

Alcohol Ataxia Tolerance: Extinction Cues, Spontaneous Recovery, and Relapse

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This article reviews ethanol ataxia tolerance experiments with rats that investigate spontaneous recovery after extinction and how extinction-related cues reduce this recovery. Tolerance to the effects of many drugs including ethanol is partly the result of Pavlovian conditioning. Tolerance to the ataxic (and other) effects of ethanol depends critically upon the circumstances in which the drug is administered. Tolerance shows other characteristics common in Pavlovian conditioning, e.g., it can be extinguished and is subject to spontaneous recovery. The analogy of spontaneous recovery to instances of relapse in humans potentially makes such spontaneous recovery relevant to both researchers and clinicians. Recently, "extinction cues" have been found to reduce spontaneous recovery and other relapse-like effects in the animal conditioning laboratory. These cues may work in part by activating an association formed during the extinction process, and thus they may serve as memory retrieval cues. Research assessing spontaneous recovery using an ethanol ataxia method, as well as other Pavlovian conditioning methods, has contributed to an understanding of the properties and utility of extinction cues. These topics are addressed and the potential implications of this research for treating substance abusers is considered.

For some time, and with both human and nonhuman populations, a goal of research in psychology and biomedical fields has been to develop, assess and refine effective treatment interventions for substance abusers. Because of the chronically relapsing nature of substance abuse disorders, in more recent years a companion goal has been to develop, assess and refine substance abuse relapse-prevention strategies (e.g., Brownell, Marlatt, Lichtenstein, & Wilson, 1986; DiClemente, 2003; Marlatt & Gordon, 1980, 1985; Polaschek, 2003; Prochaska & DiClemente, 1982). Brooks and his associates (e.g., Brooks, 2000; Brooks & Bouton, 1993, 1994; Brooks & Bowker, 2001; Brooks, Palmatier, Garcia, & Johnson, 1999) have been specifically interested in determining whether previous studies on spontaneous recovery reduction in appetitive conditioning and taste-aversion were applicable to drug relapses; that is, response-recovery after extinction when the unconditioned stimulus (US) used in conditioning is a drug. Specifically, we investigated whether a reminder cue from extinction could reduce spontaneous recovery of ethanol tolerance.

Many basic researchers agree that Pavlovian conditioning plays an important role in drug effects such as tolerance, withdrawal, craving, and overdose. For decades Siegel and others (e.g., Siegel, 1983, 1991; Siegel, Hinson, Krank, & McCully, 1982) have provided considerable evidence for this view. Environmental/perceptual stimuli associated with drug-US administration become conditioned stimuli (CSs) which can elicit drug-compensatory conditioned responses (CRs) that oppose the drug's effects. Drug-associated CSs can comprise a rather large set of stimuli present in the milieu of drug administration, including the

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room/setting in which drugs are taken (e.g., Larson & Siegel, 1998; Siegel et al., 1982; White, Roberts, & Best, 2002), discrete stimuli within a setting (e.g., Siegel, 1983), and interoceptive stimuli/drug onset cues (e.g., McDonald & Siegel, 2004; Sokolowska, Siegel, Kim, 2002). A substantial body of evidence has been generated showing that Pavlovian conditioning effects occur with drugs along much the same lines as those occur in other Pavlovian conditioning preparations (e.g., effects such as acquisition, extinction, latent inhibition, conditioned inhibition, external inhibition; see Siegel, 1978, 1983, 1989, for reviews). Considerable research and anecdotal observation with humans has accumulated which is consistent with these findings (e.g., Ehrman, Robbins, Childress, & O'Brien, 1992; Siegel & Ramos, 2002). Many conditioning processes are recognized as contributing crucially to human drug experiences such as drug tolerance, drug craving, and drug addiction (e.g., Baker & Tiffany, 1985; Siegel, 1983, 1989; Siegel et al., 1982; see also Domjan, 2003). And many of the conditioning phenomena which support the compensatory CR account of the effects of morphine and heroin have been demonstrated with other drugs of abuse including cocaine, amphetamine, barbiturates, benzodiazepines, antipsychotics, and ethanol (e.g., Siegel, 1983; Siegel & Larson, 1996; see Siegel & Larson, 1998, for a review of ethanol research).

