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Post-Retrieval Extinction Attenuates Cocaine Memories

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Recent studies have shown that post-retrieval extinction training attenuates fear and reward-related memories in both humans and rodents. This noninvasive, behavioral approach has the potential to be used in clinical settings to treat maladaptive memories that underlie several psychiatric disorders, including drug addiction. However, few studies to date have used a post-retrieval extinction approach to attenuate addiction-related memories. In the current study, we attempted to disrupt cocaine-related memories by using the post-retrieval extinction paradigm in male Sprague Dawley rats. Results revealed that starting extinction training 1 h after cocaine contextual memory was retrieved significantly attenuated cocaine-primed reinstatement of conditioned place preference (CPP) and relapse of cocaine CPP (drug-free and cocaine-primed) following 30 days of abstinence. However, animals that did not retrieve the contextual cocaine memory before extinction training, or animals that began extinction training 24 h after retrieval (outside of the reconsolidation window), demonstrated normal cocaine CPP. Conversely, animals that received additional CPP conditioning, rather than extinction training, 1 h after reactivation of cocaine memory showed enhanced cocaine CPP compared with animals that did not reactivate the cocaine memory before conditioning. These results reveal that a behavioral manipulation that takes advantage of reconsolidation and extinction of drug memories may be useful in decreasing preference for, and abuse of, cocaine.
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INTRODUCTION

Drug addiction is considered by many as a disorder of aberrant learning and memory (Hyman, 2005; Torregrossa *et al*, 2011). With each drug use, environmental cues and contexts become strongly associated with the rewarding effects of the drug. Over time the cues/contexts alone are capable of stimulating drug-related memories that induce craving and relapse (Shaham *et al*, 2003; Volkow *et al*, 2006). Thus, targeting drug-associated memories has been a major focus in addiction research, as therapies capable of disrupting such memories carry important implications for the treatment of addiction.

Consolidated memories were once thought to be permanently encoded memory traces (Glickman, 1961; McGaugh, 1966), but more recent studies have shown that some memories (including memories associated with addiction) can be rendered labile following retrieval/reactivation (Nader *et al*, 2000; Lee *et al*, 2005). This labile property, termed reconsolidation, is a time-dependent process (<6 h), in which consolidated memories become transiently unstable shortly after retrieval and are susceptible to updating or disruption. In recent years, several studies have exploited this reconsolidation process by injecting animals with amnestic agents either before or immediately after retrieval (during reconsolidation) to attenuate previously consolidated drug-related memories (Lee *et al*, 2005; Lee *et al*, 2006; Valjent *et al*, 2006; Fricks-Gleason and Marshall, 2008; Milton *et al*, 2008; Fuchs *et al*, 2009; Sanchez *et al*, 2010). However, many of these amnestic agents (eg, protein synthesis inhibitors) are not suitable for human use, and thus other reconsolidation-based behavioral or pharmaceutical avenues are needed for the treatment of addiction.

As an alternative to harsh amnestic agents, Monfils *et al* (2009) recently described a noninvasive, behavioral approach to attenuate memories by post-retrieval extinction training. In this procedure, fear-conditioned animals were given an isolated retrieval trial followed by extinction training at time points inside (10 or 60 min) or outside (24 h) of the reconsolidation window. They found that presenting an extinction session during, but not outside of, the reconsolidation window attenuated reinstatement, renewal, and spontaneous recovery of fear memories (Monfils *et al*, 2009). Subsequent studies in other laboratories have shown that post-retrieval extinction reduces fear and reward-related memories in both animals and humans (Clem and Huganir, 2010; Schiller *et al*, 2010; Flavell *et al*, 2011; Rao-Ruiz *et al*, 2011; Xue *et al*, 2012), indicating that these methods have the potential to be translated into clinical applications. However, other studies have failed to

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replicate such findings in fear-related memories (Chan *et al*, 2010; Costanzi *et al*, 2011; Ishii *et al*, 2012). Additionally, reports have challenged the reconsolidation theory behind post-retrieval extinction (Millan *et al*, 2013) and the notion that memories are completely erased following post-retrieval extinction (Ma *et al*, 2012). In the current study, we tested whether single-session post-retrieval extinction or post-retrieval reconditioning is able to alter cocaine-related memories in rats using the conditioned place preference (CPP) paradigm.

