Extinction Learning as a Model of Drug Treatment and Relapse: A Behavioral Overview

John J. Widholm*

Department of Psychology, College of Charleston, Charleston, SC 29424, USA

Abstract: Extinction is the process by which a previously established stimulus relationship is broken by the removal of reinforcers and/or biologically relevant stimuli, causing a reduction in responding. Given the importance of this phenomenon in terms of understanding not only learning and behavior, but also of enhancing our understanding of drug addiction and treatment, there is renewed attention being given to the study of extinction in the behavioral, neuroscientific, and therapeutic disciplines. The purpose of the current review is to provide an overview of the basic Pavlovian extinction paradigm and its relevance for treating drug addiction and discuss the typical "threats to extinction" as they model the tendency for drug relapse.

Keywords: Pavlovian learning, drug addiction, cue-based therapy, contextual control, spontaneous recovery, renewal, reinstatement, rapid reacquisition.

INTRODUCTION

Extinction is an important process of learning that is typically defined as the removal of reinforcers and/or biologically relevant stimuli from a previously established stimulus relationship that results in the reduction in responding. This historically important behavioral endpoint [1] is receiving renewed attention [2-7], causing a change in our understanding of the phenomenon. Given the success of applying Pavlovian learning paradigms to our understanding of drug addiction [8, 9] and the use of extinction procedures as a therapeutic tool to reduce the motivational salience of drug-related stimuli [10, 11] there is an increased interest in studying the neurobiological, neuropharmacological, and neurophysiological correlates of extinction with the goal of improving and/or expediting the extinction process [12-14]. The purpose of the current review is to provide a brief summary of the basic Pavlovian extinction paradigm and its relevance for treating drug addiction and discuss the typical "threats to extinction" as these model (and make predictions about) the tendency for drug relapse.

EXTINCTION (AND ACQUISITION) PARADIGM

The importance of Pavlov's contribution to the study of psychology cannot be overstated because it provided a formal methodology to understand associative learning processes [1]. Briefly, stimuli that innately elicit a reflexive response are referred to as Unconditional Stimuli (US; they elicit a response without prior conditions or prior learning) and the responses that are elicited are called Unconditional Responses (UR). Some traditional examples of USs (and corresponding URs) include food (salivation), cold (piloerection), and light (pupillary constriction). When neutral stimuli (e.g., bell, tone, light, etc.) are presented that predict and provide information about the occurrence of a US, they become Conditional Stimuli (CS; their ability to elicit a response is conditional on being predictive of a US) and the corresponding response is called the Conditional Response (CR). This process of conditioning CRs is referred to as acquisition. Modern Pavlovian theory views conditioning as an active process whereby the organism is an "information seeker" and conditioning results, not because stimuli are simply paired together, but rather because the CS allows the organism to better predict the US. In the absence of this relationship, conditioning is unlikely to obtain [15]. For example, when rats are exposed to shocks (US) that are always preceded by the signaling of a tone (CS), they exhibit a strong fear to the tone. However, rats exposed to many more shock trials that are not reliably correlated with a tone show very little fear to the tone, even though they are exposed to the same amount of tone-shock trials and receive more total shock trials [16]. In addition, research has shown that the associations that are formed can combine to produce more complex hierarchical associative structures indicating that Pavlovian conditioning produces more than just a static mental representation of the stimulus elements [15].

Following acquisition, the CR can be reduced or eliminated through the process of extinction in which the CS is repeatedly presented in the absence of US, resulting in the gradual loss of the CR. Fig. (**1**) diagrams a typical forward Pavlovian acquisition and extinction procedure and plots the theoretical (but typical) acquisition and extinction curves.