Alcohol abuse poses a serious challenge to researchers and practitioners as it appears to be linked to many human problems (e.g., those related to sexual behavior, aggression, crime, treatment, relapse, performance deficits in driving, etc.; Abbey, 2002; Allsop, Saunders, & Phillips, 2000; Birnbaum & Parker, 1997; Bushman & Cooper, 1990; Donovan & Jessor, 1985; Easdon & Vogel-Sprott, 2000; Herzog, 1999; McCreary & Sadava, 2000; Steele, Southwick, & Pagano, 1986; Wechsler, Lee, Nelson, & Lee, 2003). Our lab has conducted research on alcohol tolerance which can be viewed as having the potential to positively impact at least a subset of those problems. A tolerance conditioning method was used with ethanol as the drug and ataxia (loss of coordination) as the measurable effect of ethanol. The main research objective was to assess a memory-based explanation of the relapse-like effect known as spontaneous recovery. Spontaneous recovery is one of several well-known conditioning phenomena (renewal and reinstatement are examples of others) which indicates that diminished or extinguished responses should robustly recover after a period of treatment and/or abstinence. Prior research in our laboratory using other conditioning methods provided empirical evidence and theoretical grounding for the ethanol tolerance project, and a brief overview of those follow.

After summarizing background research and theory relevant to drug tolerance conditioning and spontaneous recovery, the article proceeds to the general method and procedures used in our experiments, describes experiments demonstrating extinction and spontaneous recovery of ethanol tolerance, and describes the potential to reduce spontaneous recovery obtained by a cue correlated with tolerance extinction. The article continues by summarizing empirical attempts to rule out a number of explanations for that cue's ability to reduce spontaneous recovery, and closes with experimental conclusions and clarifications, as well as implications relevant to understanding, and perhaps helping to prevent, drug-use relapses.

Background Research and Theory

Using an appetitive conditioning method with rats (magazine entry), Brooks (e.g., 2000) found that a cue (a brief unimodal stimulus such as a light or buzzer) can reduce spontaneous recovery. Spontaneous recovery is the reappearance of CRs, such as those potentially contributing to tolerance, after time passes following extinction when the conditioned stimulus (CS) is presented again (e.g., Brooks, 2000; Pavlov, 1927). Two groups of rats illustrate our original spontaneous recovery reduction (Brooks & Bouton, 1993). The rats initially learned a food-cup checking response elicited by a tone that signaled food. The checking CR was extinguished for both groups by repeatedly presenting the tone without food. During extinction, both groups received several presentations of a light-off cue (a cue that was explicitly arranged to be an “extinction cue”) intermixed with the tones. This procedure was intended to associate the cue with extinction of the CR elicited by the tone. Both groups were tested for spontaneous recovery six days after the extinction procedure ended. In the *No Cue* group the tone alone was tested. It elicited strong recovery of the response; with the response just as strong as it was at the end of the initial conditioning phase. Of key interest was performance in the *Cue* group whose subjects were presented with the tone preceded by the light cue. That cue reduced the strength of the spontaneous recovery elicited by the tone CS.

The extinction cue’s ability to reduce spontaneous recovery has been replicated several times with this method (e.g., Brooks, 2000; Brooks & Bowker, 2001). And this effect of the cue has generality. Using the same appetitive conditioning method, Brooks and Bouton (1994) have also demonstrated that the extinction cue can reduce the renewal effect. The renewal effect is the recovery of an extinguished behavior that can occur when the context (e.g., physical location) is changed after extinction. The ability of a cue from extinction to reduce spontaneous recovery has also been reported in taste aversive conditioning (Brooks et al., 1999).