MATERIALS AND METHODS

Animals

Male Sprague Dawley rats (initial weight ~300–325 g, Charles River Laboratories, Raleigh, NC) were pair-housed under a reversed 12 h/12 h light/dark cycle and had *ad libitum* access to food and water. Animals were housed in a temperature- and humidity-controlled, AAALAC-accredited, animal facility at the Medical University of South Carolina (MUSC). All experiments were approved by the Institutional Animal Care and Use Committee at MUSC and conducted according to specifications of the NIH as outlined in the Guide for the Care and Use of Laboratory Animals. A total of 84 rats were used in these experiments.

Conditioned Place Preference

CPP experiments utilized methods previously employed by our laboratory (Harris and Aston-Jones, 2003b; Harris *et al*, 2004; Harris *et al*, 2005; Sartor and Aston-Jones, 2012b; Sartor and Aston-Jones, 2012a). Briefly, the CPP apparatus consisted of two distinct compartments that were separated by a removable partition. In a pre-test acclimation session, animals were allowed free access to both sides of the chamber for 15 min via a doorway in the partition. The time spent on each side of the chamber was recorded automatically. None of the animals had an initial bias for either side of the chamber on the pre-test as indicated by the group average. After 2 days, animals were conditioned for 1 (Experiment 3) or 3 days (Experiment 1 and 2). During conditioning, the animals were injected with cocaine (10 mg/kg, NIDA Research Triangle Park, NC) and confined to one side of the chamber by a solid partition for 30 min, or injected with saline and confined to the other side of the chamber for 30 min. Injections were given on both sides of the apparatus for each animal in a balanced fashion in morning and afternoon sessions (at least 4 h apart). Following conditioning, animals received retrieval-extinction or retrieval-reconditioning training described below. In all experiments, the time spent on both sides of the chamber was automatically measured via photobeam breaks and custom software.

In the retrieval session for all experiments, rats were placed in the cocaine- (Ret) or saline-paired (No Ret) side for 3 min (drug-free), and in the extinction session (also called initial CPP test) rats had free access to both sides of the chamber for 15 min (drug-free). In Experiment 1, 1 day after conditioning, animals were confined to the cocaine-paired (retrieval group) or saline-paired chamber (no retrieval group) for 3 min and were then placed back into their home cage. After 1 h, animals received a 15-min drug-free extinction test in which animals had free access to both sides of the chamber via a doorway in the partition. On subsequent days, animals received one such extinction test per day until preference for the cocaine-paired was extinguished (<75 s spent in the cocaine-paired side for 2 consecutive days). The next day, animals received a reinstatement test in which a cocaine injection (10 mg/kg) was given immediately before the CPP test.

In Experiment 2, 1 day after conditioning, animals were confined to the cocaine-paired (retrieval group) or saline-paired chamber (no retrieval group) for 3 min, and then placed back into their home cage. Animals then received a 15-min extinction session (also called initial CPP test) 1 or 24 h later. After the extinction session, animals were returned to their home cage and were tested again for relapse of cocaine CPP after 30 days of abstinence in a drug-free or cocaine-primed (10 mg/kg) state.

In Experiment 3, 1 day after receiving a single conditioning session, conditioned animals were confined to the cocaine-paired (retrieval group) or saline-paired chamber (no retrieval group) for 3 min and then returned to their home cage. After 1 h, animals received a 30-min cocaine CPP reconditioning session. The next day all animals were tested for cocaine preference. In these experiments, animals were only given one conditioning session before the retrieval-reconditioning manipulation to avoid a ceiling effect with preference scores.

Data Analysis

Preference scores were calculated as the time spent in the cocaine-paired side minus the time spent in the saline-paired side on the CPP test. The resulting preference scores were compared within or between groups using Student's *t*-test, one-way analysis of variance (ANOVA) followed by Newman–Keuls *post-hoc* test, or two-way ANOVA followed by Bonferroni *post-hoc* test. GraphPad Prism v5 was used for statistical analysis. The risk of Type 1 error (α) was set at $P<0.05$.

RESULTS

Experiment 1: The Effects of Post-Retrieval Extinction on Cocaine-Induced Reinstatement of CPP

Experiment 1 was designed to test whether post-retrieval extinction training altered reinstatement of extinguished cocaine CPP (Figure 1a). No differences in initial cocaine CPP scores were observed between Ret ($n=8$) and No Ret ($n=7$) groups ($t_{13}=0.66$, $P>0.05$). However, rats that were placed in the cocaine-paired side on the retrieval session (Ret) did not reinstate cocaine CPP when subsequently tested with a cocaine prime, whereas rats that did not retrieve the cocaine memory before extinction (No Ret) robustly reinstated cocaine CPP ($t_{13}=3.1$, $P<0.01$; Figure 1b). The lack of reinstatement observed in the Ret group is not likely due to an enhancement of extinction, as the rate of extinction was similar in the two groups ($t_{13}=0.52$, $P>0.05$; Figure 1c).