Our understanding of drug addiction and ability to predict the likelihood of relapse has been enhanced greatly by the application of Pavlovian models of learning [8, 9, 17, 18]. Within this paradigm, a drug of abuse (e.g., cocaine or heroin) is a US that innately elicits a response in the user and stimuli that are associated with drug use (drug syringe, needle, etc.) can become associated and elicit similar (or in some cases, opposite; see [19]) responses. For example, a drug-dependent patient that began injecting heroin (US) with

*Address correspondence to this author at the Department of Psychology, College of Charleston, 57 Coming Street, Charleston, SC 29424, USA; Tel: (843) 953-8194; Fax: (843) 953-7151; E-mail: widholmj@cofc.edu

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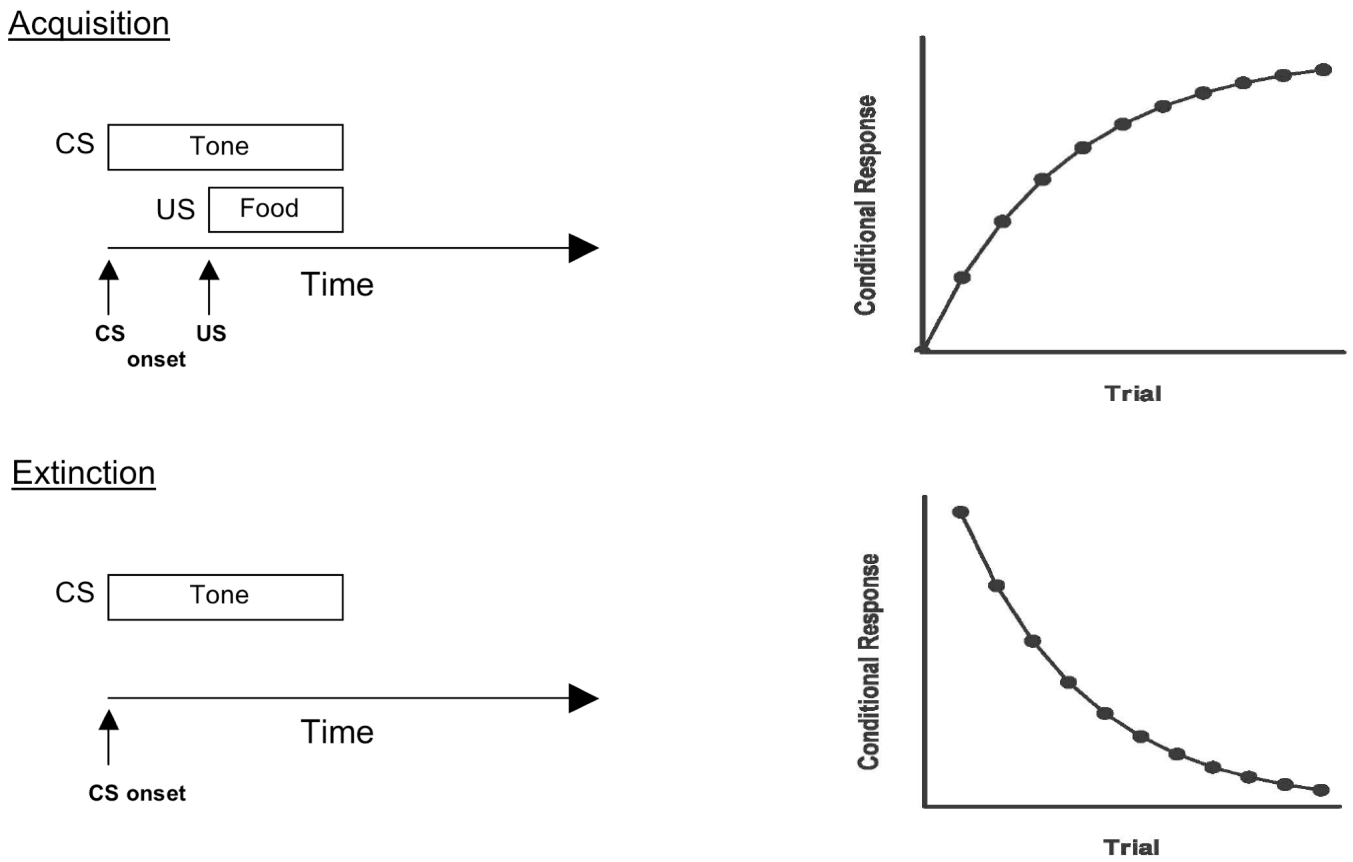

