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Reconsolidation of drug memories

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Abstract

Persistent, unwanted memories are believed to be key contributors to drug addiction and the chronic relapse problem over the lifetime of the addict. Contrary to the long-held idea that memories are static and fixed, new studies in the last decade have shown that memories are dynamic and changeable. However, they are changeable only under specific conditions. When a memory is retrieved (reactivated), it becomes labile for a period of minutes to hours and then is reconsolidated to maintain long-term memory. Recent findings indicate that even well-established long-term memories may be susceptible to disruption by interfering with reconsolidation through delivery of certain amnestic agents during memory retrieval. Here I review the growing literature on memory reconsolidation in animal models of addiction, including sensitization, conditioned place preference and self-administration. I also discuss (a) several issues that need to be considered in interpreting the findings from reconsolidation studies and (b) future challenges and directions for memory reconsolidation studies in the field of addiction. The findings indicate promise for using this approach as a therapy for disrupting the long-lasting memories that can trigger relapse.

Keywords

Addiction; Alcohol; Amnesia; Cocaine; Conditioned place preference; Drug abuse; Memory; Morphine; Reconsolidation; Self-administration

1. Introduction

One of the most challenging aspects of drug addiction is the craving and relapse that occur for many years. The persistence of drug-seeking and drug-taking behaviors suggests that drug-associated learning and memory processes contribute to this relapse. Repeated drug-taking behavior engages neural circuitry involved in learning and memory of drug-related information (Berke and Hyman, 2000; O'Brien et al., 1992; Robbins et al., 2008; Robbins and Everitt, 2002; Robinson and Kolb, 2004; White, 1996; Wise, 2000). The ability to attenuate drug-associated memories in drug addicts is important because this attenuation is expected to suppress the cycle of relapse to drugs. Persistent drug-taking behavior involves consolidation of memory for the drug and drug-associated cues and contexts. With each drug use, drug-related memories are reactivated (retrieved) and are believed to be *reconsolidated* to maintain these memories (Milton and Everitt, 2010; Tronson and Taylor, 2007). After memory reactivation, the memory is thought to become destabilized so that it is susceptible to disruption by amnestic agents for a short period of time (h). Thus, we can

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exploit this window of lability to disrupt drug-associated memories by providing appropriate amnestic agents to dampen the memories that influence the motivation to seek and take drugs. Drug abuse studies in animal models of addiction demonstrate that reconsolidation can be disrupted by amnestic agents given near the time of memory reactivation. The vast majority of studies on reconsolidation have been conducted on fear conditioning; these studies are not generally discussed further, and the reader is referred to several excellent reviews on the reconsolidation of fear and other non-drug-related memories (Alberini, 2005; Dudai, 2004, 2006; Dudai and Eisenberg, 2004; Nader and Einarsson, 2010). Here I give a brief background on reconsolidation and review studies that focus on drug abuse models, including sensitization, conditioned place preference, conditioned approach, and self-administration.

2. Background on reconsolidation

The traditional consolidation hypothesis postulated that memories are initially labile after acquisition but become strengthened over time and, as a result, are less susceptible to amnestic treatment (McGaugh, 1966). However, some studies demonstrated that memories that were already consolidated could be retrieved or “reactivated” and therefore became susceptible to disruption if the appropriate amnestic agent was present at the time of reactivation (Misanin et al., 1968; Schneider and Sherman, 1968). This ability to disrupt the expression of memory was referred to as “cue-dependent amnesia” with the idea that reactivated memories became re-stabilized if no amnestic agent was on board at the time of retrieval but became weakened if an amnestic agent was present at the time of cue presentation as a reminder of the previously-consolidated memory. For approximately 20 years following those observations, few studies followed up on the findings that well-formed memories could become labile and thus susceptible to disruption by amnestic agents (Przybyslawski and Sara, 1997; Sara, 2000). Interest in the phenomenon was renewed after publication of a study by Nader et al. (2000a) in which they briefly reactivated fear memories and showed that subsequent fear expression was suppressed when the protein synthesis inhibitor anisomycin was given into the amygdala shortly after reactivation. The phenomenon of memory reactivation followed by memory restabilization is now known as reconsolidation.

The ability to disrupt reconsolidation in a reactivation-dependent manner has been observed in a wide variety of tasks and species (Alberini, 2005; Nader et al., 2000b; Riccio et al., 2006; Sara, 2000). Several pharmacological manipulations that disrupt consolidation also disrupt reconsolidation of the same task (Nader et al., 2000a; Przybyslawski et al., 1999; Sangha et al., 2003). However, numerous studies have also shown that consolidation and reconsolidation have dissociable component processes (Alberini, 2005; Lee et al., 2004). For instance, infusion of an antisense oligodeoxynucleotide for brain-derived neurotrophic factor (BDNF) blocks consolidation but not reconsolidation, and administration of antisense for the transcription factor Zif268 blocks reconsolidation but not consolidation (Lee et al., 2004). This divergence in consolidation and reconsolidation disruption has been observed for different tasks; for example, inhibition of protein synthesis in the hippocampus disrupts the consolidation but not reconsolidation of an inhibitory avoidance memory (Taubenfeld et al., 2001), and inhibition of protein synthesis in the amygdala disrupts consolidation but not reconsolidation of taste aversion memory (Bahar et al., 2004). The studies described above suggest that different behavioral paradigms can engage different molecular machinery when the memory undergoes consolidation *vs.* reconsolidation.

The function of memory reconsolidation has been debated. Some investigators have described reconsolidation as a continuation of long-term consolidation events that gradually stabilize memories (Alberini, 2005, 2011; Dudai and Eisenberg, 2004). Regardless of

whether reconsolidation represents a sustained consolidation process, the proposed consequences of reconsolidation are that memories may be strengthened (Inda et al., 2011; Lee, 2008) or updated to maintain the relevance of the memory after the organism gains new information (Dudai, 2004; Hupbach et al., 2007; Lee, 2009).

Six general issues should be considered in the study of memory reconsolidation, some of which are specific to drug-associated memories (see Box 2 for details). Briefly, the issues are: (1) inclusion of appropriate control groups; (2) the timing of delivery of the amnestic agent relative to when the reactivation session is given; (3) whether the drug of abuse is present during the reactivation period and during the subsequent test for memory expression; (4) the time period over which memory is tested to determine the permanence of memory disruption; (5) consideration of the temporal aspects of the reactivation session; and related to this issue, (6) whether disruption of reconsolidation *vs.* an effect on extinction occurs by the amnestic agent.

Earlier reconsolidation experiments primarily focused on aversive learning paradigms, with an emphasis on disruption of reconsolidation as a potential treatment for post-traumatic stress disorder (Debiec and Ledoux, 2004; Misanin et al., 1968; Nader et al., 2000a). Only more recently have investigators demonstrated that appetitive memories also undergo reconsolidation, and these studies reveal the potential for targeting the reconsolidation process as a treatment for drug addiction. Several other investigators first posited that memory reconsolidation processes should be targeted to disrupt memories underlying addiction behavior (Lee et al., 2005; Miller and Marshall, 2005; Milton and Everitt, 2010; Sara, 2000; Taylor et al., 2009). Here I review reconsolidation studies that have been conducted using three animal models of addiction: the behavioral sensitization model, the conditioned place preference (CPP) model, and the self-administration model. The purpose of this review is three-fold. One purpose is to organize the growing literature on reconsolidation in drug addiction models according to neurotransmitter and cellular systems and according to the different model systems used to test particular amnestic agents. A second purpose is to provide a critique of the studies given the importance of necessary control groups and considerations for interpreting findings from reconsolidation studies. A third purpose is to point out the gaps in our knowledge regarding reconsolidation of addiction-related memories and how such gaps might be addressed for future studies in addiction models.

One qualification needs to be pointed out in considering the processes affected by amnestic agents in the studies discussed below. Studies over the past decade discuss the process of reconsolidation disruption based on the findings that after treatment with a particular amnestic agent either prior to or just a after reactivation session, the behavior in question is absent or significantly decreased compared with controls not given the amnestic agent and also compared with controls given the amnestic agent after a long delay or in the absence of a reactivation session. However, it is important to keep in mind that the absence of behavior after this treatment may be due to processes that are not necessarily dependent on disruption of memory reconsolidation, including for example, extinction processes, changes in motivational state during the testing phase (which may or may not be dependent on memory processes), or temporary amnestic effects. Thus I discuss the findings from the standpoint that certain amnestic agents for drug-induced behaviors lead to the absence of that behavior, with the idea that in the presence of appropriate control groups (see Box 2), the interpretation is that memory reconsolidation has been disrupted. Such findings suggest this interpretation but do not necessarily rule out other possibilities. In discussing the studies below, I qualify each by describing whether standard controls were included, when the amnestic agent was delivered relative to the reactivation session, and whether reinstatement was examined to help rule out effects on extinction. Permanent effects of amnestic agents on

behavior are more difficult to demonstrate because there may be conditions that allow for the re-expression of a trained behavior that was previously absent. As our knowledge of memory reconsolidation processes increases, more refined and rigorous experiments to rule out alternative explanations will no doubt be applied to future studies.

An additional consideration while reviewing the effects of amnestic agents on the disruption of reconsolidation of drug-associated memories is the particular drug of abuse being tested. Several important differences between different classes of drugs of abuse have been found regarding the mechanisms and brain regions that contribute to drug-seeking and drug-taking behaviors (for review, see Badiani et al., 2011). Thus, reconsolidation of drug-associated memories may not necessarily rely on the same mechanisms or brain areas, and future work will need to systematically compare the effects of amnestic agents across more than one class of drug of abuse.

3. Reconsolidation and appetitive memories

A typical protocol for reconsolidation studies using CPP and self-administration tasks is to train animals for the task and, following either extinction or forced abstinence, administer a reactivation session preceded or immediately followed by the amnestic agent. A test for the expression of memory is usually conducted within the next few days. Some studies also test for memory several days or weeks later and assess whether the memory can be reinstated by the drug or the drug-associated cue.

3.1. Sensitization studies

Only a few studies have examined the reconsolidation of memories underlying drug-conditioned locomotor sensitization. Valjent et al. (2006) demonstrated that cocaine-induced conditioned sensitization was not affected by systemic anisomycin given immediately after a reactivation session. That is, conditioned locomotor sensitization was not affected when tested at a later time after the effects of anisomycin had subsided. Their studies used a reactivation procedure in which a cocaine injection was given to mice that were placed in the cocaine-associated context where the single trial had taken place. In contrast to this finding, Bernardi et al. (2007) reported that systemic anisomycin treatment given immediately after a reactivation session in which rats were placed into the cocaine-associated context but did not receive a cocaine injection blocked the conditioned locomotor effects of cocaine. This effect was not found after a longer reactivation session or when anisomycin was injected just 25 min after the reactivation session. The discrepancy between the two studies may be due to species differences, but also may be attributed to the presence of cocaine during the reactivation session, which may have overridden the ability of anisomycin to disrupt memory reconsolidation in this paradigm.