Additional research has helped rule out several possible alternative explanations of the potential for an extinction cue to reduce spontaneous recovery (Brooks, 2000; Brooks & Bowker, 2001; Brooks & Bouton, 1993; Brooks et al., 1999). No evidence was found that the cue produces generalization decrement during testing. A familiar cue presented during testing but not during extinction does not reduce spontaneous recovery or renewal. Familiar or novel cues not connected with extinction do not influence spontaneous recovery of the response; those cues do not reduce the conditioned response by generalization decrement or by distracting the animals from perceiving the CS (Brooks & Bouton, 1993, 1994; Brooks, 2000; Brooks et al., 1999, 2004). For a cue to reduce a relapse-like effect, it must be presented during the extinction procedure and during testing. Failed retardation, summation, and post-cue conditioning tests have suggested that the cue reduces relapse-like effects by some mechanism other than conditioned inhibition (Brooks & Bouton, 1993; Brooks & Bowker, 2001).

Bouton’s (1993) memory account of conditioning can explain the extinction cue’s effect. Conditioning results in the formation of a “CS-US” association or memory. Then, as conditioning proceeds presentation of the CS comes to activate that memory and the CR is elicited. Extinction does not destroy the conditioning memory but rather results in the encoding of a separate association involving the

CS (a “CS-no US” memory). As extinction proceeds, that memory increasingly interferes with retrieval of the conditioning memory. The extinguished CS activates or retrieves the extinction memory and a weakened CR results. Immediately following the completion of the extinction phase, presentation of the CS activates strong retrieval of the recently-formed extinction memory and little or no CR occurs. However, the extinction memory is context specific; that is, following the extinction phase, retrieval of the extinction memory depends on the presentation of the CS along with some or all of the non-CS circumstances that were present during extinction. Changes of physical setting (provided by the experimental apparatus) and/or the passage of time are instances of experimentally-studied changes from the circumstances of extinction that result in a failure to retrieve the extinction memory. These changes are theorized to result in less interference by the extinction memory with retrieval of the conditioning memory, and the CS thus elicits a strong CR again (e.g., spontaneous recovery or renewal).

Bouton’s theory interprets the extinction cue as a physical component of the extinction context. Upon presentation in testing, the cue could at least partially reinstate some of the circumstances of extinction. It may therefore facilitate retrieval, or activation, of the otherwise “forgotten” extinction memory (CS-no US). According to this account, facilitated retrieval of the extinction memory should result in the CS eliciting a relatively weak CR, consistent with the cue’s potential to reduce spontaneous recovery and renewal.

This empirical and theoretical base guided the use of a different preparation in our lab, the ethanol ataxia method, to investigate the potential effect of an extinction cue on spontaneous recovery of conditioned and extinguished ethanol tolerance. This method was chosen for several reasons including that it involves a drug commonly abused by humans, it is an established method in the drug/conditioning research literature (e.g., Larson & Siegel, 1998; Weise-Kelly & Siegel, 2001), and is sensitive to environmental stimulus manipulation. In addition, it is relatively easy to use, is non-invasive, and produces reliable overt behavioral data.

General Method and Procedures

In the experiments described below, the subjects were male and female adult Wistar rats kept on ad libitum food and water. General experimental procedures (details described in Brooks et al., 2000) utilized a single rat at a time and were conducted in a distinctive laboratory room with walls covered with black and white lettering and geometric shapes. Lighting was provided by one 60 W bulb located behind the apparatus. Ataxia was assessed using a box made of acrylic plastic. The box floor was smooth fabricated wood flooring. One end of the box was attached to the wooden table top it rested on via hinges. A crank and pulley system was used to manually raise the unhinged end of the floor. A laser attached to the raised end of the box projected onto a wall-mounted protractor to indicate floor inclination angle. A strobelight was centered above the box. Ethanol was mixed in 9% physiological saline to form a 15% v/v solution, which was administered IP at a dose of 1.5 g/kg. When ethanol was not injected, 0.9% physiological saline was, in the same volume. The CS is considered to be comprised of the strobelight and the other characteristics of the laboratory room. Slip angles were