Fig. (1). Schematic depicting typical acquisition and extinction procedures with theoretical learning curves. Note: CS = Conditional Stimulus; US = Unconditional Stimulus.

a friend (CS) may find that they have heroin cravings when they are in the presence of the friend or if they see others using similar drug-related paraphernalia (e.g., needle and syringe). Data from self-report and neurological studies consistently find increases on measures of craving in response to drug-related stimuli (e.g., [20, 21]). These cravings then serve to increase the likelihood (*via* negative reinforcement) of drug seeking behavior. Similar to findings from conditioning studies utilizing food [22] and/or shock [2], extinction procedures in which drug related stimuli are repeatedly presented but are not followed by the drug can be used to attenuate the CRs [12,13, 23]. As such, cue-based drug treatment therapies [11, 24, 25] based on extinction principles have been utilized to reduce cue-induced drug cravings and minimize the risks of relapse once the patient returns to the environment in which drug addiction occurred. However, these types of therapies are often of limited success, due in part to a misunderstanding of and/or the inability to control for relevant variables that affect extinction learning that may include any of the following; an underestimation of the role context plays in learning [2], insufficient time to allow for consolidation of extinction learning [26], and/or the inability to control for the pervasive threats to extinction that include renewal, spontaneous recovery, reinstatement, and/or rapid reacquisition [10].

Although it has been known since Pavlov's earliest experiments [1] that extinction doesn't completely erase the associations formed during acquisition because of the discovery that the CR recovers with time (spontaneous recovery), some early models of associative learning assumed that extinction involved the destruction of the original CS-US association (e.g., [27]). Although the assumption of associative erasure has since been dismissed by most, early cue-based therapies evolved from these assumptions and (perhaps due to this misattribution) have had limited success in preventing relapse in drug-dependent patients [28, 29]. More recently, other threats to extinction have been uncovered; including renewal, reinstatement, and rapid reacquisition and each suggests that not only does (at least) some portion of the original association persist following extinction, they also suggest that new learning occurs during extinction that is context-dependent. What follow is a brief overview of each behavioral phenomenon and a discussion of its relevance for drug treatment.

THREATS TO EXTINCTION

Renewal Effect

The renewal effect refers to the reappearance (i.e., renewal) of the CR when the environment is changed from that used during extinction. Research on this phenomenon has uncovered compelling evidence on the importance of context in extinction learning (e.g., [7]). Stimuli that predict (and are temporally proximal to) the US become CSs while the background environmental cues present during learning that do not directly elicit the target CR become contextual cues [2, 4-7, 22, 30-32]. For example, in an appetitive conditioning experiment [31] a tone (CS) was paired with food (US) in one animal test chamber (context A) to elicit a

headjerking response (CR). Following acquisition, the rats underwent extinction in a different test chamber (context B) and were then tested in context A after the CR had been extinguished. Testing in context A caused a renewal of responding that was not evident in rats in which acquisition, extinction, and testing all occurred in the same context (A). This is an example of ABA renewal and it has been reliably demonstrated in appetitive (e.g., food; [31, 33] and aversive conditioning (e.g., shock; [2, 30]). Furthermore, AAB and ABC renewal have also been shown to occur [2, 22, 33].

Bouton and colleagues have adopted a memory-based model of conditioning and attribute the renewal effect to a byproduct of acquisition-extinction ordering. Because extinction learning occurs after acquisition, the CS acquires multiple "meanings" (i.e., it both predicts the presence and absence of the US) which are stored as distinct memories [4-7]. The context is then used to disambiguate the CS to allow the recollection of the appropriate memory. In their view, the context doesn't directly control responding, but rather serves to set the occasion for which response is correct (see [34]; figure 9). That AAB and ABC renewal occurs argues against any interpretation of renewal due solely to excitatory conditioning of the context alone since neither context B (in AAB) nor context C (in ABC) was used for the conditioning trials. Furthermore, it highlights a consistent finding in extinction studies; the behavioral effects of extinction are context-specific whereas the effects of acquisition more readily generalize to other contexts.