3.2. Conditioned place preference studies

Most studies examining the reconsolidation of drug-associated memories have been done using the drug-induced CPP model. We discuss the CPP studies below according to three categories of amnestic agents: protein synthesis inhibitors, neurotransmitter receptor agonists/antagonists, and compounds that affect down-stream cell-signaling pathways and transcription factors. The subjects in most of these studies were tested in the absence of the drug during the reactivation session, and many studies measured the ability of the amnestic agent to disrupt place preference of the drug-associated environment in the absence of drug on the test day; the cases where the drug of abuse is present during either of these sessions are identified. The absence or presence of the drug of abuse is important from two standpoints. First, its presence during the *reactivation session* (which constitutes either a training or a reinstatement session) minimizes the chances that there is a competing

extinction process occurring during reactivation. Second, the presence of the drug of abuse during the *test day* constitutes a reinstatement session if it follows extinction, and therefore provides the additional advantage of ruling out whether the effect of the amnestic agent was to promote extinction (in which reinstatement is likely to occur) or to block reconsolidation (in which no reinstatement should occur).

3.2.1. Protein synthesis inhibitors—Several studies have demonstrated that systemic administration of the protein synthesis inhibitor anisomycin given at the time of a reactivation session leads to the absence of expression of place preference behavior (Fan et al., 2010; Milekic et al., 2006; Robinson and Franklin, 2007b; Valjent et al., 2006) (but see Yim et al., 2006). Valjent et al. (2006) found an absence of cocaine- and morphine-induced CPP expression when systemic anisomycin was administered just after reactivation the previous day. Interestingly, the lack of CPP expression on the test day required the presence of the drug during the reactivation session, since re-exposure to only a saline injection followed by anisomycin in the drug-paired compartment during reactivation did not alter later CPP. Milekic et al. (2006) systemically administered one of the protein synthesis inhibitors, anisomycin or cyclohexamide, immediately after reactivation of a morphine-induced CPP memory. They demonstrated that the subsequent absence of CPP expression required simultaneous exposure to the morphine-paired context and morphine itself during memory reactivation, similar to the finding by Valjent et al. (2006), and they also showed that this effect could persist for up to 4 wk. Interestingly, the same treatment with systemic inhibitors on the last day of conditioning (acting as the reactivation session) produced only transient effects on CPP. Milekic et al. (2006) went on to demonstrate that anisomycin delivered directly into either the dorsal hippocampus, the basolateral amygdala (BLA), or the nucleus accumbens (but not the VTA) led to the absence of later CPP expression, and this effect persisted the day after another conditioning session. Robinson and Franklin (2007b) produced a lack of CPP expression by anisomycin administered intracerebroventricularly (i.c.v.) when given immediately after exposure to the morphine-paired compartment but no effect when it was given immediately after exposure to *both* the morphine *and* vehicle-paired compartments, suggesting that there may have been some aversion that developed to the morphine-paired compartment when it was paired with anisomycin during the reactivation session. In cocaine-induced CPP in mice, Fan et al. (2010) gave systemic injections of either anisomycin or cyclohexamide just after a preference test in the drug-free state or just after an additional conditioning session with cocaine and saline. Anisomycin administration led to the lack of subsequent place preference behavior, and this effect was dependent on reactivation, indicating the likelihood of reconsolidation disruption by this agent. Place preference remained absent when rats were tested in the drug-free state, and it was also absent when tested 1.5 months later under cocaine-reinstatement conditions in which a cocaine-priming injection was given. However, in opposition to the findings by Robinson and Franklin (2007b) above, when Fan et al. (2010) delivered anisomycin after an additional cocaine conditioning session (but not after a saline conditioning session), mice did not demonstrate CPP in a subsequent test. It is important to note that the study by Fan et al. (2010) used a biased procedure in which mice were confined to the initially non-preferred compartment during cocaine training, while Robinson and Franklin (2007b) used a counterbalanced procedure. Thus, the differences in ability to reactivate and subsequently produce an absence of CPP expression in the CPP procedure may depend on which processes drive the motivation to choose the drug-paired compartment (increased approach toward the drug-paired side *vs.* decreased avoidance for the initially-non-preferred, now drug-paired side).

In contrast to the above findings, Yim et al. (2006) delivered anisomycin into the BLA of rats just after reactivation in a morphine-induced CPP task and found no change in subsequent CPP, suggesting that no disruption of reconsolidation occurred. They attempted

to reactivate the memory in three ways: by exposing animals to the CPP apparatus in a drug-free state, by exposing animals to the CPP apparatus after morphine injection, and by exposing animals to the CPP apparatus after morphine injection and confining them to the previously morphine-paired compartment. One of the reasons that they may not have observed altered CPP expression is that protein synthesis in the BLA may not be necessary for reconsolidation of the memory for the morphine-associated context in the CPP task. The difference from the Milekic et al. (2006) study discussed above may have been that, in the Milekic study, rats were trained for morphine-induced CPP by giving morphine injections paired with one chamber but no alternating saline injections paired with the opposite chamber rather than the more standard procedure of pairing morphine with one chamber and saline with the opposite chamber of the CPP apparatus. This was done to avoid a second, potentially interfering, contextual memory of saline with the opposite CPP compartment. In general, protein synthesis inhibitors given after reactivation have led to a lack of subsequent CPP expression, suggesting that these inhibitors disrupt drug-associated CPP memories.

3.2.2. Neurotransmitters and receptors—Several studies have examined the roles of various neurotransmitters and their receptors in reconsolidation of CPP memories, most notably NMDA receptors (Brown et al., 2008; Itzhak, 2008; Kelley et al., 2007; Popik et al., 2006; Sadler et al., 2007; Zhai et al., 2008) and beta-adrenergic receptors (Bernardi et al., 2006; Fricks-Gleason and Marshall, 2008; Robinson and Franklin, 2007a, 2010; Robinson et al., 2011b). Sadler et al. (2007) demonstrated a reduction in the expression of established amphetamine-induced CPP after post-reactivation injections of systemic MK801 were given over 10 reactivation sessions that were standard CPP test sessions in the drug-free state. This diminished CPP expression was persistent for several days. The effect was absent if MK801 was delayed 1 h after reactivation sessions and appeared to be due to disruption of memory reconsolidation, although effects on extinction cannot be completely ruled out. Consistent with this finding, Kelley et al. (2007) found that a single systemic injection of MK801 given immediately prior to exposure to all chambers of the CPP apparatus (the reactivation session) led to the absence of subsequent CPP expression, and this effect was persistent and not reversed by a cocaine-primed reinstatement session. However, there were no controls (either delayed administration of the amnestic agent or no-reactivation controls), so it is possible that these results were due to a non-specific effect of MK801. In this same study, the NMDA partial agonist, D-cycloserine (DCS), produced the same effects when given over the same time frame of re-exposure to the CPP chambers. The observation that DCS promotes extinction (Walker et al., 2002) but that the same effects were found with both an NMDA antagonist, by which reconsolidation was purported to be disrupted, and an NMDA agonist that is known to promote extinction suggests that MK801 may have disrupted reconsolidation and DCS promoted extinction. This is consistent with their failure to reinstate CPP with a cocaine priming injection after MK801, but not DCS, treatment because extinction of behavior is partially defined by the ability to reinstate the behavior (in this case, with a drug-priming injection) while disruption of memory reconsolidation would not be expected to result in re-emergence of the behavior with a drug-priming injection (see Box 2, point 6). Since these agents were administered prior to the reactivation session, it is also possible that the effect on CPP was partially due to state-dependent effects, although the same group subsequently demonstrated that post-reactivation injection of MK801 also led to an absence of both drug-free and cocaine-primed CPP (Itzhak, 2008). The findings by Brown et al. (2008) testing the effects of MK801 are generally consistent with the above studies. In this study, systemic MK801 was given 30 min prior to two reactivation sessions in which rats were placed into the CPP apparatus but given a cocaine priming injection in an attempt to fully reactivate the cocaine-associated memory. Subsequent testing in the presence of a cocaine priming injection revealed that MK801 given before reactivation led to the lack of cocaine-primed reinstatement the next day in a reactivation-dependent manner.

The NMDA antagonist ketamine given systemically immediately after a reactivation session in the drug-paired compartment has also been shown to lead to the absence of subsequent expression of morphine CPP when tested a few days later (Zhai et al., 2008). This effect was dependent on reactivation in the drug-paired compartment and was not altered by a low-dose morphine priming injection. In addition, the NMDA antagonist memantine given systemically 20 min prior to two extinction sessions in which rats were confined to either the morphine- or saline-paired compartment (Popik et al., 2006) produced a lack of CPP expression when later tested in the absence of drug and also after a morphine-priming injection given 3 wk later; however, this effect was not tested in the absence of reactivation sessions.

A few studies have examined the impact of *localized* injections of NMDA receptor antagonists on drug-associated memories in the CPP task (Wu et al., 2012; Zhou et al., 2011). The NMDA glycine modulatory site antagonist, 7-chlorothiokynurenic acid (7-CTKA), was given into either the VTA or substantia nigra prior to reactivation in a cocaine CPP task (Zhou et al., 2011). Administration of 7-CTKA into the VTA, but not into the substantia nigra, reduced subsequent expression of CPP in a reactivation-dependent manner, and CPP expression remained blunted after a cocaine-priming injection. The role of the NMDA antagonist D-(−)2-amino-5-phosphonopentanoic acid (D-APV) injected into the nucleus accumbens core was examined for its role in morphine-induced CPP and morphine plus naloxone-precipitated conditioned place aversion (Wu et al., 2012). Morphine CPP was established and D-APV was given just prior to or just after memory reactivation. D-APV given prior to reactivation produced absence of CPP in a reactivation-dependent manner when tested multiple times and after a morphine-priming injection. Interestingly, conditioned place aversion was not altered by D-APV given into the nucleus accumbens core, suggesting to the authors that either this brain region is not the locus of reconsolidation of aversive memories associated with the combination of morphine and naloxone or that this aversive memory does not rely on NMDA receptors. However, the reactivation conditions were different between the preference and aversion tasks in that for the preference task, rats were given a morphine injection and confined to their usual drug-paired compartment while for the aversion task, rats were allowed to freely explore all chambers in a drug-free state. Therefore, the aversive memory that leads to conditioned place aversion may not have been appropriately reactivated to disrupt reconsolidation.