measured to index ataxia. For each angle measurement the box floor began in the horizontal position (zero degrees). A slip was defined as the animal losing its grip on the floor and sliding at least half the length of the floor once the box end was raised. The slip angle was the floor inclination at which the slide began. Pre-injection (baseline) slip angles were measured 10 s and 60 s after the rat was placed in the box. Post-injection angles were measured every 2 min for 10 min. The strobelight was turned on following injection and terminated after the last postinjection angles was measured. On each trial a maximum impairment score (MIS) was calculated by subtracting the larger of the 2 pre-injection angles from the smallest of the 5 post-injection angles. Negative MISs indicate ataxic impairment; a zero MIS indicates complete tolerance. In the research described here, there were no significant differences in baseline slip angles among conditions. All inferential statistical tests used a rejection criterion of $p < 0.05$.

Extinction and Spontaneous Recovery of Ethanol Tolerance

The development of conditioned tolerance to the ataxic effects of ethanol has been demonstrated (e.g., Cunningham, 1979, 1998; Larson & Siegel, 1998; Siegel, 1983; Siegel & Larson, 1996). However, before assessing an extinction cue's effect on spontaneous recovery, it was necessary to show that with the ataxia method ethanol tolerance could be extinguished and was subject to spontaneous recovery. One experiment (Brooks, Karamanlian, & Foster, 2000, Experiment 1) examined extinction. Three groups of rats received once-daily ethanol injections in the apparatus for 14 days. This procedure produces reliable tolerance development (i.e., mean MISs typically change from approximately -12 to near zero during the conditioning phase). A fourth group (Group Naive) did not receive conditioning. Two groups given conditioning received an extinction procedure which was identical to that for conditioning except that saline was injected instead of ethanol. Those groups received either 17 (Group E17) or 24 (Group E14) extinction trials. Group Rest, which had received conditioning, and Group Naive, were not treated in this phase. A test to assess the effect of the extinction trials involved ethanol given to all groups in the apparatus. Figure 1 shows the test results. In testing, Groups E17 and E24 were significantly impaired compared with Group Rest, indicating extinction of tolerance. Groups E17 and E24 did not differ from Group Naive, indicating that extinction was complete. Since with this method extinction is complete in 17 trials; subsequent experiments used that number, or just a few more.

When Brooks et al. (2000, Experiment 2) initially demonstrated spontaneous recovery, four groups of rats received the same conditioning and extinction procedures as for Group E17 above. A test with ethanol was administered for all groups either 1, 12, 18, or 24 days following the end of extinction. Testing one day post-extinction resulted in marked impairment during testing (MIS = -10.0), which was consistent with the measure of tolerance observed right after extinction in Group E17 above. However, it is notable that testing at each of the longer intervals revealed significantly less impairment which did not differ among the 12-, 18-, and 24-day periods (MISs ranged between -3.0 and -1.0 for those groups). The increase in tolerance from 1 to 12 or more days after extinction is related to time passing after extinction, and suggested that the spontaneous recovery effect does occur.

The spontaneous recovery of tolerance after extinction was very strong, and occurred after a delay of just 12 days.