The renewal effect has also been observed in animal models of drug self-administration. The possibility for ABA and AAB renewal was assessed in rats trained to self-administer a heroin-cocaine mixture (i.e., a speedball) in the presence of discrete drug cues [35]. Following extinction to the drug cues in the same (A) or different (B) context, the rats were subsequently tested for renewal in either context. They found a powerful ABA renewal effect in their study, but (surprisingly) did not demonstrate AAB renewal [35]. Research with animals has reliably demonstrated ABA renewal with a variety of drugs including cocaine [13, 36], heroin [37], nicotine [38], and alcohol [39].

Because animal drug self-administration studies are an operant paradigm (i.e., the rats emit lever presses in order to receive drug infusions accompanied by discrete stimuli), one interpretation of the renewal effect in these studies is that the context is serving as an operant discriminative stimulus that signals the availability of reinforcement. From this perspective, responding renews not because of an uncovering of the original association (Pavlovian) but rather due to an increased tendency to respond while in the presence of stimuli that signal drug availability for responding. However, [36] manipulated their procedure to assess both Pavlovian and operant interpretations and concluded that the context served as a Pavlovian occasion setter and not as an operant discriminative stimulus. Furthermore, when alternative forms of reinforcement were available, the extent to which contextual renewal occurred was reduced [36].

The renewal effect has implications regarding drug treatment and relapse, suggesting that a drug addict who acquires a drug habit in one environment (e.g., home) and undergoes cue-exposure therapy in a clinic is likely to experience renewal of drug cravings when confronted with drug-associated stimuli when back home. The animal research indicates that when the environment for extinction and post-extinction testing are the same, renewal does not occur and this finding has been replicated in the human therapeutic literature. Cue-based exposure studies of spider-phobics [40-42], smokers [43], and social drinkers [44] have all found that that the CR is less likely to return if the test context and the extinction context match. Therefore, a similar reduction in the renewal of drug cravings might be obtained if therapy occurred in (or approximated) the environments in which drug use was learned. Unfortunately, few attempts appear to have been made to accomplish this with drug-dependent patients and the results appear equivocal [45].

In addition, it appears that renewal (and/or relapse) can be attenuated by conducting extinction sessions in multiple contexts. Rats that underwent extinction training in several novel contexts exhibited less of a renewal effect suggesting that the generalizability of extinction learning can be increased by conducting it in multiple contexts [46]. Lastly, evidence from [36] suggests that alternative forms of reinforcement for recovering addicts may help to minimize the extent to which renewal occurs.

Spontaneous Recovery

Following the extinguishing of the CR, it can spontaneously reappear with the passage of time [1, 3, 47]. The importance of time as the critical variable is demonstrated in [3] in which rats were presented with two CSs (noise and light) that signaled the presentation of two possible USs (food or sucrose). Following acquisition, both stimuli were subjected to conditions of extinction and tested again one or eight days later. Spontaneous recovery occurred to the CS that was tested eight days following extinction but did not occur to the CS tested one day after extinction. Similarly, [48] observed similar temporal effects on spontaneous recovery in which rats tested six days after extinction demonstrated recovery of the CR while those that were tested 5 hours after extinction showed little recovery. Similar spontaneous recovery effects have also been demonstrated with drugs in animal models. Rats that underwent extinction exhibited higher levels of drug-related responding after 28 days of forced abstinence than after 7 days of forced abstinence [49].

Regarding the importance of temporal variables, the incubation effect refers to an increase in CR magnitude with increasing delays after acquisition. For example, [50] manipulated the delay between acquisition of cocaine-associated stimuli and the testing of those stimuli for 1 day, 1 month, 3 months, and 6 months and found that the tendency to respond in the presence of drug-associated CSs increased as a function of time since acquisition through the first 3 months [50]. This phenomenon has also been demonstrated in fear conditioning with enhancements in conditioned fear in rats that increase with the passage of time since acquisition [e.g., 51]. These data suggest that the passage of time, whether it occurs before extinction-based therapy (i.e., incubation), or after (spontaneous recovery) can be an important predictor of the tendency to relapse.