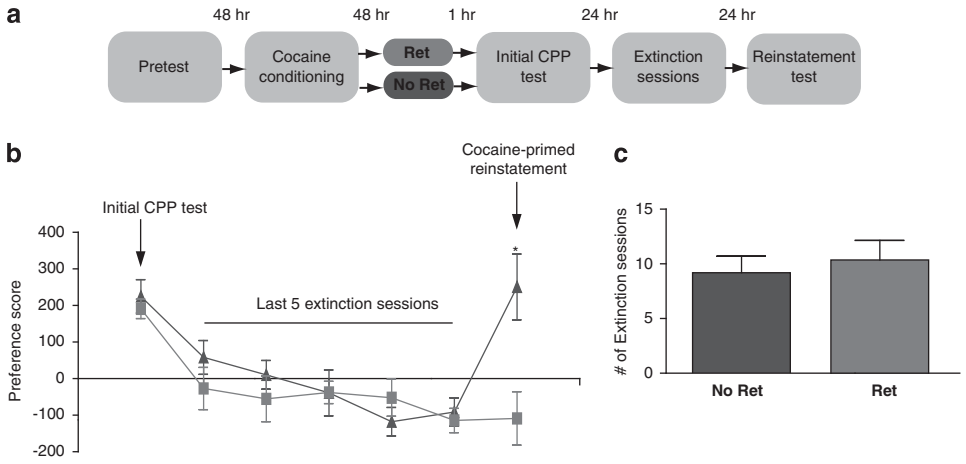

Figure 1 Post-retrieval extinction training blocks cocaine-primed reinstatement of CPP. (a) Schematic of the experimental procedure. Two days after cocaine conditioning, animals were exposed to the cocaine- (Ret) or saline-paired (No Ret) context for 3 min, and then received an extinction test 1 h later. On subsequent days, animals received one extinction test per day until preference for the cocaine-paired was extinguished, and then extinguished animals received a cocaine-primed reinstatement test the next day. (b) Extinction training 1 h after retrieval of a cocaine contextual memory (during the reconsolidation window, Ret group, $n=8$) significantly blocked cocaine-primed reinstatement of a cocaine preference (at 2nd arrow) compared with animals that did not retrieve cocaine memory before extinction (No Ret, $n=7$) (*$P<0.01$ indicates a significant difference from Ret group by *t*-test). No significant difference in initial expression of cocaine preference was observed between the two groups (at first arrow; $P>0.05$). (c) The number of sessions to reach extinction criteria did not differ between groups ($P>0.05$). Data are expressed as means (±SEM).