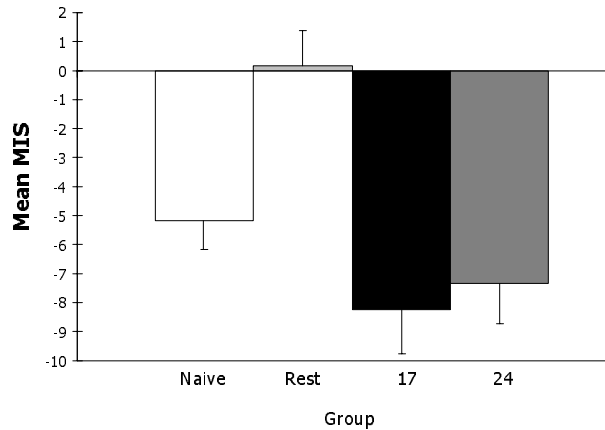


Figure 1. Mean maximum impairment scores (MIS) for Groups Naïve, Rest, E17, and E24 on the test of the effects of extinction in Groups E17 and E24 of Experiment 1 in Brooks, Karamanian, and Foster (2000). Groups E17 and E24 demonstrated complete extinction of tolerance and did not differ from Group Naïve which did not receive conditioning or extinction of tolerance. Group Rest received only conditioning and testing but no extinction. Copyright by *Psychopharmacology*, reprinted by permission.

An Extinction Cue Reduces Spontaneous Recovery of Ethanol Tolerance

Having established that ataxic tolerance to ethanol extinguishes and is subject to spontaneous recovery, the effect on spontaneous recovery of a cue presented during extinction was assessed. In an initial experiment (Brooks, Vaughan, Freeman, & Woods, 2004, Experiment 3), two groups received the standard ethanol tolerance conditioning procedure described earlier. They then received extinction during which a 15-s buzzer (see Brooks et al., 1999) was presented that served as the extinction cue. It was presented on 75% of the extinction trials and terminated approximately 30 s before the baseline slip angles were measured. This procedure was analogous to that of the original extinction cue appetitive conditioning experiments (e.g., Brooks & Bouton, 1993) and was designed to permit an association to form between the cue and the experience of tolerance extinction.

Both groups were tested 18 days after extinction in the box with ethanol injected. One group was tested with the cue that had been presented during extinction. The presentation of the cue during testing for this group followed the same procedure as on cued extinction trials. The other group was tested identically except that no cue was presented. There were no differences between the groups either in the development of ataxic ethanol tolerance during conditioning, or during extinction. During testing, the group tested without the extinction cue demonstrated strong spontaneous recovery of conditioned tolerance; its mean MIS was above zero (+2.5). However, the group that was tested with the cue from extinction was less tolerant, with a mean MIS of -4.4. The extinction cue significantly reduced spontaneous recovery of ataxic ethanol tolerance. This important result merited clarification and replication.

Narrowing Interpretation of the Extinction Cue's Effect

In parallel with the prior research using other conditioning preparations, it was important to assess possible explanations for the cue's tolerance-reducing potential on the spontaneous recovery test (e.g., Bouton's memory retrieval theory, conditioned inhibition, generalization decrement, etc.). It was also worth assessing whether the spontaneous recovery effect identified above is truly associative, and whether testing without the cue right after extinction produces a tolerance increase which might be interpreted as a renewal effect. This section summarizes experiments which address those issues.

A separate experiment (Brooks et al., 2004, Experiment 4), that replicated the extinction cue's effect on spontaneous recovery, assessed the importance of presenting a cue during extinction, and addressed the possibility that the cue's CR-reduction potential is mediated by non-associative processes. For instance, during testing the cue may have produced generalization decrement, a loss of response that could be caused by any cue in combination with the CS. Or the cue may have produced behavioral disruption/distraction or external inhibition by the potentially unexpected introduction of a cue. Three groups of rats received the standard conditioning procedure. Two of them (Groups Ext Cue & No Cue) received cued extinction. A third group (Group Neut Cue) received the same number of cue presentations as the other two groups but received those prior to conditioning rather than during extinction. Group Neut Cue did not receive cued extinction. The cue was intended to be associatively *neutral* (i.e., not presented during conditioning or extinction) prior to testing. Each group was tested with the CS and ethanol injected. Groups Ext Cue and Neut Cue were tested with the cue; Group No Cue was tested the same way except with no cue. If any cue presented during testing simply disrupts the CR, or produces generalization decrement, the neutral cue should also reduce the spontaneous recovery of tolerance CRs. If a cue's potential to reduce spontaneous recovery depends on its presentation specifically during extinction, then only the extinction cue should reduce spontaneous recovery.