Additionally, the extent to which extinction trials are massed or spaced over time also appears to have an effect on

the likelihood of spontaneous recovery. Rats trained with either massed (interval of 4 minutes between trials) or spaced (24 hours between trials) extinction trials and tested for fear 24 hours later differentially expressed spontaneous recovery with rats who underwent massed extinction procedures demonstrating recovery and rats who underwent spaced extinction procedures did not [52]. This effect appears to be due to (at least in part) to an asymmetry in temporal variables (i.e., temporal context) between extinction training and testing. For example, [53] manipulated the time between extinction trials in rats (four minutes *vs* 16 minutes between trials) and tested the rats for spontaneous recovery 16 minutes after extinction testing. Only the 4-minute ITI group showed recovery when tested 16 minutes after extinction suggesting that there was greater generalization between extinction and testing when the intervals in extinction and testing were similar.

The phenomenon of spontaneous recovery predicts that an abstinent drug-dependent patient is at risk of relapse that may increase with time [49]. It is unclear how long cravings can be elicited following extinction, but [21] observed cue-induced cravings for cocaine addicts following a 12 month period of abstinence. The behavioral research also suggests that spontaneous recovery could be minimized in abstinent patients by spacing the cue-exposure therapy trials over time both within and between each session to allow for spontaneous recovery to occur followed by further extinction training [10]. Meta-analytic studies have shown that the tendency to relapse in cocaine-addicted patients decreases with longer (i.e., >= 90 days) as opposed to shorter (i.e., 21 days) treatment periods, further supporting the idea that extended treatment periods may be necessary to overcome the effects of cue-induced relapse [54].

Lastly, it has been shown in animal studies that presenting extinction-related cues during testing can attenuate spontaneous recovery, presumably by enhancing extinction-related memories [48, 55-58]. For example, [56] found that visual stimuli (house light off or illuminated keylight) presented prior to the CS (tone) during extinction could then be used as a cue to reduce the extent to which the spontaneous recovery of magazine entries (CR) occurred in rats when tested six days following the completion of extinction. These data suggest that providing abstinent patients cues related to extinction training might enhance extinction-related memories and serve as an effective tool in combating the tendency for spontaneous recovery [10].

Reinstatement

Reinstatement refers to the reappearance of the CR following post-extinction exposure to the US (or, in some cases, drug-related CSs). For example, following the extinction of fear in rats that had undergone tone (CS) - shock (US) conditioning, independent presentations of the US can reinstate fear in the rats without any need for further CS-US pairings [59]. It was concluded that the data support the idea that individual events (i.e., memories) within the learned association are susceptible to degradation during extinction and that independent presentations of the US re-energize the memory and cause reinstatement. Moreover, presentations of other USs that were not used in conditioning (but were similar to the US used in conditioning) were found to result in reinstatement of the CR [59]. For example, when a loud, unpredictable noise was substituted for shock as the reinstating stimulus, the CR was reinstated to the CS.

More recent investigations have revealed that reinstatement may be another form of the renewal effect that is contextually-dependent [60]. Rats that underwent fear conditioning and extinction in a conditioning chamber (context A) did not show the reinstatement effect when the US was presented in the conditioning chamber (context A) but tested in lever-press operant chambers (context B). Conversely, rats that were subjected to the US in the lever press operant chambers showed a large reinstatement effect when tested in this context. The idea that extinction and reinstatement effect changes to individual elements within the original association [59] are not supported by these findings [60] but rather suggest that the reinstatement effect is a function of contextual conditioning brought on by the pairing of the reinstating US and the context in which it occurs. That is, rather than interpreting the reinstatement effect as a re-energizing of elements within the original CS-US association, an association between the context and US is formed. Such an association is absent during extinction which serves to change the extinction context. Thus, the presence of the reinstating US makes the context more like it was during conditioning making reinstatement analogous to an ABA renewal effect [see 61].