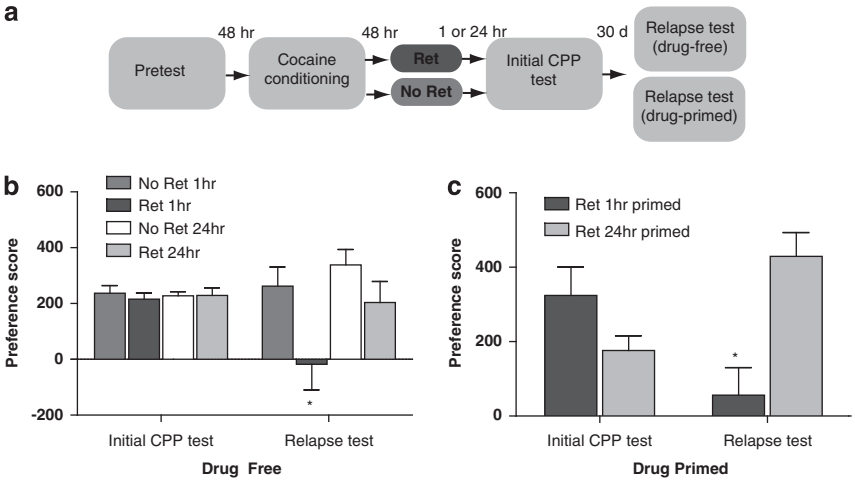

Figure 2 Post-retrieval extinction attenuates relapse of cocaine CPP following abstinence. (a) Schematic of the experimental procedure. Two days after a conditioning, animals were confined to the cocaine- (Ret) or saline-paired (No Ret) context for 3 min, and then received an extinction test 1 h later. Following 30 days of abstinence, animals were again tested for relapse of cocaine CPP in a drug-free or drug-primed test. (b) Presenting an extinction session 1 h after retrieval of cocaine contextual memory (Ret 1 h, $n=7$, Ret 1 h primed, $n=10$) significantly attenuated relapse of both drug-free and (c) cocaine-primed CPP following abstinence compared with animals that did not receive retrieval pairing 1 or 24 h before extinction training (No Ret 1 h, $n=8$; No Ret 24 h, $n=5$), or to animals that began extinction training outside the reconsolidation window (24 h after retrieval pairing; Ret 24 h, $n=9$; Ret 24 h primed, $n=7$). *$P<0.05$ indicates a significant difference from other relapse test scores via Bonferroni *post-hoc* test. Data are expressed as means (±SEM).

Experiment 2: The Effects of Post-Retrieval Extinction on Relapse of Cocaine CPP Following Abstinence

In Experiment 2, we examined whether post-retrieval extinction altered relapse of cocaine CPP following 30 days of abstinence (Figure 2a). Initial preference scores did not differ between groups (F values <0.6, $P>0.05$). However, both drug-free (Figure 2b) and cocaine-primed (Figure 2c) CPP relapse scores were significantly reduced in animals that received an extinction test 1 h after a retrieval session (Ret 1 h, $n=7$; Ret 1 h primed, $n=10$) compared with animals that did not retrieve the cocaine memory (placed in the saline-paired side for a no retrieval session; No Ret 1 h and 24 h, $n=8$ and 5, respectively; Figure 2b and c). Similarly, animals that had one extinction test 1 h after a retrieval session subsequently exhibited less preference than animals that received extinction followed by retrieval outside of the reconsolidation window (Ret 24 h and Ret 24 h primed, $n=9$ and 7, respectively) (drug-free: $F_{3,50}=2.8$, $P<0.05$, Figure 2b; drug primed: $F_{1,30}=13.35$, $P<0.01$, Figure 2c).

Experiment 3: The Effects of Post-Retrieval Reconditioning on Cocaine CPP

Although the above and other results show that post-retrieval extinction can be used to attenuate reward-related memories, it is unclear whether post-retrieval reconditioning can strengthen or enhance cocaine-related memories. In these experiments, animals were given one conditioning session, rather than three sessions, to avoid a CPP ceiling effect. The next day, animals were briefly confined to the cocaine- (Ret, $n=7$) or saline-paired side (No Ret, $n=7$). They then were reconditioned with cocaine (10 mg/kg, i.p.) 1 h later, and cocaine place preference was tested the next day (Figure 3a). Animals that were reconditioned following placement in the cocaine-paired side on the retrieval session (Ret) showed a significant increase in CPP scores compared with animals that were placed in the saline-paired side on the retrieval session (No Ret) before reconditioning ($t_{12}=3.0$, $P<0.05$), indicating that post-retrieval reconditioning may enhance reward-related memories (Figure 3b).

DISCUSSION

Overview of Results

The current studies provide evidence that post-retrieval extinction training is an effective, noninvasive method to attenuate cocaine-related contextual memories. First, we demonstrated that commencing extinction training 1 h after cocaine contextual memory was retrieved significantly attenuated cocaine-primed reinstatement of CPP. Animals that did not retrieve the memory before extinction strongly reinstated cocaine CPP after a cocaine prime. The reduction in reinstatement does not appear to be a result of enhanced extinction, as the rate of extinction did not differ between groups. Second, we found that retrieval before a single extinction session had long-lasting effects on drug memory, as this manipulation reduced relapse of drug-free and cocaine-primed CPP following 30 days of abstinence. This long-lasting effect is particularly important for the treatment of addiction because drug-related memories that elicit craving and relapse may persist even after prolonged abstinence (Gawin and Kleber, 1986). Third, we showed that reconditioning, rather than extinction, during reconsolidation (following retrieval of the cocaine–context memory) increased CPP expression, a finding that is consistent with Millan *et al* (2013) who showed the retrieval-extinction procedure potentiated reacquisition of alcoholic beer self-administration. Enhancement of reward-related memories, particularly natural rewards (food, social interaction, etc) may be used as a treatment for addiction, as motivation for natural rewards have been shown to be diminished following chronic drug use (Barr *et al*, 1999; Harris and Aston-Jones, 2003a). Thus, by strengthening natural rewards that compete with drug memories, post-retrieval reconditioning could possibly be used to reduce drug relapse. Together, these results indicate that retrieval-extinction manipulations can be employed to alter cocaine-related behaviors and could potentially be utilized for the treatment of drug addiction.

