimental pharmacotherapies, albeit none of them are considered high-through-put screening tools. In this respect, the CS-induced and S^+-induced reinstatement, renewal, and abstinence models are preferred by investigators because they engender expeditious response acquisition or robust drug seeking in experimental subjects. However, paradigms like the contextual reinstatement and abstinence models, which produce drug seeking in response to passive cue exposure, are stronger in face and predictive validity. A greater degree of experimental control is achieved in the contextual reinstatement model, which involves a single cue manipulation that is uniform across subjects, but effect size is sacrificed. Similarly, extinction training promotes experimental control but diminishes the face validity of reinstatement and renewal models, whereas relapse testing without prior extinction training ensures face validity but constrains data interpretation in the abstinence model. Given these unique strengths and limitations, we expect that these five models will continue to be used side by side.

Model Translation to Humans

Despite the complexity of cue-induced drug craving and relapse in humans, *in vivo* models have successfully captured several key features of this phenomenon, including the behavioral consequences and neurophysiological manifestations of cue reactivity [1,[43]]. Drug seeking in laboratory animals is mediated by a corticolimbic neurocircuitry that corresponds well to the neural substrates implicated in cue reactivity and cue-induced craving by human brain imaging studies [1,[43]]. We anticipate that this research will advance *in vivo* and *in silico* model development and medication development, the latter of which will provide us additional tools to assess the predictive validity of these models.

Conclusions

Several sophisticated *in vivo* models are available to study the neurobiology of cue-induced drug craving and relapse after abstinence. The models reviewed here range in face and predictive validity. However, they complement one another and have contributed critical information to our understanding of the influence of explicit and contextual environmental stimuli on drug seeking. Future studies using these models will be applied increasingly to to test novel anti-craving pharmacotherapies and to explore complex interactions between environmental cues, epigenetic factors, stress, and social factors which likely co-regulate cue-induced craving and relapse in humans.

Acknowledgments

We sincerely apologize to those whose seminal work could not be included in this review paper due to space limitations. This work was supported in part by NIDA R01 DA17673 (R.F.), DA17673-S1 (D.R.), and NIDA T32 DA007244 (H.L.).

References

1. Sinha R, Li CS. Imaging stress- and cue-induced drug and alcohol craving: association with relapse and clinical implications. Drug Alcohol Rev 2007;26:25–31. [PubMed: 17364833]
2. Newlin DB. A comparison of drug conditioning and craving for alcohol and cocaine. Recent Rev Alcohol 1992;10:147–64.
3. Markou A, et al. Animal models of drug craving. Psychopharmacology (Berl) 1993;112:163–82. [PubMed: 7871016]
4. Robinson TE, Berridge KC. Addiction. Annu Rev Psychol 2003;54:25–53. [PubMed: 12185211]
5. Thomas MJ, et al. Neuroplasticity in the mesolimbic dopamine system and cocaine addiction. Br J Pharmacol 2008;154:327–42. [PubMed: 18345022]
6. Neisewander JL, et al. Fos protein expression and cocaine-seeking behavior in rats after exposure to a cocaine self-administration environment. J Neurosci 2000;20:798–805. [PubMed: 10632609]
7. Di Ciano P, Everitt BJ. Differential control over drug-seeking behavior by drug-associated conditioned reinforcers and discriminative stimuli predictive of drug availability. Behav Neurosci 2003;117:952–60. [PubMed: 14570545]
8. Meil WM, See RE. Conditioned cued recovery of responding following prolonged withdrawal from self-administered cocaine in rats: an animal model of relapse. Behav Pharmacol 1996;7:754–763. [PubMed: 11224470]
9. Fuchs RA, et al. Predictive validity of the extinction/reinstatement model of drug relapse. Psychopharmacology 1998;135:151–60. [PubMed: 9497020]
10. Sutton MA, et al. Extinction-induced upregulation in AMPA receptors reduces cocaine-seeking behaviour. Nature 2003;421:70–75. [PubMed: 12511956]
11. Fuchs RA, et al. Different neural substrates mediate cocaine seeking after abstinence versus extinction training: a critical role for the dorsolateral caudate-putamen. J Neurosci 2006;29:3584–3588. [PubMed: 16571766]