Several CPP studies have explored the impact of post-reactivation propranolol on subsequent drug-seeking behavior (Bernardi et al., 2006; Fricks-Gleason and Marshall, 2008; Robinson et al., 2011a,b; Robinson and Franklin, 2007a, 2010). Bernardi et al. (2006) demonstrated that systemic propranolol given just after a reactivation session produced a lack of cocaine-seeking behavior in a reactivation-dependent manner when assessed the next day in a drug-free CPP test. Additional studies by this group (Bernardi et al., 2009) demonstrated that systemic or intra-BLA injection of the beta-2 adrenergic receptor antagonist, ICI 118,551, and the alpha-1 antagonist, prazosin, also led to the absence of cocaine-seeking behavior in a reactivation-dependent manner when assessed in a drug-free CPP test the next day. Fricks-Gleason and Marshall (2008) demonstrated that expression of cocaine-induced place preference was also absent even after multiple testing sessions in the drug-free state and after three low-dose priming injections of cocaine when animals received 13 injections of propranolol given post-reactivation (extinction sessions), but not after a single propranolol injection given post-reactivation. The authors concluded that the daily injections of propranolol likely disrupted reconsolidation of the cocaine-associated memory because animals did not demonstrate reinstatement, although it should be noted that rats were not tested for the effects of multiple propranolol injections in the absence of the multiple reactivation sessions. Morphine-induced CPP was also absent after post-reactivation treatment with propranolol. Robinson and Franklin (2007a) determined that the

centrally-acting antagonist propranolol, but not the peripherally-acting antagonist nadolol, led to the absence of expression of morphine-induced place preference for up to 1 wk, although this effect was overridden by a morphine-primed reinstatement. A follow-up study by this same group (Robinson et al., 2011a) demonstrated that propranolol did not disrupt morphine CPP expression when rats were first given *chronic* morphine treatment prior to training, suggesting that this stronger CPP memory may have been less easily disrupted. Two additional studies by these investigators tested the effect of memory age and strength and also of novelty of the reactivation conditions in morphine-induced CPP. The strength of the memory was manipulated by the number of pairings with the CPP chamber (4 *vs.* 8) (Robinson and Franklin, 2010). Repeated reactivation sessions (reactivation sessions = extinction sessions) paired with post-reactivation propranolol led to the absence of later CPP when fewer cocaine training sessions (4 pairings) were given. However, when more cocaine pairing sessions were given (8 pairings), the same treatment with propranolol given after reactivation sessions led to lower CPP expression when these sessions were given 30 days *vs.* 1 day after training, and the behavior was not reinstated by a morphine-priming injection. These findings are consistent with a previous fear conditioning study in which weak conditioning could be disrupted by microinjection of anisomycin into the lateral and basal nuclei of the amygdala, but disruption of behavior after strong fear conditioning required a delay in delivery of reactivation sessions (30–60 days later), suggesting that this memory becomes labile only after a delay (Wang et al., 2009). The second follow-up study by this group examined morphine-induced CPP and demonstrated that propranolol was effective at producing an absence of later CPP if it was given after the first *vs.* the second reactivation session (reactivation session = first extinction session) (Robinson et al., 2011b), suggesting that when the reactivation session was novel (and no extinction had yet taken place), reconsolidation was the primary process that was disrupted by propranolol (see points (4) and (5) of Section 4 below for additional discussion of this issue).

Other neurotransmitter systems that have been examined include $GABA_A$ and $GABA_B$ receptors, cannabinoid CB1 receptors, muscarinic receptors, nitric oxide (NO) systems, and those neurotransmitter systems affected by amphetamine (Blaiss and Janak, 2006; Heinrichs et al., 2010; Itzhak and Anderson, 2007; Kelley et al., 2007; Robinson et al., 2011a; Robinson and Franklin, 2010; Yu et al., 2009; Zhai et al., 2008). Midazolam given post-reactivation (reactivation sessions = extinction sessions) in morphine-CPP has been shown to lead to lower expression of place preference behavior, but the reactivation dependence of this effect was not tested (Robinson and Franklin, 2010). A follow-up study by the same group (Robinson et al., 2011a) demonstrated a lack of effect of midazolam in animals that were given *chronic* morphine treatment, suggesting that the memory for morphine CPP was stronger and perhaps less easily disrupted. The $GABA_B$ receptor agonist baclofen given post-reactivation for several sessions (reactivation sessions = extinction sessions) may have either promoted extinction or impaired the reconsolidation of morphine CPP, but again, this drug was not tested in the absence of the reactivation sessions, so it is possible that non-specific effects of baclofen occurred independent of reconsolidation disruption (Heinrichs et al., 2010). Yu et al. (2009) demonstrated that the CB1 receptor antagonist rimonabant given immediately after reactivation led to the absence of methamphetamine-associated CPP memory in mice for up to 2 wk in a reactivation-dependent manner, and CPP expression was not reinstated by a methamphetamine priming injection. A role for the muscarinic receptor antagonist scopolamine has also been demonstrated in morphine-(Zhai et al., 2008) and cocaine-induced (Kelley et al., 2007) CPP. Scopolamine given systemically just after reactivation led to the lack of subsequent CPP expression when tested a few days later (Zhai et al., 2008); this effect was reactivation dependent, and CPP was not restored by a low-dose morphine priming injection. Consistent with this finding, Kelley et al. (2007) found that scopolamine given immediately prior to reactivation produced a lack of subsequent CPP for cocaine that persisted for nearly 40 days, although unlike in the Zhai et al. study, CPP was

reinstated with a cocaine priming injection. Although the absence of no-reactivation controls and injection of scopolamine prior to the reactivation session cannot rule out other possible effects of this agent, their finding is in agreement with Zhai et al. (2008) and suggests that reconsolidation of a morphine-associated memory may be disrupted by systemic scopolamine when animals are tested in the drug-free state. The neuronal nitric oxide synthase (NOS) inhibitor 7-NI given prior to a reactivation session led to the lack of later cocaine CPP expression when tested up to 2 wk after reactivation that was not restored by a cocaine-priming injection in mice, suggesting that NO may be necessary for reconsolidation (Itzhak and Anderson, 2007), although other non-specific effects cannot be ruled out because 7-NI treatment was given prior to reactivation and non-reactivated controls were not tested. In accordance with the notion that reconsolidation is also a way to strengthen memories, Blaiss and Janak (2006) demonstrated that post-reactivation amphetamine administration enhanced the expression of subsequent morphine CPP in a reactivation-dependent manner, suggesting that amphetamine may enhance the reconsolidation of a morphine CPP memory.

3.2.3. Cell signaling pathways and transcription factors—Miller and Marshall (2005) were the first to report the disruption of reconsolidation of cocaine-associated memories in a CPP task. They examined the role of the extracellular signal-regulated kinases 1 and 2 (ERK1 and ERK2) in cocaine memories. Activation of ERK has been implicated in activation of immediate-early genes important for behaviors induced by drugs of abuse (Berhow et al., 1996). Phosphorylation of ERK (pERK) produces increases in the levels of the transcription factors ets-like gene-1 (Elk-1), cAMP response element binding (CREB), and ultimately in Fos. Miller and Marshall first showed that placement in the cocaine-paired chamber after training increased pERK2, pCREB and pElk-1 levels in the nucleus accumbens core but not in the shell. Microinjection of an inhibitor of ERK kinase MEK (U0126) into the nucleus accumbens core immediately after a reactivation session led to later absence of CPP expression tested up to 2 wk later and also suppressed the increase in pERK, pCREB, pElk-1 and Fos levels normally found after memory reactivation. These effects were dependent on reactivation, suggesting the importance of these molecules in maintaining memory for CPP. Valjent et al. (2006) produced findings consistent with those of Miller and Marshall when they systemically injected the ERK inhibitor SL327 prior to cocaine exposure in the drug-paired compartment to reactivate memory. The ERK inhibitor led to absence of CPP expression for up to 2 wk later, and this effect was accompanied by blockade of increased levels of pERK and phosphorylated glutamate receptor 1 (pGluR1) in the dorsal striatum and nucleus accumbens. In addition, morphine-induced CPP expression was also absent after treatment by this ERK inhibitor given before reactivation, and CPP was not restored by a morphine priming injection (Valjent et al., 2006). However, in contrast to the Miller and Marshall study, the ERK inhibitor effects in the Valjent et al. study required simultaneous exposure to the CPP chamber and cocaine during the reactivation session; these discrepancies may be due to differences in the species used, the training procedure, or the route of administration. Overall, however, these inhibitors were administered *prior* to reactivation sessions so it would be important to assess whether post-reactivation ERK inhibitors produce similar findings.

Other signaling pathways have also been implicated in the reconsolidation of drug-induced CPP memories (Brown et al., 2007; Li et al., 2010; Theberge et al., 2010; Yang et al., 2011). Li et al. (2010) demonstrated that the expression of cocaine-induced CPP was accompanied by elevated activity levels of cyclin-dependent kinase 5 Cdk5 and the levels of its coactivator, p35, in the BLA but not in the central amygdala. Cdk5 in the nucleus accumbens has been shown to influence cocaine-induced behaviors (Benavides et al., 2007; Taylor et al., 2007). Li et al. (2010) went on to show that inhibition of Cdk5 with beta-butyrolactone in the BLA but not in the central amygdala produced an absence of expression

of cocaine CPP for up to 2 wk, and CPP was not reinstated by a cocaine priming injection, suggesting that inhibition of Cdk5 disrupts the reconsolidation of cocaine-induced CPP. The transcription factor, NFkappa-B, appears to be involved in morphine-induced CPP memory. Inhibition of NFkappa-B by intracerebroventricular injection of SN50 2 h prior to reactivation produced a lack of subsequent CPP expression for up to 2 wk and CPP was not restored by a morphine-priming injection (Yang et al., 2011). This effect was reactivation-dependent and was blocked by treatment with the histone deacetylase inhibitor sodium butyrate, suggesting that NFkappa-B downstream signaling affects histone deacetylases (Lubin and Sweatt, 2007). The transcription factor, Zif268, also appears to be involved in the reconsolidation of memory for cocaine-induced CPP. When Zif268 antisense oligodeoxynucleotide (ASO) was given into the BLA or into the nucleus accumbens core prior to memory reactivation, it led to the absence of subsequent CPP expression in a reactivation-dependent manner (Theberge et al., 2010). Another class of molecules that impacts cell signaling via extracellular matrix molecules is matrix metalloproteinases (MMPs), which have been examined for their ability to disrupt reconsolidation in cocaine-induced CPP. The MMPs are a family of molecules that, among other functions, degrade the extracellular matrix and are involved in learning and memory (Kaczmarek et al., 2002; Wright and Harding, 2009). Brown et al. (2007) demonstrated that a broad inhibitor of MMPs given i.c.v. either prior to or just after cocaine-primed reactivation led to the lack of expression of later cocaine-primed CPP reinstatement in a reactivation-dependent manner. This effect required simultaneous exposure to the cocaine and the context for apparent full memory reactivation, since injection of the MMP inhibitor given in the absence of either the CPP apparatus or cocaine injections did not have an effect on the expression of cocaine-primed CPP. The role of glycogen synthase kinase-3beta (GSK-3beta), a serine/threonine protein kinase present in dopaminergic terminals (Leroy and Brion, 1999), was tested in cocaine CPP (Wu et al., 2011). The activity of GSK-3beta was elevated in the BLA, but not central amygdala, after a reactivation session in animals with established cocaine CPP. Inhibition of GSK-3beta with SB216763 within the BLA, but not the central amygdala, produced a dose-dependent reduction in the expression of CPP, and this effect was not present in non-reactivated or delayed (6 h) control groups. Further, CPP expression was absent in the highest dose for up to 2 wk and was not restored by a cocaine priming injection, suggesting that GSK-3beta in the BLA disrupts memory reconsolidation for cocaine CPP.