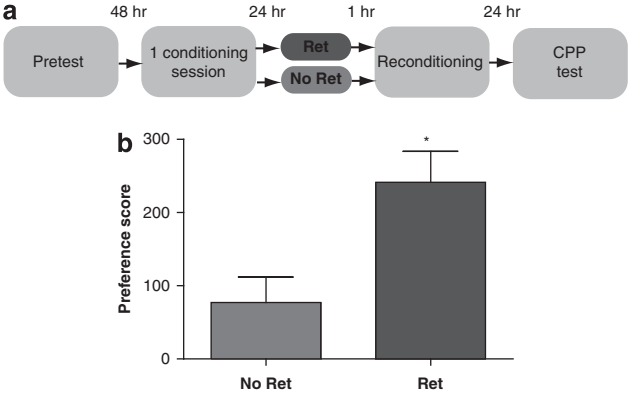

Figure 3 Cocaine conditioning during reconsolidation enhances cocaine CPP. (a) Schematic of experimental procedure. One day after a single conditioning session, animals were exposed to the cocaine- (Ret, $n=7$) or saline-paired context (No Ret, $n=7$) for 3 min, and were reconditioned 1 h later. Animals were tested for cocaine preference the following day. (b) A significant increase in cocaine CPP was observed when animals were reconditioned following reactivation of cocaine memory (*$P<0.05$ indicates a significant difference from No Ret group by *t*-test). Data are expressed as means (±SEM).

Post-Retrieval Extinction as a Potential Treatment for Addiction

Cues and contexts associated with drug use are major contributing factors to craving and relapse (Shaham *et al*, 2003). Cue-exposure therapy (CET), an extinction-based treatment performed in a clinical setting, was developed in an attempt to diminish cue–drug associations and reduce relapse in human addicts (O'Brien *et al*, 1990). Unfortunately, this type of extinction therapy had limited success in preventing relapse in humans or animals (Conklin and Tiffany, 2002; Crombag and Shaham, 2002), signifying a need for alternative cognitive-behavioral strategies for the treatment of addiction. The recent development of post-retrieval extinction therapy, however, may offer a more efficacious method of reducing addiction-related memories (Auber *et al*, 2013; Hutton-Bedbrook and McNally, 2013). In this paradigm, the strengths of both extinction and reconsolidation are combined by presenting an extinction session during the reconsolidation process, when the memory is labile, to disrupt the consolidated memory trace. Because post-retrieval extinction is thought to directly perturb drug memories, rather than forming new memories to suppress drug memories (as in extinction therapy), this new approach may be more effective at reducing relapse compared with extinction alone (Monfils *et al*, 2009). Indeed, using the post-retrieval extinction paradigm, our current results and other recent findings have shown that this method is effective at reducing reinstatement and/or renewal of drug- (cocaine, morphine and heroin), sugar- and fear-related memories in rodents and humans (Monfils *et al*, 2009; Clem and Huganir, 2010; Schiller *et al*, 2010; Flavell *et al*, 2011; Rao-Ruiz *et al*, 2011; Xue *et al*, 2012). Thus, in light of these new findings, post-retrieval extinction has the potential to be a clinically applicable therapy for the treatment of addiction and other psychiatric disorders.