Animal research using drugs as reinforcers have found effects identical to those obtained in the learning literature. Using the conditioned place preference (CPP) paradigm in rats, following the extinction of a preference for a particular location that was associated with cocaine injections, the preference could be reinstated following an injection of cocaine without any further conditioning trials [62]. Animal drug self-administration paradigms have found similar reinstatement effects. Early demonstrations of drug reinstatement in monkeys [63] and rats [64, 65] found that priming injections following extinction elevated responding to levels seen during acquisition. These results corroborate the data from abstinent drug-dependent patients who report experiencing stronger drug cravings shortly after acute exposure to a drug than before [66]. Additionally, [64] demonstrated a similar generalization effect to that obtained by [59] and were able to induce reinstatement with drugs of similar interoceptive effects of cocaine (e.g., amphetamine, morphine). However, the conclusions of [2,4-7] suggest that the environment in which the priming exposure is given is an important predictor of the likelihood of drug-induced relapse and the data from some animal drug self-administration studies support this proposition (e.g., [67]).

Rapid Reacquisition

Rapid reacquisition, as the name implies, refers to the enhanced rate of CR elicitation to a previously extinguished CS. While it seems intuitive to assume that additional CS-US pairings following extinction would result in more rapid reacquisition (and early research supported this idea; [68, 69]), the early data now appear ambiguous as alternative interpretations to rapid reacquisition have been proposed (e.g., spontaneous recovery, renewal). Furthermore, recent research has discovered that some conditioning preparations result in rapid reacquisition and others do not [70]). For

example, rapid reacquisition has been demonstrated in conditioning reflexive movements of the nictating membrane in rabbits [71] and in a contextual fear conditioning procedure [72]. However, [70] produced both slow and rapid reacquisition in an appetitive conditioning procedure and attributed the difference (in part) to the number of trials needed during acquisition with large numbers of trials creating rapid reacquisition and fewer acquisition trials, rapid reacquisition was unlikely. Additionally, reacquisition can be slowed following large numbers of extinction trials [72]. It has been proposed that rapid reacquisition is likely another form of ABA renewal in which the contexts differ in terms of US presentation [7]. For example, rats learn that CS-US pairings are part of acquisition and CS-only trials are part of extinction and this difference in which the trials unfold serve as a contextual background. If correct, presentation of CS-US trials during reacquisition would "transport" the rat to the acquisition context and responding would be renewed (i.e., ABA renewal). Consistent with this prediction, when some CS-US trials were added to extinction conditions to equate this aspect of context, reacquisition was slowed [73].

While the research is still unclear about the extent to which rapid reacquisition reflects a true enhancement of learning that is not attributable to other extinction related phenomenon (e.g., spontaneous recovery), some of the research suggests that this phenomenon may be applicable to the treatment of drug-dependent patients. As [70] have suggested, the extent to which rapid reacquisition occurs appears dependent on the number of trials used during acquisition. Many drug addicts come to treatment with many years of drug experience and many experiences over which stimuli are conditioned (e.g., over learning). Based on the findings of [72] and others, massive numbers of extinction trials may be necessary in this situation to reduce the possibility of a rapid relearning of drug-related associations following treatment.

SUMMARY

The renewed interest in animal extinction learning has provided novel ways to interpret the variables that affect extinction-based therapies for treatment of drug-dependence. The "threats to extinction" indicate that much of what was learned during acquisition remains after extinction and these threats model common forms of relapse in drug addicts. Neurobiological, neuropharmacological, and/or neurophysiological research designed to understand and/or facilitate the extinction process has clinical implications and the behavioral research suggests that treatments capable of enhancing extinction-related memories (e.g., [2,4-7]) or generalization of learning beyond the extinction context (e.g., [46]) may enhance the effectiveness of those treatments.

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