Figure 2 shows mean MISs (\pm SEM) for the groups on the last trial of conditioning and the first trial of the spontaneous recovery test. A *change score* was analyzed to represent the change in MISs from the final conditioning trial to the first test trial. The change score was determined by calculating the total MIS distance between the trials for each rat and specifying the sign indicating the direction of change (e.g., a MIS of +2 in conditioning to a MIS of -4 during testing yields a change score of -6). Positive scores indicate increased tolerance from conditioning to test; negative scores indicate decreased tolerance. In addition to standardizing conditioning performance (asymptotic conditioning levels could influence CR magnitude during testing), this measure provides an efficient index of the *degree* of change in tolerance from conditioning to testing. The mean change scores for Groups No Cue, Ext Cue, and Neut Cue were +2.33, -4.43, and +1.14, respectively. Group Ext Cue had a significantly lower score than No Cue, indicating that the extinction cue reduced SR. This replicated the original demonstration of the extinction cue's potential to reduce tolerance spontaneous recovery. Groups Neut Cue and No Cue did not differ, indicating that the cue which was not presented during extinction did not reduce spontaneous recovery of tolerance. The neutral cue result indicates that the extinction cue did not reduce spontaneous recovery by

non-associative process such as generalization decrement, behavioral disruption, or external inhibition. The pattern of results indicates that the extinction cue's effect during testing depends on its presentation during extinction.

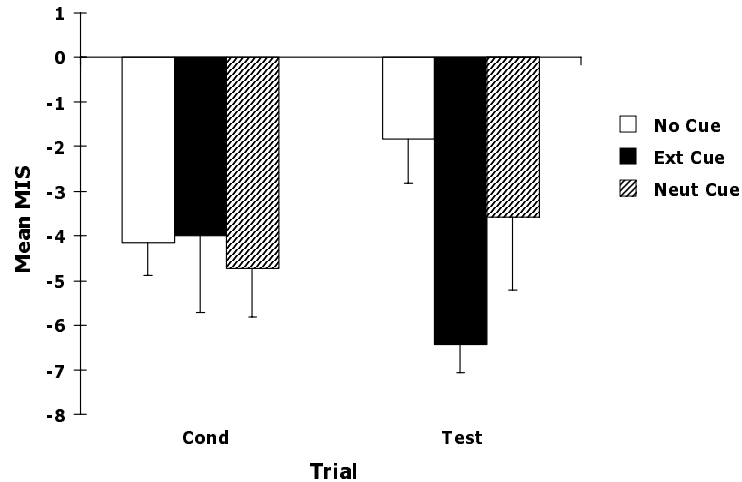


Figure 2. Mean maximum impairment scores (MIS) for Groups No Cue, Ext Cue, and Neut Cue on the last trial of conditioning (Cond) and the first trial of the spontaneous recovery test (Test) of Experiment 4 in Brooks, Vaughan, Freeman, and Woods (2004). During spontaneous recovery testing, Group No Cue demonstrated strong ethanol tolerance which was significantly reduced by the extinction cue (Group Ext Cue) but not by the neutral cue (Group Neut Cue).

One might wonder whether the increases in ataxic tolerance interpreted as spontaneous recovery were associative and thus depended upon initially learning the CS-US association. Alternate possibilities are that tolerance increase was not due to temporal pairings of the CS and US, or to the predictive validity of the CS (e.g., Resorla, 1968). Instead, with the ataxia method used here tolerance might be due to mere US exposure and/or an unconditioned decrease in impairment over time. Or tolerance behavior (resisting slipping/remaining upright) might have been reinforced by an operant contingency. Brooks et al. (2004, Exp. 1) addressed these possibilities. Control groups received the CS and US unpaired during a conditioning phase (but not after conditioning). During that phase (but not after) they received equivalent exposure to the apparatus but received ethanol injections several hours later in the home cage. The unpaired procedure prevented spontaneous recovery; i.e., no increase in ethanol tolerance was observed after the extinction phase unless the CS and US were paired prior to that phase. The unpaired procedure resulted in no discernable change in tolerance even during the conditioning phase.