Limitations of Post-Retrieval Extinction

Although reconsolidation-based therapies offer a pragmatic approach to attenuate drug-related memories, subtle boundary conditions may limit the application of these treatments (Nader and Einarsson, 2010; Auber *et al*, 2013). For example, the strength, age and type of drug memory determine whether it is susceptible to reconsolidation-based amnestics. Additionally, the type and length of retrieval and extinction may also influence reconsolidation processes (Pedreira and Maldonado, 2003). In the current experiments, we show that a single post-retrieval extinction session is capable of reducing cocaine-primed reinstatement of CPP and relapse of CPP following protracted abstinence (drug-free and cocaine-primed), whereas other reports used multiple retrieval-extinction sessions to attenuate drug-related memories (Ma *et al*, 2012; Xue *et al*, 2012; Millan *et al*, 2013). Because experiences that produce new learning are required to initiate reconsolidation following reactivation (Pedreira *et al*, 2004; Morris *et al*, 2006; Sevenster *et al*, 2012, 2013), it is unclear whether multiple retrieval-extinction sessions are necessary, as activation of reconsolidation processes would likely diminish following repeated daily sessions. The behavioral paradigm used, however, may determine whether multiple retrieval-extinction sessions are needed to attenuate drug-related memories. Preliminary unpublished findings from our laboratory indicate that a single post-retrieval extinction session was not sufficient to reduce renewal of cocaine seeking in a self-administration paradigm (number of lever presses during renewal test: No Ret $= 53 \pm 12$, Ret $= 49 \pm 10$; $n = 2$ and 3 for No Ret and Ret groups, respectively), whereas Xue *et al* (2012) showed that repeated post-retrieval extinction sessions attenuated renewal of cocaine and heroin self-administration. Lastly, some studies have shown that post-retrieval extinction was not effective at reducing fear or reward-related memories (Perez-Cuesta and Maldonado, 2009; Chan *et al*, 2010; Costanzi *et al*, 2011; Flavell *et al*, 2011; Ishii *et al*, 2012; Ma *et al*, 2012; Millan *et al*, 2013), although specific methodological and boundary conditions (species differences; behavioral paradigm used; type of reinforcer; length of conditioning, retrieval and/or extinction; time between retrieval and extinction training) may explain the divergent results between studies.

Ma *et al* (2012) recently reported that post-retrieval extinction does not completely erase morphine-related memories, as morphine CPP was reinstated by a priming injection following 4 weeks (but not at 1 week) of abstinence. However, we found that a cocaine prime following 30 days of abstinence did not reinstate cocaine CPP in animals that had retrieval training. This supports the possibility that our retrieval manipulation interfered with the memory of the cocaine–context association in a long-lasting fashion. Taken together, there appear to be certain conditions under which post-retrieval extinction training attenuates reward-related memories. However, further elucidation of the boundary conditions and molecular mechanisms by which post-retrieval extinction (and possibly the reversal, extinction-retrieval manipulation) (Millan *et al*, 2013) reduces drug-seeking behaviors is needed.

A few recent studies have started to shed some light on molecular targets involved in post-retrieval extinction. Rao-Ruiz *et al* (2011) showed that endocytosis of GluA2-AMPARs in the dorsal hippocampus is necessary for attenuation of contextual fear-related memories using the post-retrieval extinction protocol. Because GluA2-AMPARs also has a role in cocaine-evoked neuroplasticity and seeking behaviors (Boudreau *et al*, 2007; Mameli *et al*, 2007; Famous *et al*, 2008), it is possible that similar mechanisms regulate drug seeking during retrieval-extinction manipulations. In another study, Xue *et al* (2012) revealed that PKMζ, an atypical constitutively active isoform of protein kinase C, was elevated in the infralimbic cortex and decreased in the basolateral amygdala following post-retrieval extinction of cocaine-seeking behaviors, though it is unclear if PKMζ has an essential role in post-retrieval extinction. Thus, these initial studies have revealed two potential molecular targets involved in post-retrieval extinction. However, additional studies are needed to generate a better understanding of the boundary conditions that govern memory reconsolidation, and further define the underlying molecular mechanisms involved in post-retrieval extinction and identify new reconsolidation-based targets for the treatment of drug addiction.

In summary, maladaptive learning and memory processes contribute importantly to the pathophysiology of several psychiatric disorders. Although cognitive-behavioral therapies have had limited success in the treatment of addiction and anxiety, recent studies suggest that post-retrieval extinction therapy has the potential to permanently attenuate drug- and fear-associated memories. Here, we showed that post-retrieval extinction blocks expression of cocaine memories following protracted abstinence, and that post-retrieval conditioning can be used to enhance reward-related memories. Moreover, our results revealed that a single post-retrieval extinction session may be effective in attenuating drug seeking under the proper conditions. These new data carry important implications for the treatment of addiction, as post-retrieval extinction might be used to diminish drug-context associations, and post-retrieval reconditioning could be utilized to compete with drug rewards by strengthening and/or facilitating the restoration of natural reward processes in addicts. However, as most of the studies to date have used animals with limited drug histories, more work is needed to determine the efficacy of post-retrieval extinction in patients and/or animal suffering from chronic drug use. Future studies that address these unanswered questions will determine the clinical utility of post-retrieval extinction therapy to persistently reduce relapse behaviors.

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The authors declare that they have no competing financial interests in relation to the work described. The authors declare that over the past 3 years, GA-J has received compensation from Ironwood Pharmaceuticals, Elsevier S.V., and the National Institutes of Health. However, no compensation was received for compounds or devices used in this research. GCS declares that he received no compensation from outside entities over the past 3 years.

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