12. Feltenstein MW, See RE. The neurocircuitry of addiction: an overview. Br J Pharmacol 2008;154:261–74. [PubMed: 18311189]
13. Feltenstein MW, See RE. NMDA receptor blockade in the basolateral amygdala disrupts consolidation of stimulus-reward memory and extinction learning during reinstatement of cocaine-seeking in an animal model of relapse. Neurobiol Learn Mem 2007;88:435–444. [PubMed: 17613253]
14. Lee JL, et al. Cue-induced cocaine seeking and relapse are reduced by disruption of drug memory reconsolidation. J Neurosci 2006;26:5881–5887. [PubMed: 16738229]
15. Fuchs RA, et al. The role of the basolateral amygdala in stimulus-reward memory and extinction memory consolidation and in subsequent conditioned cued reinstatement of cocaine seeking. Eur J Neurosci 2006;23:2809–13. [PubMed: 16817884]
16. McLaughlin J, See RE. Selective inactivation of the dorsomedial prefrontal cortex and the basolateral amygdala attenuates conditioned-cued reinstatement of extinguished cocaine-seeking behavior in rats. Psychopharmacology 2003;168:57–65. [PubMed: 12845418]
17. Hollander JA, Carelli RM. Cocaine-associated stimuli increase cocaine seeking and activate accumbens core neurons after abstinence. J Neurosci 2007;27:3535–3539. [PubMed: 17392469]
18. Fuchs RA, et al. Differential involvement of the core and shell subregions of the nucleus accumbens in conditioned cue-induced reinstatement of cocaine seeking in rats. Psychopharmacology (Berl) 2004;176:459–65. [PubMed: 15138757]
19. Berglind WJ, et al. A BDNF infusion into the medial prefrontal cortex suppresses cocaine seeking behavior in rats. Eur J Neurosci 2007;26:757–766. [PubMed: 17651427]
20. Fuchs RA, et al. The role of the dorsomedial prefrontal cortex, basolateral amygdala, and dorsal hippocampus in contextual reinstatement of cocaine seeking in rats. Neuropsychopharmacology 2005;30:296–309. [PubMed: 15483559]
21. Fuchs RA, et al. Nucleus accumbens shell and core involvement in drug context-induced reinstatement of cocaine seeking in rats. Psychopharmacology (Berl) 2008;200:545–56. [PubMed: 18597075]
22. Fuchs RA, et al. Interactions of the basolateral amygdala with the dorsal hippocampus and dorsomedial prefrontal cortex regulate drug context-induced reinstatement of cocaine-seeking in rats. Eur J Neurosci 2007;26:487–98. [PubMed: 17650119]
23. Ciccocioppo R, et al. Effect of selective blockade of mu(1) or delta opioid receptors on reinstatement of alcohol-seeking behavior by drug-associated stimuli in rats. Neuropsychopharmacology 2002;27:391–9. [PubMed: 12225696]
24. Mason BJ. Treatment of alcohol-dependent outpatients with acamprosate: a clinical review. J Clin Psychiatry 2001;62:42–48. [PubMed: 11584875]
25. Anton RF. Naltrexone for the management of alcohol dependence. N Engl J Med 2008;359:715–21. [PubMed: 18703474]
26. Bachteler D, et al. The effects of acamprosate and neramexane on cue-induced reinstatement of ethanol-seeking behavior in rat. Neuropsychopharmacology 2005;30:1104–10. [PubMed: 15668725]
27. Crombag HS, et al. Effect of dopamine receptor antagonists on renewal of cocaine seeking by reexposure to drug associated contextual cues. Neuropsychopharmacology 2002;27:1006–15. [PubMed: 12464457]
28. Crombag HS, et al. Context-induced relapse to drug seeking: a review. Philos Trans R Soc Lond B Biol Sci 2008;363:3233–43. [PubMed: 18640922]
29. Bossert JM, et al. Activation of group II metabotropic glutamate receptors in the nucleus accumbens shell attenuates context-induced relapse to heroin seeking. Neuropsychopharmacology 2006;31:2197–209. [PubMed: 16341024]
30. Marinelli PW, et al. Effects of opioid receptor blockade on the renewal of alcohol seeking induced by context: relationship to c-fos mRNA expression. Eur J Neurosci 2007;26:2815–23. [PubMed: 18001278]
31. Hamlin AS, et al. The neural correlates and role of D1 dopamine receptors in renewal of extinguished alcohol-seeking. Neuroscience 2007;146:525–36. [PubMed: 17360123]
32. Hamlin AS, et al. Renewal of extinguished cocaine-seeking. Neuroscience 2008;151:659–70. [PubMed: 18164822]

33. Peters J, et al. Infralimbic prefrontal cortex is responsible for inhibiting cocaine seeking in extinguished rats. J Neurosci 2008;28:6046–53. [PubMed: 18524910]
34. Bossert JM, et al. Differential effects of blockade of dopamine D1-family receptors in nucleus accumbens core or shell on reinstatement of heroin seeking induced by contextual and discrete cues. J Neurosci 2007;27:12655–63. [PubMed: 18003845]
35. Grimm JW, et al. Effect of cocaine and sucrose withdrawal period on extinction behavior, cue-induced reinstatement, and protein levels of the dopamine transporter and tyrosine hydroxylase in limbic and cortical areas in rats. Behav Pharmacol 2002;13:379–88. [PubMed: 12394414]
36. See RE, et al. The role of dorsal vs ventral striatal pathways in cocaine-seeking behavior after prolonged abstinence in rats. Psychopharmacology (Berl) 2007;194:321–31. [PubMed: 17589830]
37. Hearing MC, et al. Relapse to cocaine-seeking increases activity-regulated gene expression differentially in the striatum and cerebral cortex of rats following short or long periods of abstinence. Brain Struct Funct 2008;213:215–27. [PubMed: 18488248]
38. Lu L, et al. Central amygdala ERK signaling pathway is critical to incubation of cocaine craving. Nat Neurosci 2005;8:212–9. [PubMed: 15657599]
39. Grimm JW, et al. Time-dependent increases in brain-derived neurotrophic factor protein levels within the mesolimbic dopamine system after withdrawal from cocaine: implications for incubation of cocaine craving. J Neurosci 2003;23:742–7. [PubMed: 12574402]
40. McFarland K, Ettenberg A. Reinstatement of drug-seeking behavior produced by heroin-predictive environmental stimuli. Psychopharmacology 1997;131:86–92. [PubMed: 9181640]
41. Di Ciano P, Everitt BJ. Neuropsychopharmacology of drug seeking: Insights from studies with second-order schedules of drug reinforcement. Eur J Pharmacol 2005;526:186–98. [PubMed: 16288737]
42. Aguilar, et al. Neurobiological mechanisms of the reinstatement of drug-conditioned place preference. Brain Res Rev 2009;59:253–77. [PubMed: 18762212]
43. Kalivas PW, Volkow ND. The neural basis of addiction: a pathology of motivation and choice. Am J Psychiatry 2005;162:1403–13. [PubMed: 16055761]