Overall, the studies described above suggest that manipulation of several neurotransmitter systems and downstream pathways by pharmacological agents disrupts drug memory reconsolidation in a CPP task. Additional CPP studies have examined the capacity for *non-pharmacological* manipulations to disrupt memory reconsolidation. One recent study found that total sleep deprivation in the interval of 0–6 h following memory reactivation but not 6–12 h after reactivation produced a lack of morphine CPP expression in a reactivation-dependent manner, and the behavior was not reinstated by a morphine priming injection (Shi et al., 2011). Another morphine-induced CPP study demonstrated that a stressor (cold swim stress) given just after memory reactivation produced a lack of CPP expression when tested up to 2 wk later, and CPP was not reinstated by a morphine priming injection (Wang et al., 2008). The effect on CPP was blocked by the glucocorticoid antagonist RU38486 given into the BLA but not into the central amygdala. Paradoxically, however, intra-BLA RU38486 or systemic corticosterone produced the same disruptive effects, indicating that increases or decreases in glucocorticoid receptor activation may lead to memory disruption. These findings are consistent with studies on the effects of stress in humans (Schwabe and Wolf, 2010) and aversive memory studies describing similar effects of RU38486 on the disruption of reconsolidation (*e.g.*, Taubenfeld et al., 2009). A recent study examined the ability of post-reactivation extinction sessions to reduce the expression of established morphine-induced CPP behavior (Ma et al., 2011). This study was based on earlier findings that the

expression of fear is absent if a brief reactivation period is followed by an extinction session (Monfils et al., 2009), with the premise that the fear memory will be revaluated if extinction is given during the reconsolidation window but not if extinction is given after a period when the reconsolidation window has closed (but see Chan et al., 2010). In the CPP study (Ma et al., 2011), morphine-CPP was established and then CPP test sessions (to reactivate memory) were given alone or were followed by longer confined extinction sessions in each CPP chamber given either 10 min or 3 h after each CPP test session. Disruption of reconsolidation would be demonstrated by the lack of spontaneous recovery or morphine-primed reinstatement. They found that with the 10 min post-reactivation extinction, spontaneous recovery was absent for up to 4 wk and reinstatement did not occur after a 1 wk interval but returned after a 4 wk interval. These studies demonstrated that CPP was only transiently disrupted, and future studies will need to explore whether long-term absence of drug-seeking behavior can be produced by this non-pharmacological approach.

All of these CPP studies discussed tested the ability of amnestic agents to disrupt the reconsolidation of memory for the *reinforcing* effects of drugs of abuse. However, the *negative affective state* that accompanies withdrawal from drugs (forced abstinence in animal studies) is believed to be a potent contributor to relapse in humans (Kassel, 2010; Sinha, 2008). Taubenfeld et al. (2010) conducted a unique study to determine whether the memory for drug-associated contexts was linked to a subsequent withdrawal response, and if so, whether the motivational withdrawal response could also be diminished with amnestic agents. They first trained rats for morphine-induced CPP and then reactivated the memory with an additional conditioning session followed by systemic cyclohexamide. After another conditioning session, they delivered naltrexone to precipitate withdrawal in the same morphine-paired compartment. Rats normally display aversion a few days later, but animals given cyclohexamide just after prior memory reactivation demonstrated neither place preference for the morphine-paired chamber (disruption of reconsolidation) nor place aversion after naltrexone treatment. Several additional control groups led the authors to conclude that a memory for the drug-paired context was necessary to create the link between the drug-reinforced response and the motivational (but not physical) signs of withdrawal. They went on to show that this context-dependent withdrawal was dependent on both protein synthesis and PKA activity within the dorsal hippocampus immediately after a reactivation session. This finding is important because it suggests that memories that underlie both positive and negative affective states associated with drugs of abuse may be targeted for disruption. These findings are distinctive from those from a recent study that examined morphine-conditioned place aversion (discussed above) (Wu et al., 2012), in that no impact of nucleus accumbens core $_{D}$-APV treatment given prior to reactivation was observed on subsequent aversion to the morphine plus naloxone-paired compartment. Although a different brain region and neurotransmitter system was targeted in each of these two studies, animals in the Wu et al. study were trained only for conditioned place aversion, supporting the idea that the *link* between a memory for the rewarding effects of morphine and naloxone-precipitated withdrawal effects may be necessary to disrupt memory for both.

3.3. Conditioned approach studies

Conditioned approach behavior (Box 1) is produced by repeatedly pairing a discrete CS such as a light with a reward such as sucrose, but the delivery of sucrose is independent of the animal's behavior. Over time, animals demonstrate an increased number of approaches toward the CS (Brown and Jenkins, 1968). In a Pavlovian conditioned approach procedure, Blaiss and Janak (2007) tested whether post-reactivation administration of either systemic amphetamine or anisomycin would alter conditioned approach toward sucrose. Rats were trained with a compound light/tone conditioned stimulus (CS) followed by availability of sucrose. No effect of either drug was found on Pavlovian conditioned approach behavior,

independent of the number of training trials rats received and independent of whether reactivation included presentation of the sucrose after the CS presentation. In contrast to these findings, Lee and Everitt (2008c) examined Pavlovian approach behavior for sucrose reward in an autoshaping procedure. Approach behavior was absent after systemic MK801 (but not propranolol) when given 30 min prior to a reactivation session. They concluded that the motivational properties of this Pavlovian CS undergo reconsolidation that is dependent on NMDA receptor activation. The discrepancy with the Blaiss and Janak (2007) study was attributed by Lee and Everitt (2008c) to the difference in procedure, with Blaiss and Janak using a goal-tracking rather than a sign-tracking procedure that may be less subject to interference by amnestic agents; thus memory underlying goal-tracking behavior may be less vulnerable to disruption. Alternatively, different agents were used, and in the case of the study by Lee and Everitt, these agents were given prior to rather than after reactivation, and this prior treatment may have made the memory more easily amenable to disruption.

3.4. Self-administration studies

Relatively few self-administration studies have addressed whether several of the same disruptors of memory reconsolidation for CPP behavior disrupt instrumental behavior such as lever pressing or nose poking for rewards. The ability to disrupt drug-associated memories in self-administration studies is significant because the self-administration model has the highest validity for human addiction. In contrast to the relatively few drug exposures that are administered by the investigator in sensitization and CPP studies and in which animals are generally not considered to be in the same state of drug-dependence as after self-administration training, self-administration studies allow for hundreds of reward exposures and reward pairings with contextual cues (the self-administration chamber) alone or along with discrete cues such as a cue light, presumably resulting in stronger memories more closely resembling the situation in human addicts. Moreover, the non-contingent drug administration in CPP studies *vs.* contingent drug administration in self-administration studies may engage different features of drug-associated memories and underlying neural circuitry and neurochemistry. Thus, the critical issue is whether such well-consolidated memories can be disrupted by amnestic agents delivered during memory reactivation. Below I first review studies involving self-administration of other rewards, most notably sucrose, followed by studies involving drug self-administration.

3.4.1. Sucrose self-administration—Several studies have tested the effects of various amnestic agents on sucrose self-administration (Diergaarde et al., 2006; Hernandez and Kelley, 2004; Hernandez et al., 2002; Lee and Everitt, 2008a,b,c; Mierzejewski et al., 2009; Wang et al., 2005). Wang et al. (2005) tested the effects of intra-amygdala (lateral and basal) infusion of anisomycin on incentive learning in a self-administration task. For this task, they trained rats to lever press for food and sucrose in a food-deprived state using two different levers (one for food, one for sucrose). To decrease the motivational state and devalue the reward, rats were food sated and given a session in which they were allowed *ad libitum* access to either food pellets or sucrose in this food-sated state so that they learned to devalue one of the rewards. To test whether protein synthesis was necessary within the lateral and basal amygdala during incentive learning (the devaluation session), they delivered anisomycin into these amygdala regions just after the devaluation session. A choice test for lever-pressing behavior in the absence of any rewards would demonstrate whether devaluation occurred if lever pressing was reduced for the devalued reward but not for the non-devalued reward. If anisomycin blocked the ability to devaluate the reward, then the number of lever presses on each lever should be equally high on the choice test. Their findings demonstrated that anisomycin produced equal responding on both levers during the choice test, suggesting that anisomycin impaired the reconsolidation of incentive learning.

Further studies by Lee and Everitt (2008c) used a Pavlovian-instrumental transfer (PIT; Box 1) procedure to determine whether MK801 or propranolol would disrupt memory reconsolidation. Rats were trained to lever press for sucrose and subsequently given a stimulus associated with sucrose availability (CS+) or another stimulus associated with sucrose non-availability (CS−) in the absence of the lever. Rats then received either MK801 or propranolol 30 min prior to a reactivation session (CS+). On the test for PIT, lever presses in the presence of the CS+ and CS− and absence of any CS were measured. MK801 but not propranolol produced a subsequent lack of PIT, suggesting that reconsolidation of the memory underlying the motivational properties of a sucrose reward-associated CS is dependent on NMDA receptors. Lee and Everitt (2008b) used a sucrose self-administration task in an additional study to determine whether the disruption of reconsolidation of appetitive memories was dependent on the *contingency* of the stimulus presentation during reactivation. In this study, they trained rats to lever press for sucrose and then reactivated the memory by either presenting the CS non-contingently in the absence of levers or allowing the animal to nose poke for presentation of the CS. MK801 was systemically injected prior to reactivation or just after reactivation. When MK801 was given *prior to contingent* reactivation, it led to the absence of subsequent cue-induced sucrose-seeking behavior but did not alter sucrose seeking if it was given either *after contingent* reactivation or *prior to non-contingent* reactivation. In a third type of study, Lee and Everitt (2008a) examined reconsolidation of a sucrose-associated memory by testing the acquisition of a new response (Box 1) with a conditioned reinforcement procedure. In this procedure, rats are first trained to self-administer sucrose (or drug; see below) by nose-poke responding, and each sucrose reinforcement is paired with the presentation of a light CS. Reactivation of the CS-sucrose memory is done by allowing rats to nose poke for the CS. The conditioned reinforcing properties of the CS are then tested in a second phase in which rats are allowed to press a lever for conditioned reinforcement (presentation of the CS). The goal in this study was to attempt to disrupt reconsolidation of the sucrose-CS memory at the end of the first phase, which would be manifest as a failure to acquire the new response because rats would no longer associate the conditioned reinforcing properties of the CS with the sucrose and therefore would not press the lever for presentation of the CS alone. Lee and Everitt (2008a) found that rats given systemic MK801 either prior to or just after reactivation failed to acquire the new response, and this effect was reactivation dependent, suggesting that MK801 disrupted reconsolidation of the memory for the sucrose-associated CS. In addition, they showed that MK801 given prior to, but not after, reactivation of the new response (lever presses) lowered maintenance of responding for several days, suggesting a disruption of reconsolidation of memory for the conditioned reinforcing properties of the CS. This study demonstrated that there are different temporal requirements for NMDA activation relative to memory reactivation that are likely to be task dependent.

In another study by this group measuring the acquisition of a new response, Milton et al. (2008b) found that when systemic propranolol was given just after the reactivation session (nose poke for the CS only), rats did not acquire the new lever-pressing response for the CS, suggesting that propranolol disrupted the reconsolidation of memory for the sucrose-associated CS. Consistent with the disruptive effects of this agent, studies by Diergaarde et al. (2006) also suggested that there were disruptive effects of systemic propranolol on the reconsolidation of an instrumental memory in a sucrose-seeking task. They trained rats to nose poke for sucrose, but one nose-poke hole signaled sucrose *availability* and the other signaled sucrose *reward*. After a 3 wk withdrawal, reactivation for 20 min but not for 10 or 0 min in the absence of cues followed by propranolol decreased nose poking in both holes the next day, suggesting that both the memory for the context associated with sucrose *availability* as well as the memory for the context associated with sucrose *reward* were dampened.