This experiment also supported the view that ataxic tolerance with this method does not result from operant-reinforcement processes. To assess this, other control groups initially received the standard conditioning procedure described earlier, except the box was never tilted in that phase. This should prevent behavioral practice (via standing on an incline) or reinforcing outcomes (via not slipping down an incline) from contributing to tolerance. However, tolerance in those groups developed at the same rate, and to the same degree, as other groups in the experiment which received the standard conditioning procedure. Thus, the strong

tolerance observed upon testing after a delay following extinction appears to be an instance of Pavlovian spontaneous recovery.

Another issue required clarification. In principle, certain procedures used during extinction might yield an extinction cue with a characteristic akin to that of the physical background stimuli (called the context) of extinction. If so, testing immediately after extinction but without the cue could result in a strong increase in tolerance CRs. Testing the CS in the absence of a physical extinction context immediately after extinction produces a strong increase in other CRs. That increase with a change of physical setting after extinction is called the renewal effect (e.g., Bouton, 1993; Bouton & Bolles, 1979). If the absence of the extinction cue immediately after extinction causes renewal of the CR, then cue absence in delayed testing might also cause renewal. Thus, in delay tests the potential effect of cue absence (i.e., renewal) could be confounded with the effect of the passage of time, making quite questionable a claim that increased tolerance in delay tests constitutes the spontaneous recovery effect. In turn no claim could be made that the extinction cue reduces that effect. However, in fact when tolerance was tested immediately after extinction and without the cue (Brooks et al., 2004, Exp. 3) there was no increase compared with a group never given the cue. Therefore, in these experiments when tolerance increased at 12 or more days after extinction, the increase was related to the passage of time and thus represented spontaneous recovery. A renewal effect probably was not obtained because the cue was unlikely to have been encoded as a static element of extinction because cue presentations were brief (15-s), did not occur on every extinction trial, and were separated in time from the focal CSs (e.g., the strobelight). The cue does not appear to have been encoded as a crucial contextual stimulus but instead may have functioned as a discrete occasion setter (see Brooks & Bowker, 2001).

Finally, the extinction cue might reduce spontaneous recovery by acquiring the properties of a conditioned inhibitor during extinction of the CSs. Preliminary unpublished results from summation and retardation of acquisition tests suggest that the extinction cue did not acquire inhibitory properties, but additional research will be necessary to confirm that.

Conclusions and Implications

A cue presented on most extinction trials reduced the spontaneous recovery of ethanol tolerance when that cue was also present during recovery testing. This cue's potential to reduce tolerance during testing depends on its presentation during extinction. An equally familiar cue not presented during extinction does not appear to influence spontaneous recovery. The results of several experiments argue against explanations of the cue's effect based on generalization decrement, disruption, external inhibition, and to a preliminary extent, conditioned inhibition. These findings closely parallel findings involving an extinction cue's effect on spontaneous recovery and renewal in appetitive conditioning (e.g., Brooks, 2000; Brooks & Bouton, 1993, 1994), and on spontaneous recovery in taste-aversion conditioning (Brooks et al., 1999).

A reasonable explanation for the pattern of ethanol tolerance results reviewed here is provided by Bouton's (1993) memory theory. According to this formulation the extinction cue may become associated with a memory involving

the CS which formed during extinction (i.e., a CS-no US memory) and that becomes less accessible with the passage of time after extinction. Then, by enhancing the retrieval of that memory, the cue may reduce spontaneous recovery. The results described here are consistent with Bouton's view that spontaneous recovery occurs because of a failure to retrieve the extinction memory once time has passed following extinction. Relapses may occur in part because of forgetting clinical treatment information. They extend Bouton's theory to a conditioning preparation in which it appears that compensatory CRs spontaneously recover but can be suppressed again by a cue correlated with extinction.