Table 1

Procedural Comparison of Cue-induced Relapse Models and Related Paradigms

Animal Model	Drug Regimen	Drug Exposure	Cue Presentation during Training	Extinction Training/ Cue Presentation	Testing in Drug-free State	Cue Presentation during Testing	Key References
CS-induced Reinstatement	Self-administration	Sub-chronic	Explicit CS	Yes/No CS	Yes	Response-contingent	[8,12–8]
Contextual Reinstatement	Self-administration	Sub-chronic	Distinct Context	Yes/Different context	Yes	Passive	[20–2]
S+-induced Reinstatement	Self-administration	Sub-chronic	Drug + S^+ + CS^+ No Drug + S^- + CS^-	Yes/No S_D or CS	Yes	Both	[23,26]
Renewal	Self-administration	Sub-chronic	Distinct Context+ Explicit CS	Yes/CS + Different context	Yes	Both	[27,29–2]
Abstinence	Self-administration	Sub-chronic	Contextual stimuli (+/−Explisit CS)	No/+/− Alternate context	Yes	Passive	[6,11,35–9]
Runway	Passive administration	Repeated	Drug + S^+ No Drug + S^-	Yes/S−	Yes	Passive	[40]
Second-order Schedule	Self-administration	Sub-chronic Limited	Non-Explicit CS	No	Yes Limited	Response- contingent	[41]
Place Conditioning	Passive administration	Repeated	Contextual stimuli	Yes/Same Context	No Drug priming	Passive	[42]

Table 2

Cue-induced Drug Relapse Model Comparison Summary

	CS-induced Reinstatement Model	Contextual Reinstatement Model	S^+-induced Reinstatement Model	Renewal Model	Abstinence Model
Applications	• *In vivo* identification of neural substrates, neuroadaptations, and experimental therapies seeking produced by an that mediate drug explicit CS	• *In vivo* identification of neural substrates, neuroadaptations, and experimental therapies that mediate drug seeking produced by contextual stimuli	• *In vivo* identification of neural substrates, neuroadaptations, and experimental therapies that mediate drug seeking produced by a S^+/CS^+ combination	• *In vivo* identification of neural substrates, neuroadaptations, and experimental therapies that mediate drug that mediate drug seeking produced by a context/CS combination	• *In vivo* identification of neural substrates, neuroadaptations, and experimental therapies that mediate drug seeking after abstinence.
Advantages	• Rapid acquisition of instrumental responding • Robust drug seeking permits repeated testing designs • Suitable for studying CS-drug associative learning and memory consolidation	• Passive uniform context exposure across subjects • Reinstatement reflects drug context-induced incentive motivation for drug without the influence of conditioned reinforcement	• Rapid acquisition of instrumental responding • Reliable drug seeking permits repeated testing designs • Suitable for studying interaction between stimulus types	• Rapid acquisition of instrumental responding • Robust drug seeking permits repeated testing designs • Suitable for investigating interaction between stimulus types	• Robust drug seeking • Absence of extinction training increases face validity • Suitable for studying the Incubation phenomenon
Disadvantages	• Unlike in humans, reinstatement may reflect motivation for the CS due to conditioned reinforcement • Extinction training produces neuroplasticity and reduces model face validity	• Context must be salient and multi-modal for reliable reinstatement • Context may act as either occasion setter or weakly associated Pavlovian CS • Extinction training produces neuroplasticity and reduces face validity	• Stimulus discrimination training is lengthy and tedious • Reinstatement may reflect conditioned reinforcement • Extinction training produces neuroplasticity and reduces face validity	• Context may act as either occasion setter or weakly associated Pavlovian CS • Reinstatement may reflect conditioned reinforcement • Extinction training produces neuroplasticity and reduces face validity	• Drug seeking may reflect exogenous factors, including response habit and innate motivation • Repeated testing is precluded by extinction learning during testing • Forced vs. self-imposed abstinence may involve different mechanisms
Key references	[8,12–8]	[20–2]	[23,26]	[27,29–2]	[6,11,35–9]