In some studies, no effects of anisomycin or cyclohexamide have been found on the reconsolidation of memories underlying the instrumental component of the self-administration task. Hernandez et al. (2002) showed in a sucrose self-administration task that anisomycin given into the nucleus accumbens just after training sessions could disrupt the consolidation of memory underlying this instrumental task, but that once the memory was learned, anisomycin given post-session for three sessions into the nucleus accumbens had no effect. This study indicates that protein synthesis in the nucleus accumbens was no longer required once the instrumental training was consolidated. A follow-up study by Hernandez and Kelley (2004) examined the impact of systemic anisomycin on sucrose self-administration to address the possibility that protein synthesis at brain sites other than the nucleus accumbens might contribute to the reconsolidation of an appetitive instrumental task. They found that rats given systemic anisomycin post-session for four sessions (sessions 10–14) decreased subsequent sucrose self-administration. They attributed this effect to a conditioned taste aversion to the sucrose produced by systemic anisomycin effects. To circumvent this problem, they then trained animals to self-administer sucrose, and during the reactivation session (similar to a standard self-administration session), they replaced the sucrose pellets with chocolate pellets to avoid conditioned taste aversion to sucrose. Anisomycin still had no impact on subsequent sucrose self-administration, suggesting to the authors that well-established memories for instrumental responding are not labile and susceptible to disruption by protein synthesis inhibition. However, the condition of the reactivation session should also be considered. Since it is unclear which aspects of the memory need to be reactivated to render the memory labile, it is possible that the novel chocolate pellets given on the reactivation day did not permit sufficient memory reactivation to cause it to be labile for disruption by anisomycin. However, consistent with the absence of anisomycin effects on instrumental behavior, Mierzejewski et al. (2009) trained rats to lever press for saccharin and reported that systemic cyclohexamide just after several short reactivation sessions had no effect on subsequent saccharin self-administration. These findings suggest that a well-established memory for an appetitive instrumental task involving sucrose or saccharin self-administration may not rely on protein synthesis for the maintenance of that memory or that these types of memories may be more difficult to disrupt when tested under maintenance responding conditions. This issue is further addressed below with regard to suppression of instrumental responding after training for drug self-administration.

3.4.2. Drug self-administration—The drug self-administration studies conducted to date are summarized in Table 1, which describes the main features of the study design and results. Nearly all self-administration studies have tested the ability of amnestic agents to disrupt the reconsolidation of memories for cocaine-associated discrete *cues*, and a few studies have tested the ability of amnestic agents to disrupt reconsolidation of memories for the cocaine-associated *context*.

Several studies by Everitt and coworkers examined the reconsolidation of cocaine-associated memories using the drug self-administration model, with most of these studies focused on disrupting the reconsolidation of memories for the cocaine-associated cues. In the first of these studies, Lee et al. (2005) examined reconsolidation of a cocaine-associated memory by testing the acquisition of a new response (described above and in Box 1) to examine the ability of anisomycin to disrupt the memory of a conditioned reinforcer. Anisomycin given into the BLA just after reactivation impaired (delayed) the acquisition of a new response, and this effect occurred in a reactivation-dependent manner. This finding suggested for the first time that memory for a discrete cocaine-associated cue could be impaired in rats trained for drug self-administration.

The relatively broad-spectrum amnestic agents anisomycin, tetrodotoxin (TTX), and the $GABA_A$ and $GABA_B$ agonists, muscimol and baclofen, respectively, have since been used to block the reconsolidation of drug memories in a variety of self-administration protocols. Anisomycin given i.c.v. immediately after reactivation of an ethanol-associated cue prevented the expression of cue-induced ethanol-seeking behavior when tested 24 h and 7 days later (von der Goltz et al., 2009). Three studies examined the ability of amnestic agents to disrupt reconsolidation of the cocaine-associated context such that subsequent exposure to the context after extinction altered the expression of cocaine-seeking behavior. The first of these studies (Fuchs et al., 2009) demonstrated that anisomycin given into the BLA after reactivation attenuated drug context-induced reinstatement. This effect occurred only if animals were given a reactivation session lasting for 15 or 60 min, but not if animals were given a reactivation session lasting for 5 or 120 min, suggesting that 5 min was insufficient to destabilize the memory and that 120 min was too long and produced extinction. The second study (Ramirez et al., 2009) examining the role of drug context-induced cocaine-seeking behavior delivered either TTX or anisomycin after reactivation into four different brain regions: the dorsal hippocampus, the dosolateral caudate-putamen, the dorsomedial prefrontal cortex, and the BLA. Administration of TTX into the dorsal hippocampus and the BLA attenuated drug context-induced reinstatement, but despite sensitivity of the dorsal hippocampus to TTX effects, anisomycin in this region had no impact, suggesting that memory reconsolidation for the drug context is independent of protein synthesis in the dorsal hippocampus. In a third, follow-up study by the same group (Wells et al., 2011), an interaction between the BLA and the dorsal hippocampus was demonstrated in a disconnection study to determine the impact of this disconnection on cocaine-associated context-induced reinstatement. Anisomycin was delivered into the BLA and the GABA agonists baclofen and muscimol were delivered into the contralateral dorsal hippocampus to inactivate this region just after reactivation. Disconnection of the BLA and dorsal hippocampus reduced context-induced reinstatement in a reactivation-dependent manner, and this effect did not occur in animals that had ipsilateral treatment of these drugs. Moreover, this blunted effect was still present 3 wk later, suggesting that the BLA and dorsal hippocampus interact to influence memory reconsolidation for the cocaine-paired context.

In the same study that examined the impact of anisomycin on memory reconsolidation while testing for the acquisition of a new response, Lee et al. (2005) also examined the role of the transcription factor Zif268 in the reconsolidation of cocaine-associated memories. Elevated levels of Zif268 are found within several brain areas involved in reward, and increases in this protein are found when a predictive relationship between the stimulus and cocaine has been established (Thomas et al., 2003), implicating Zif268 in memory reactivation or memory reconsolidation. Similar to when anisomycin was given into the BLA just after reactivation, they found that Zif268 ASO given into the BLA 90 min prior to reactivation impaired the acquisition of a new response, and this effect occurred in a reactivation-dependent manner. These findings were consistent with their previous work demonstrating that Zif268 ASO in the hippocampus disrupted reconsolidation of contextual fear (Lee et al., 2004) and extended the role of Zif268 in the reconsolidation of cocaine-associated memories.

In a subsequent extensive cocaine self-administration study, Lee et al. (2006a) trained animals in a cocaine self-administration task and demonstrated that Zif268 ASO given into the BLA prior to cue reactivation suppressed subsequent cocaine-seeking behavior induced by the cocaine cue. This effect of Zif268 ASO was also present when reactivation took place 27 days after discontinuing self-administration and tested 3 days later. This lengthy withdrawal period from daily cocaine intake produces an “incubation of craving” effect, which is manifested as an increase in lever responding in both the absence and presence of a

drug-associated CS (Grimm et al., 2001; Tran-Nguyen et al., 1998). Thus, Zif268 ASO administration suppressed the expression of this incubation effect. In addition, the suppressive effect of Zif268 ASO occurred in rats that were given extinction sessions followed by reinstatement with a cocaine cue. Finally, using a second-order schedule of reinforcement, Zif268 ASO given 90 min prior to reactivation reduced maintenance responding for cocaine. Interestingly, Zif268 ASO had no effect on subsequent cocaine-seeking behavior in control rats that were not reactivated but were placed into the self-administration chambers in the absence of cue light presentations, indicating that re-exposure to the context alone in Zif268 ASO-treated rats did not suppress later responding to the cue. This finding is in accordance with the CPP studies described above in which both the CPP cues and the drug were required during the reactivation session to demonstrate subsequent apparent disruption of these memories. Further, these findings are in line with the notion that directly-reactivated memories, but not indirectly-reactivated memories, are susceptible to disruption by amnestic agents during reactivation (Debiec et al., 2006). A further test for a role of Zif268 within circuitry potentially underlying reconsolidation was conducted by Theberge et al. (2010). They found that, while previous work (see above) had demonstrated a clear role for Zif268 in the BLA on reconsolidation of the drug-CS memory using the acquisition of a new response (Lee et al., 2005), infusion of Zif268 ASO into the nucleus accumbens core 90 min prior to reactivation did not affect reconsolidation of this same drug-CS memory. In contrast, this same treatment in the nucleus accumbens core appeared to disrupt reconsolidation of a cocaine-associated memory in a CPP task (see above), suggesting that nucleus accumbens core Zif268 is important for memory underlying Pavlovian associations involved in a CPP task but not for memory underlying the conditioned reinforcing effects of the CS associated with cocaine self-administration.

In an interesting approach to further understand a role for Zif268 in memory reconsolidation, Hellemans et al. (2006) demonstrated that memory for the conditioned withdrawal (aversive) effects of heroin-seeking behavior appeared to also be disrupted by Zif268 ASO treatment in the BLA. In this study, rats were trained to self-administer heroin and subsequently given several pairings of a compound CS with naloxone-precipitated withdrawal to create a memory of the CS-withdrawal association. Zif268 ASO treatment in the BLA prior to reactivation of this new aversive memory reversed the decrease in heroin-seeking behavior in a reactivation-dependent manner, indicating that both appetitive and aversive memories associated with drugs of abuse can be manipulated by Zif268 within the BLA.

A handful of additional self-administration studies have manipulated the activity of neurotransmitter receptors or their downstream signaling pathways to determine whether blockade of these receptors or pathways disrupts reconsolidation. Milton et al. (2008a) delivered the NMDA receptor antagonist D(−)-2-amino-5-phosphonopentanoic acid (D-APV) into the BLA either immediately prior to or immediately after the reactivation session in the acquisition of a new response in animals trained to self-administer cocaine. When D-APV was given just prior to, but not after, the reactivation session, rats did not acquire the new instrumental response to the previously-paired cocaine cue up to 29 days later. These studies suggest that NMDA receptors in the BLA are necessary for disrupting the reconsolidation of memories for drug-associated stimuli but that the role of these receptors in this brain area may be limited to facilitating memory destablilization during reactivation so that it can become susceptible to disruption, in accordance with fear conditioning studies demonstrating an important role for NR2B receptors (Ben Mamou et al., 2006). They further showed that D-APV treatment before reactivation, but not after reactivation or in the absence of any reactivation, decreased Zif268 levels in the BLA, again implicating this transcription factor in memory for the conditioned reinforcing properties of the cocaine-paired cue. Milton et al. (2008a) also demonstrated that pre-reactivation systemic treatment with the

NMDA antagonist MK801 decreased the expression of cue-induced cocaine-seeking behavior in a reactivation-dependent manner, suggesting the ability of this compound to disrupt reconsolidation of the cocaine-associated cue. In contrast to these findings, a study by Brown et al. (2008) demonstrated a clear lack of an effect of MK801 on cocaine-seeking behavior in the same set of studies that found an effect of MK801 on the reconsolidation of CPP behavior (see above). Prior to two different types of reactivation sessions, systemic MK801 failed to alter subsequent cocaine-seeking behavior. One difference in this study *vs.* all other self-administration studies to date is that both a cocaine injection and cocaine-associated cues were given during the reactivation sessions and the subsequent test for cocaine-seeking behavior. The presence of cocaine itself may therefore have impaired the ability to render the memory labile and susceptible to disruption by MK801, or the unconditioned effects of cocaine on the reinstatement day may have overridden any suppressive effects of MK801 on memory.