The basic finding that ataxic ethanol tolerance can be extinguished and is subject to spontaneous recovery deserves emphasis. Demonstrations of extinction imply that tolerance, withdrawal and craving can be diminished by cue exposure techniques. This corroborates the efficacy of CS-exposure as a treatment component for the abuse of alcohol and other drugs in humans (e.g., Collins & Brandon, 2002; Drummond, 2000; Heather, 1991; Marlatt, 1990). These experiments appear to provide the first demonstration of spontaneous recovery using a Pavlovian conditioning preparation with a drug as the US. In addition, they eliminate many alternative accounts of recovery of the conditioned response. Spontaneous recovery indicates that extinction does not produce unlearning of the original CS-US association that forms during conditioning. Here the spontaneous recovery of ethanol tolerance was very strong. The effect suggests that after extinction, tolerance (and withdrawal and craving) becomes much more robust with the mere passage of time when previously drug-associated CSs are reintroduced. This conclusion was supported by tests programmed soon after extinction as well as those administered 12-24 days after extinction. This suggests that while alcohol treatment interventions which incorporate exposure therapy can be effective, time-dependent changes analogous to those which produce spontaneous recovery after extinction should be expected to contribute to relapses after treatment. Increased intensity of withdrawal is clinically consequential (Baker, Piper, McCarthy, Majeskie, & Fiore, 2004), potentially making abstinence more difficult and relapse more likely. Therefore, without effective relapse-prevention components even exposure therapy techniques effective in clinical settings may not induce long-term abstinence in substance abusers. To be more effective, exposure therapy should incorporate techniques that reduce the potential influence of time dependent changes, and utilize other phenomena which can suppress the return of drug-seeking and drug-taking behaviors.

Pavlovian conditioning theory indicates that drug tolerance is dependent on drug-associated stimuli (CSs) and is indicative of withdrawal symptoms. That is, to a significant extent, withdrawal symptoms are enhanced and/or produced by drug-compensatory CRs which have their basis in CS-drug associations (e.g., Baker et al., 2004; Siegel, 1983). By extension, spontaneous recovery of ethanol tolerance may be caused by the recovery of associative processes responsible for withdrawal symptoms that occurs as time has passed following CS- exposures. To a significant extent, the development and manifestation of tolerance responses to many CNS depressant effects of ethanol likely follow the same Pavlovian associative learning principles as for ataxic tolerance to ethanol. Thus, spontaneous recovery of ataxic tolerance CRs might serve as a model for the recovery of withdrawal symptoms such as delirium tremors, irritability, anxiety, and subjective alcohol

cravings—symptoms which may motivate instrumental actions characteristic of abstinence failure (i.e., drug seeking and drug taking; see Baker et al., 2004).

Extinction cues that reduce tolerance CRs might reduce the recovery of withdrawal responses and thus could potentially reduce the motivation to abandon abstinence. A cue from the extinction setting would serve to suppress spontaneous recovery of compensatory responses, possibly resulting in fewer withdrawal symptoms and higher abstinence rates. Already this view appears to have some connection to the clinic. A cuing method analogous to the one used in our experiments maintained reductions in alcohol craving in humans (Collins & Brandon, 2002); this research may help establish procedures that increase the generalizability of exposure therapy for the treatment of substance abuse relapse in humans. One does not have to know with certainty the mechanism of the extinction cue effects reported here to begin to appreciate their potential clinical implications. Brief exteroceptive cues could be tested for their potential to minimize relapses in humans (e.g., Conklin & Tiffany, 2002; Siegel & Ramos, 2002). Our findings emphasize the potential importance of behavior-based components of relapse treatments, and suggest that post-treatment relapses related to the passage of time after treatment could be reduced by timely presentations of stimuli associated with therapy interventions.

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