Two additional studies found that the expression of cue-induced ethanol-seeking behavior was absent after MK801 treatment (von der Goltz et al., 2009; Wouda et al., 2010), and a recent study reported that MK801-induced disruption of Pavlovian conditioned approach behavior and PIT for ethanol-associated stimuli (Milton et al., 2012). In the first study examining cue-induced ethanol-seeking behavior, systemic MK801 was delivered just after reactivation, and this treatment decreased cue-induced ethanol-seeking behavior in a reactivation-dependent manner (von der Goltz et al., 2009). In the second study (Wouda et al., 2010), systemic MK801 was also given immediately after reactivation and produced a strong trend toward reduced cue-induced ethanol-seeking behavior. A third ethanol study (Milton et al., 2012) found that the expression of both Pavlovian conditioned approach behavior and PIT were lower after a single administration of systemic MK801 given 30 min prior to reactivation. In general, memory for ethanol-associated cues appears to be susceptible to disruption by MK801, especially if this antagonist is given multiple times or prior to reactivation rather than after reactivation.

Considering that NMDA antagonists generally have been shown to block reconsolidation of drug-associated memories, it may be predicted that an NMDA agonist may enhance the reconsolidation process to strengthen memories. The NMDA partial agonist D-cycloserine (DCS) given into the BLA prior to reactivation appeared to potentiate reconsolidation of a cocaine-associated memory, as measured by cue-induced cocaine-seeking behavior (Lee et al., 2009). In our own studies, we found that DCS given into the nucleus accumbens prior to a short reactivation session with cocaine (injected intraperitoneally as in a typical reinstatement protocol) also potentiated subsequent cocaine-induced reinstatement without altering cue-induced reinstatement (unpublished results). These data are consistent with fear conditioning studies demonstrating apparent enhancement of reconsolidation after DCS when the reactivation session was relatively brief (Lee et al., 2006b).

A few self-administration studies have followed up on the finding that propranolol, which has been shown to disrupt reconsolidation in fear conditioning studies (Debiec and Ledoux, 2004; Przybyslawski et al., 1999) and CPP studies (see above), also disrupts reconsolidation of drug-related memories in animals trained to self-administer drug. In the acquisition of a new response task, Milton et al. (2008b) reported that propranolol given just after reactivation of a cocaine-associated memory impaired the acquisition of a new response, suggesting that propranolol reduced the conditioned reinforcing properties of a previously cocaine-paired cue. In an ethanol self-administration study (Wouda et al., 2010), propranolol given just after reactivation reduced subsequent cue-induced reinstatement, but this was apparent only after additional reactivation sessions given 1 and 2 wk later, suggesting that either there were delayed effects of propranolol on this well-established ethanol-associated memory or that multiple reactivation sessions were necessary to disrupt this memory. A

third study by Milton et al. (2012) found that systemic propranolol given 30 min prior to memory reactivation did not alter the expression of Pavlovian conditioned approach behavior or PIT for ethanol-associated memories, similar to their findings in sucrose self-administering rats (discussed above) (Lee and Everitt, 2008c). These findings suggest that propranolol may disrupt some, but not all, aspects of drug-associated memory or that propranolol acts differently on drug-associated memories depending on the drug of abuse.

One self-administration study has explored the effects of PKA signaling on the reconsolidation of a cocaine-associated memory (Sanchez et al., 2010). Infusion of the PKA inhibitor Rp-cAMPS into the BLA immediately after reactivation of memory with the cocaine-associated cue demonstrated that subsequent expression of cue-induced reinstatement was lower after PKA inhibitor treatment within the BLA, while cocaine-induced reinstatement was unaffected, suggesting that the reduced reinstatement was specific for the memory that was reactivated. They further demonstrated in the acquisition of a new response task that PKA inhibitor treatment in the BLA after reactivation impaired the acquisition of the new response, suggesting that this inhibitor disrupted the conditioned reinforcing properties of a previously cocaine-paired cue. An interesting difference in this study compared with previous studies is that memory reactivation took place in a *novel* chamber, in contrast to previous studies examining the cocaine-associated CS in which the same chamber was used to train and reactivate memory and also in contrast to the context-dependence of memory reactivation when a drug-associated context was used to test for memory reconsolidation (Fuchs et al., 2009; Ramirez et al., 2009; Wells et al., 2011). The novel context in the presence of the drug-paired discrete cue may in fact destabilize the memory to a greater extent because it requires updating of information (see above). The finding that presentation of the CS in a novel context can be used to disrupt reconsolidation may be important for treatment of human addicts in whom drug-associated cues could be presented within environments other than their usual drug-taking environment to reactivate and disrupt drug-associated memories.

In contrast to the animal literature, a small number of studies have been conducted in humans on reconsolidation (for review, see Schiller and Phelps, 2011) and only a few have been conducted in human addicts. Zhao et al. (2009) gave word lists to heroin addicts that included neutral, heroin-related positive, and heroin-related negative words. After reactivation of memory the next day (retrieval of word lists), a psychosocial stressor was administered. The following day, free recall of the word lists revealed that stress impaired the recall of heroin-related negative and positive words but not of neutral words. Although no non-reactivated control or non-addicted subjects were included, the preferential impairment of recall for heroin-associated word lists suggests that reconsolidation processes may have been disrupted. A second study by this same group (Zhao et al., 2011) showed that, consistent with the findings in animals on the ability of propranolol to lead to later absence of CPP expression or prevent the acquisition of a new response, human heroin addicts given propranolol just prior to a reactivation session demonstrated a decreased ability to remember word lists that were specific to drug-associated positive or negative words but not to neutral words, and this effect was dependent on reactivation.

4. Memory reconsolidation disruption in addiction: Challenges for future studies

Some of the differences between CPP and self-administration studies discussed above may be attributed to the differences in the number of drug-context and drug cue pairings so that drug self-administration leads to stronger memories that are more difficult to disrupt by amnestic agents. In humans, different components of memory are believed to promote relapse behavior, including conditioned approach, conditioned motivation, and conditioned

reinforcement (Milton and Everitt, 2010). In reconsolidation studies, only some of the memory processes mediating these components may become reactivated and therefore vulnerable to disruption by amnestic agents, whereas effective suppression of relapse in humans using a reconsolidation disruption approach may require disruption of memories underlying all of these components. The instrumental components of a drug self-administration task may be less easily disrupted. For example, when a CS-cocaine memory is disrupted by amnestic agents, the instrumental response is not completely disrupted. That is, after reconsolidation disruption using only the discrete cue, the ability of the cue to maintain the instrumental response is diminished, but in the absence of the cue, the instrumental response remains unless rats are also given extinction sessions (Lee et al., 2006a; Milton et al., 2008a). Therefore, a combination of extinction and reactivation to drug cues with delivery of an amnestic agent may be required to extensively reduce drug-seeking behavior down to the level of extinction responding (Taylor et al., 2009).

In considering the potential for using reconsolidation disruption as a treatment for addiction, several questions arise: (1) Does disruption of reconsolidation reduce the ability of exteroceptive and interoceptive cues and contexts to suppress the *motivation* to seek drugs? (2) Is the memory impairment from disruption of reconsolidation long lasting, or might "maintenance treatments" be required? (3) Does relapse to drug taking allow for reconsolidation and therefore re-strengthening of the memory? (4) What are considerations for optimal reactivation conditions? (5) Does extinction alter (facilitate or impair) reconsolidation of a drug memory? We briefly discuss these issues below.

(1) Does disruption of reconsolidation reduce the ability of exteroceptive and interoceptive cues and contexts to suppress the *motivation* to seek drugs?

All rodent studies rely on performance of trained behavior that is based on locomotor output (*e.g.*, approach behavior or instrumental behavior) and memory for what that particular action accomplishes. Impairments in performance may be due to a decrement in memory for what the motor output signifies in terms of reward outcome (the animal forgets the association between the lever press and its outcome) and/or it may be due to a decrement in the *motivation to seek the reward*. It is not known which aspects of memory continue to drive drug-seeking and drug-taking behavior. Presumably, conditioned associations such as conditioned approach and conditioned motivation strongly contribute to relapse, and disruption of either of these processes is expected to be highly useful for suppressing relapse. Some of the self-administration studies discussed above have focused on these specific aspects of memory, particularly the work by Everitt and colleagues. No studies to date have tested whether memory for the reinforcing effects of drugs can be diminished with the reconsolidation disruption approach using a progressive ratio schedule of reinforcement; such studies would address motivational factors in drug-seeking behavior as well as address whether this drug seeking is diminished even when the drug is available (see point 3 below).

(2) Is the memory impairment from disruption of reconsolidation long lasting, or might "maintenance treatments" be required?

A key question is whether strong memories such as addiction-related memories can be diminished by a reconsolidation disruption mechanism such that the motivation to seek drugs is suppressed over the long term. In general, stronger memories appear to be more difficult to disrupt than weaker memories in that they require a longer memory reactivation session (Diergaarde et al., 2006; Frankland et al., 2006; Milekic and Alberini, 2002; Suzuki et al., 2004) or the passage of time for the memory to become once again labile for disruption by amnestic agents (Robinson and Franklin, 2010; Wang et al., 2009), although memory lability with time likely depends on the strength of the memory (Inda et al., 2011). Well-established memories may not need to undergo reconsolidation to the same extent as

weaker or newly-formed memories, and they may recruit neural circuitry that is involved in habit memory (Robbins et al., 2008). Some studies indicate that only transient amnestic effects occur (Amaral et al., 2007; Lattal and Abel, 2004); many reconsolidation studies do not test animals beyond a few days to a week after amnestic treatment. Memory performance decrements are sometimes only partial, and relatively few studies have tested the effects of *repeated* reactivations/amnestic agent delivery to determine whether additional reactivation sessions may be necessary for greater and/or longer lasting suppression of memory. This is an important consideration for future studies because, with relatively little known about the reconsolidation process, there is no a *priori* reason to believe that a single reactivation session should completely erase a memory, especially a well-established memory. In addition, the mere passage of time after memory reactivation has not generally been explored in a systematic fashion in addiction studies, and there is evidence to suggest that the passage of time will alter the ability to disrupt memory (Debiec et al., 2002; Inda et al., 2011; Wang et al., 2009). Thus, systematic testing over time and the impact of repeated reactivation combined with amnestic agents need to be incorporated in future studies. Finally, relapse to drug-taking itself may strengthen drug memories (see below), and therefore it is possible that intermittent memory reconsolidation disruption sessions will be needed to maintain suppressed drug-seeking/taking behavior.

(3) Does relapse to drug taking cause reconsolidation and therefore re-strengthening of the memory?

One basic premise of the reconsolidation idea is that memories are believed to strengthen after reactivation and re-stabilization (Alberini, 2011). Because relapse is common in addicts, there is a chance that return to drug-taking behavior re-strengthens memories underlying interoceptive cues from the drug and associations with exteroceptive drug-related cues and contexts. A recent study using the fear conditioning model demonstrated that amnestic treatment after reactivation with the unconditioned stimulus (US), the footshock, also disrupted memory for the CS associated with the US (Debiec et al., 2010), which was attributed to the sensory features of the US. Thus, it is important for future self-administration studies to determine whether disrupting the memory for the drug of abuse (the US) by administering that drug during the reactivation session will more effectively weaken memories underlying the specific sensory features associated with the unconditioned effects of the drug. The expectation is that memories underlying the drug-CS and drug-context associations will also be weakened by amnestic agents delivered during reactivation, and therefore administration of the drug of abuse during reactivation could be an essential component to weakening multiple drug-related memories; this effect may also depend on the particular drug of abuse examined. Although several CPP studies have administered the drug of abuse during memory reactivation and during subsequent reinstatement tests, only one self-administration study to date has attempted to do this, resulting in failure to alter later drug-induced reinstatement (Brown et al., 2008). However, more recent cocaine self-administration studies in our laboratory have revealed that anisomycin given after reactivation in the presence of cocaine reduced subsequent cocaine-induced reinstatement (unpublished results). These findings demonstrate that certain amnestic agents may be able to destabilize memory associated with the drug-associated interoceptive cues if that drug is present during the memory reactivation session.

(4) What are considerations for optimal reactivation conditions?

On the one hand, the degree to which amnesia occurs is dependent on how similar the reactivation context is to the training context (Judge and Quartermain, 1982; Pedreira et al., 2002) (but see item (5) below). On the other hand, a well-established memory may become protein synthesis-independent unless it is necessary to update that memory. Thus, the novelty of the reactivation condition may contribute to memory lability (Forcato et al., 2010;

Hupbach et al., 2008; Morris et al., 2006; Pedreira et al., 2004; Rodriguez-Ortiz et al., 2005, 2008; Rossato et al., 2007; Schiller et al., 2010) because a novelty component would require updating the memory (Lee, 2009). Although one study (Tronel et al., 2005) demonstrated that updating information may occur through a standard consolidation rather than reconsolidation mechanism, this effect may have been due to second-order conditioning requiring a new memory trace rather than updating of the original trace. In addition to enhancing the lability of memories with non-pharmacological methods, certain treatments might be useful for rendering the reactivated memory more labile. Ben Mamou et al. (2006) showed that NR2B receptors were necessary for making a fear memory vulnerable to disruption of reconsolidation by anisomycin treatment during reactivation. Activation of NMDA receptors may thus promote destabilization of well-consolidated memories. Regarding whether contingent *vs.* non-contingent presentation of drug-associated stimuli is most effective for reactivating memory, in general, both contingent and non-contingent presentation of drug-associated stimuli appear to disrupt memory (see Table 1). Another potentially critical issue is the role that the drug-associated context plays in memory reactivation. This is significant because drug-associated contexts are believed to contribute to relapse in human addicts. While CPP reconsolidation studies require the drug context (and in some cases both the drug context and the drug itself) during memory reactivation to demonstrate later memory disruption by amnestic agents, there are discrepant findings in drug self-administration studies. The three self-administration studies that specifically examined drug context-induced drug-seeking behavior demonstrated the requirement for reactivation in the drug-associated context (Fuchs et al., 2009; Ramirez et al., 2009; Wells et al., 2011). On the other hand, another self-administration study that tested the ability of an amnestic agent to disrupt memory for the drug-associated discrete CS demonstrated reconsolidation disruption when rats had a memory reactivation session in a *novel* context with non-contingent CS presentation (Sanchez et al., 2010). These findings from the context-induced reinstatement studies suggest that in the absence of discrete contingent cues during self-administration training, the context is the most salient component of the memory such that for memory reactivation to be disrupted, the actual drug-associated context must be used to fully reactivate the memory. Nevertheless, the Sanchez et al. study suggests that disruption of non-contingently reactivated discrete cues within a treatment setting rather than in the drug-taking context may be a viable therapeutic strategy. Interestingly, human studies in cocaine addicts indicate that a discrete stimulus can be paired with cocaine in a laboratory setting and maintain persistent drug-seeking behavior that is resistant to extinction even in the absence of the drug (Panlilio et al., 2005). Therefore, it should be possible to use the controlled delivery of these discrete stimuli in a human laboratory setting so that the most effective strategies can be developed for disrupting memory reconsolidation.

(5) Does extinction alter (facilitate or impair) reconsolidation of a drug memory?

As discussed briefly above, the trace dominance theory (Eisenberg et al., 2003) indicates that extinction and reconsolidation processes compete with each other such that if extinction is the primary process activated, amnestic agents will block extinction, and if memory reconsolidation is the primary process activated, these agents will block reconsolidation (Pedreira and Maldonado, 2003). These two processes appear to have different biochemical mechanisms (Suzuki et al., 2004). Duvarci et al. (2006) have shown that extinction and reconsolidation can occur in the same animal, and both CPP studies and drug self-administration studies indicate that disruption of reconsolidation occurs in extinguished animals. However, depending on how much extinction has taken place, reactivation conditions may engage one process *vs.* the other (Robinson et al., 2011b). In addition, the outcome of extinction *vs.* reconsolidation may depend on whether the memory is initially weak or strong (Lee, 2009) and also when the memory is tested relative to when that

memory was formed (Inda et al., 2011; Robinson and Franklin, 2010; Wang et al., 2009). Thus, much remains to be known about how extinction and reconsolidation processes interact, and studies need to include a test for amnestic agents on extinction processes by including one or more of the following tests: spontaneous recovery, renewal, or reinstatement. It should be noted, however, that some treatments that promote extinction also suppress processes such as reinstatement and renewal (Graham et al., 2011; Graham and Richardson, 2011). Methodical investigation of molecular mechanisms involved in extinction *vs.* reconsolidation processes is expected to help differentiate these events (Suzuki et al., 2004) and lead to the ability to predict which strategies are most effective in diminishing memory. Although cue-exposure therapy (extinction) has not generally been shown to be effective for reducing relapse in humans (Conklin and Tiffany, 2002), modification of the effectiveness of extinction by pharmacological agents (Graham et al., 2011) or by combining extinction/reconsolidation approaches may lead to more promising treatments for addiction (Taylor et al., 2009).

5. Conclusions

The ability to specifically disrupt drug-associated memories in animal studies and in the few human studies to date provides an excellent foundation on which to continue to exploit the reconsolidation phenomenon to address the problem of drug relapse in humans. Self-administration studies have demonstrated that well-established memories are subject to disruption under certain conditions, providing promising prospects for treatment; however, a more systematic understanding of how to optimize conditions for disruption of reconsolidation will be needed in future studies. Because human addiction entails extended access to drug and potentially long delays before treatment, key issues for future studies in animal models include testing whether the expression of memory for drug-seeking behavior can be diminished or erased after extended access to drugs, after long-term withdrawal from drugs, and after repeated reactivation sessions under conditions that test the role of novelty of reactivation sessions. Studies that test the effects of amnestic agents in the CPP task entail only limited access to non-contingent drug administration and are thus not expected to engage circuitry involved in more compulsive drug-seeking behavior. Therefore, it is suggested that the CPP task be used as a screening tool for testing potential amnestic agents in the self-administration model. Investigation into the cellular and molecular mechanisms that underlie reconsolidation has been suggested (Miller and Sweatt, 2006; Tronson and Taylor, 2007). In addition, it will be important to compare effects of amnestic agents across different classes of drugs of abuse using the same reactivation and testing conditions to determine the extent to which different drugs of abuse engage different mechanisms and brain regions for memory disruption. Future studies will need to functionally catalogue cellular/molecular changes that occur after reactivation of both drug reward-associated memories and aversive memories associated with drug withdrawal states to advance pharmacological and non-pharmacological approaches to target memory disruption in animals and to translate these findings to human addicts.

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Abbreviations

BLA basolateral amygdala

CPP	conditioned place preference
CREB	cyclic AMP response element binding
7-CTKA	7-chlorothiokynurenic acid
D-APVD-	(−)-2-amino-5-phosphonopentanoic acid
DCSD	-cycloserine
ERK	extra-cellular signal-regulated kinase
MMP	matrix metalloproteinase
mPFC	medial prefrontal cortex
NMDA	N-methyl-D-aspartate
PIT	Pavlovian instrumental transfer
PKA	protein kinase A
TTX	tetrodotoxin
VTA	ventral tegmental area

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Box 1

Key terminology

Acquisition of a new response (ANR)

In the first phase, rats are first trained to self-administer a reward such as sucrose or drug by an instrumental response (*e.g.*, nose-pokes), and each reward is paired with the presentation of a conditioned stimulus (CS), such as a light situated above the nose-poke hole. In the second phase, acquisition of a new response is then tested by allowing rats to perform a second type of instrumental behavior, (*e.g.*, lever presses) for presentation of the CS alone. The conditioned reinforcing properties of the CS previously associated with a primary reward support the acquisition of the new, lever-pressing behavior.

Amnestic agent

A pharmacological agent used to disrupt reconsolidation. The term is used broadly here to refer to any agent that is used to attempt to disrupt the reconsolidation process; however, some of these agents have not been ruled out for their effects on other processes such as extinction.

Conditioned reinforcement

Ability of a Pavlovian conditioned stimulus to become a reinforcing stimulus because of its association with a reinforcer. Example: Second-order schedules of reinforcement maintain high levels of level-pressing behavior because the conditioned stimulus that was previously paired with primary reinforcement becomes reinforcing by itself. Conditioned reinforcing properties of drug-associated stimuli promote the acquisition of a new response (ANR; see above).

Goal-tracking

Produced by repeatedly pairing a discrete CS such as a light or retractable lever with an appetitive unconditioned stimulus (US) such as sucrose, but the delivery of the US is independent of the animal's behavior. With repeated presentations of the CS and US, the CS increases the number of approaches toward the location of the US.

Incentive learning

Ability to learn about changes in the value of a reward. Example: Changes in motivational state can be made by food depriving an animal or allowing an animal to be food sated prior to testing for lever pressing to obtain a food reward.

Pavlovian (conditioned) approach

Approach behavior toward a stimulus such as a light that is presented non-contingently and becomes associated with an appetitive US such as sucrose (also see sign-tracking).

Pavlovian-instrumental-transfer (PIT)

A Pavlovian CS alters the rate of an instrumental behavior if the CS is presented while the instrumental behavior is taking place. For example, in the first phase of training, an animal is trained to associate one CS with reward availability. In the second phase, the animal is trained to obtain that reward by an instrumental behavior, such as lever pressing. Subsequently, the animal is tested for PIT by assessing the number of lever presses in the absence of reward but in the presence of the CS. The number of lever presses increases when the CS is presented. In this way, the Pavlovian CS that predicts reward transfers control of the instrumental response.

Sign-tracking

Produced by repeatedly pairing a discrete CS such as a light or retractable lever with an appetitive unconditioned stimulus (US) such as sucrose, but the delivery of the US is independent of the animal's behavior. With repeated presentations of the CS and US, the CS increases the number of approaches toward and interaction with the CS.

Box 2

Control groups and topics for consideration in reconsolidation studies

(1) Inclusion of appropriate control groups

To determine whether an agent disrupts reconsolidation, at least one of two types of control groups needs to be conducted to rule out non-specific effects of the amnestic agent on subsequent behavior (Tronson and Taylor, 2007). The first type of control is one in which the amnestic agent is given in the absence of a reactivation session to demonstrate that the agent does not have non-specific effects on the subsequent expression of memory (*e.g.*, place preference or lever-pressing behavior); that is, one needs to test whether reactivation of the memory (and thus destabilization of the memory) is required for the amnestic agent to suppress the later expression of that behavior. This decrease in expression of the behavior is interpreted as a failure to either retrieve the memory or, if reconsolidation is disrupted, to express the behavior due to diminishment or erasure of the memory that supports the behavior. The second type of control is one in which the amnestic agent is given 6 h or greater after reactivation. The delay of 6 h is based on several fear conditioning and some appetitive studies demonstrating that the likelihood for reconsolidation to be disrupted is minimal after 6 h, and so the amnestic agent should no longer alter subsequent expression of behavior. These control groups have been discussed in detail (Tronson and Taylor, 2007).

(2) Timing of delivery of the amnestic agent relative to the reactivation session

Ideally, the agent is given immediately after the reactivation session to avoid state-dependent effects or interference with memory recall during reactivation or with performance on the reactivation day. In some cases, the effects of the agent may need to be present prior to reactivation so that the *maximal* impact of these agents within the brain occurs over the time window of reconsolidation (*e.g.*, antisense oligodeoxynucleotide (ASO) delivery). Interestingly, agents that target the NMDA receptor need to be present prior to reactivation to produce apparent memory disruption (also, see point 6 regarding extinction *vs.* reconsolidation and individual studies using NMDA receptor agonists/antagonists). This may be due to the finding that certain NMDA receptors need to be active to fully destabilize the memory (Ben Mamou et al., 2006). However, it is important to keep in mind that when the effects of these amnestic agents are present during the reactivation session, it cannot be assumed that they are targeting reconsolidation processes since they may also promote extinction processes (see point 6). Of note, even for amnestic agents that are given *post*-reactivation, there is the possibility that these agents promote consolidation of extinction if the reactivation session is essentially an extinction session, as is often the case (*e.g.*, see LaLumiere et al., 2010). In all studies discussed in this review, the timing of amnestic agent relative to the reactivation session is indicated. Finally, the time over which the amnestic agent exerts its effects also needs to be considered because these effects may need to occur over the approximately 6 h window of reconsolidation. For example, Milekic and coworkers (Milekic et al., 2006) found that a single post-reactivation injection of a protein synthesis inhibitor produced the lack of CPP expression when tested 24 h, but not 1 wk, later. In contrast, when animals received two of these inhibitor injections (one 5 h after the first), the lack of CPP expression lasted for up to 4 wk, suggesting that amnestic agent effects need to be present over much of the reconsolidation window.

(3) Consideration of whether the *drug of abuse* is present during the reactivation period and/or the subsequent test for memory expression

Most CPP studies and nearly all self-administration studies test memory in the absence of the drug during reactivation, and many CPP studies measure the ability of the amnestic agent to disrupt place preference of the drug-associated environment in the absence of drug on the test day, although more recent studies have tested for place preference both in the absence of drug and after drug-induced reinstatement. This is important to test because interoceptive cues from a drug-priming injection are likely to serve as powerful reminders of the drug-associated memory and induce strong place preference or lever-pressing behavior after animals are given extinction. Thus, absence of place preference in the presence of the drug demonstrates that the behavior is not reinstated and is likely due to reconsolidation disruption.

(4) Permanence of memory disruption

Many studies have tested for the absence of behaviors one or a few days later, but more recent studies have found that amnestic agent effects can occur for up to 6 wk after reactivation. (Also see point (6) below for discussion of spontaneous recovery). Longer-term testing for maintenance of memory disruption needs to be routinely included.

(5) Consideration of temporal aspects of the reactivation session

Since the goal of reconsolidation studies is to reactivate the original memory trace, most studies accomplish this by using what is essentially a short extinction session. In CPP studies, animals are often placed in the chamber with no drug, as in a standard test session, and in self-administration studies, animals are most often given a session in which they either perform an instrumental behavior for a drug-associated cue or they are presented with the cue non-contingently. The temporal aspect of the reactivation session is important because the trace dominance theory (Eisenberg et al., 2003) indicates that extinction and reconsolidation processes compete with each other such that if extinction is the primary process activated, amnestic agents will block extinction, and if memory reconsolidation is the primary process activated, these agents will block reconsolidation (Pedreira and Maldonado, 2003). The prevailing concept in reconsolidation studies is that reactivation sessions need to be kept brief to avoid extinction processes. The time period of exposure for reactivation is likely to vary depending on the type of experiment; for example, in fear conditioning studies, reactivation is often only 30 s but in drug abuse studies can be as much as 30 min because enough time is typically allowed for the animal to *perform* the behavior (place preference, lever pressing or nose poking). More detailed aspects of the memory reactivation process are discussed for individual studies.

(6) Whether the effect of amnestic agents is on reconsolidation *vs*. extinction processes

When interpreting whether an amnestic agent disrupts a reconsolidation process *vs.* promotes an extinction process, the definition of extinction must first be considered. Extinction in addiction studies is defined as a decrease in a particular behavioral response (*e.g.*, lever pressing or nosepoking) when the animal is presented with drug-associated contextual or discrete stimuli in the absence of the unconditioned stimulus, which is the drug of abuse. Specific molecular events are believed to underlie extinction (see Maren, 2011 for review), and it is these events that need to be considered as potential targets of amnestic agents in reconsolidation studies. The reason that the impact of amnestic agents on extinction rather than reconsolidation must be considered as an alternative interpretation is that reactivation sessions are often extinction sessions during which extinction processes are likely to occur. For example, in CPP studies, the reactivation session is most often a test session in the drug-free state rather than a conditioning session. In drug self-administration studies, the reactivation session is most often a session during which animals receive contingent presentation of the drug-associated CS.

Extinction is not an erasure of memory but is instead a new type of learning (Bouton, 1994), and defined by its susceptibility to three phenomena: (1) spontaneous recovery (Pavlov, 1927); (2) renewal (Bouton and Bolles, 1979); and (3) reinstatement (Rescorla and Heth, 1975). Spontaneous recovery is the re-emergence of the trained behavior with the passage of time, with the extent of spontaneous recovery being greater with the passage of time. In drug abuse studies, spontaneous recovery can be tested in extinguished animals by re-examining behavior after an extended interval between treatment with the amnestic agent and testing for expression of the drug-associated memory. Renewal is the re-emergence of the trained behavior when animals have been given extinction sessions in a context separate from the one they are tested in. In drug abuse studies, renewal can be tested by repeatedly administering the drug-associated CS to extinguish behavior in a context separate from the drug-training context and subsequently testing for the ability of the drug-associated CS to increase, or renew, the extinguished behavior (Crombag et al., 2008; Crombag and Shaham, 2002). Reinstatement of the trained behavior occurs when the animal has been given extinction sessions but then is re-exposed to the unconditioned stimulus (*e.g.*, a footshock in fear conditioning studies or the training drug in drug abuse studies). Thus, without performing tests for spontaneous recovery, renewal, or reinstatement, it is not possible to know whether amnestic agents promote extinction or impair memory reconsolidation, although others have argued that the likelihood of promoting extinction with certain agents such as protein synthesis inhibitors is low (Nader and Hardt, 2009). However, it should also be noted that certain pharmacological manipulations that promote extinction learning also suppress subsequent renewal and reinstatement (Graham et al., 2011; Graham and Richardson, 2011), indicating that even a test for phenomena such as these may not rule out an effect on reconsolidation *vs.* extinction. Ideally, however, studies would test for all three phenomena (*e.g.*, Duvarci and Nader, 2004; Maddox and Schafe, 2011) to assess the impact of amnestic agents on the potential for these relapse-like phenomena.

Table 1

Reconsolidation in drug-self-administration studies.

Behavioral task	Drug	Molecule(s)/brain area	Reactivation	Results and references
Acquisition of new instrumental response (ANR)[a]	Cocaine	zif 268 ASO[b] BLA 90 min prior[c]	15 min CS[d], contingent	Reduced ANR (Lee et al., 2005)
		ANI[e] immed after		Delayed ANR
Cue-induced cocaine seeking	Cocaine	zif 268 ASO BLA 90 min prior	30 min CS, non-contingent	Reduced cue-induced cocaine seeking (Lee et al., 2006a)
Cue-induced reinstate after extinction				Reduced cue reinstatement
Maint. cocaine seeking, 2nd order				Reduced cocaine seeking
ANR	Cocaine	APV BLA immed prior	15 min CS, contingent	Reduced ANR (Milton et al., 2008a)
		APV BLA immed after	15 min CS, contingent	No reduction in ANR
Cue-induced cocaine seeking		MK801 systemic 30 min prior	30 min CS, contingent	Reduced cue-induced seeking
ANR	Cocaine	Propranolol systemic immed after	10 min CS, contingent	Reduced ANR (Milton et al., 2008b)
Cue-induced cocaine seeking	Cocaine	D-Cycloserine BLA 20 min prior	30 min CS, non-contingent	Increased cue-induced cocaine seeking (Lee et al., 2009)
ANR	Cocaine	zif 268 ASO, NAcore 90 min prior	15 min CS, contingent or 15 min CS, non-contingent	No reduction in ANR (Theberge et al., 2010)
Context-induced cocaine seeking	Cocaine	ANI or TTX in BLA, dHippo, dlCPu, dmPFC immed after	Context 15 min	Reduced by TTX in BLA and dHippo but not ANI in dHippo; No reduction by TTX or ANI in dlCPu or dmPFC (Ramirez et al., 2009)
Context-induced cocaine seeking	Cocaine	ANI in BLA immed after	Context 5, 15, 60, 120 min	Reduced if reactivation = 15 or 60 min (Fuchs et al., 2009)
Context-induced cocaine seeking	Cocaine	ANI in BLA + baclofen/muscimol in dHippo immed after	Context 15 min	Reduced by contralateral
				No reduction by ipsilateral (Wells et al., 2011)
Cue + cocaine-induced cocaine seeking	Cocaine	MK801 systemic 30 min prior	15 min, cocaine ip + CS contingent 2 h cocaine SA + CS contingent	No reduction with either reactivation protocol (Brown et al., 2008)
Cue-induced cocaine seeking and ANR	Cocaine	PKA (Rp-cAMPS) in BLA immed after	10 s × 3 CS over 3 min non-contingent in novel chamber	Reduced cue-induced cocaine seeking and ANR (Sanchez et al., 2010)
Cue-induced ethanol seeking	Ethanol	MK801 or acamprosate systemic or ANI lateral ventricle immed after	5 min CS + discriminative cue + low EtOH, contingent	Reduced cue-induced ethanol seeking from MK801 and ANI (von der Goltz et al., 2009)
Cue-induced ethanol seeking	Ethanol	Propranolol immed after	20 min presented × 40 CS VI30, non-contingent	Reduced only after 2–3 reactivations (Wouda et al., 2010)
		MK801 immed after		No reduction but strong trend toward reduction
Conditioned approach	Ethanol	MK801 systemic 30 min prior or Propranolol systemic 30 min prior	25 CS+ and 25 CS−, non-contingent	Reduced conditioned approach (Milton et al., 2012) No reduction in conditioned approach
Pavlovian-instrumental transfer (PIT)	Ethanol	MK801 systemic 30 min prior or	6 CS+, non-contingent	Reduced PIT

Behavioral task	Drug	Molecule(s)/brain area	Reactivation	Results and references
		Propranolol systemic 30 min prior		No reduction in PIT
Conditioned withdrawal	Heroin	zif 268 ASO BLA 90 min prior	2 min, continuous CS, non-contingent	Reduced conditioned suppression (Hellemans et al., 2006)

[a]ANR, acquisition of a new instrumental response.

[b]ASO, antisensense oligodeoxynucleotide

[c]Prior to or immediately after refers to amnestic drug injection relative to reactivation session.

[d]CS, conditioned stimulus (single or compound).

[e]ANI, anisomycin.