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Preventing the recovery of extinguished ethanol tolerance

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ABSTRACT

There is substantial evidence that drug-paired cues become associated with drug effects. From a Pavlovian perspective, these cues act as conditioned stimuli and elicit conditioned compensatory responses that contribute to drug tolerance. Here we report two experiments with rats in which we studied the extinction of the associative tolerance to the ataxic effect of ethanol. Experiment 1 evaluated whether changes in the temporal and physical contexts after extinction training provoke recovery of the extinguished tolerance. The results showed successful extinction, spontaneous recovery and renewal of the extinguished tolerance, but no summation of renewal and spontaneous recovery. Experiment 2 evaluated whether using massive extinction trials and delivering extinction in multiple contexts attenuates the renewal effect. The results showed that both manipulations reduced renewal of the extinguished tolerance to the ataxic effect of ethanol; however, these manipulations used in combination did not appear to be more effective in reducing recovery than each by itself. The present results may help guide further research that evaluates behavioral ploys to prevent the recovery of extinguished responses.

1. Preventing the recovery of extinguished ethanol tolerance

Organisms learn about the relationships between events in their lives through Pavlovian conditioning; with that information they represent their world and act accordingly (Rescorla, 1988). There are several situations in which Pavlovian conditioning is important for the adaptation of organisms to environmental changes (e.g., Domjan, 2005). Of relevance for the present study, Pavlovian conditioning appears to be involved in the development and maintenance of drug tolerance (Siegel et al., 2000), helping organisms to predict and compensate the imminent effects of drugs using the information provided by cues previously paired with them.

From a Pavlovian perspective, the administration of a drug causes a disturbance in the homeostasis of the organism (i.e., unconditioned stimulus, US), to which the body reacts by modifying several physiological parameters (i.e., unconditioned response, UR) that tend to reduce the disturbance and reestablish internal balance (i.e., acute tolerance; Ramsay et al., 1996; Ramsay and Woods, 1997). Interestingly, the effects of drugs become associated with the environmental stimuli (i.e., conditioned stimulus, CS) that were present at the moment of drug intake. Through the pairing of these events, these cues come to elicit a response (i.e., conditioned response, CR) that mimics the compensatory UR elicited in response to the disturbance. This way, the CR anticipates the effects of drugs and helps reduce the disturbance produced by them in the organism (i.e., associative tolerance or chronic tolerance; Ramsay and Woods, 1997). Similarly, when an organism is exposed to stimuli associated with a drug in the absence of the drug itself the compensatory responses occur in reaction to the stimuli, causing what is known as withdrawal symptoms (Ramsay and Woods, 1997; Siegel et al., 2000).

Thus Pavlovian cues are relevant for organisms to anticipate the unconditioned effect of drugs, which in turn has an important role in drug-related cravings and relapses (Childress et al., 1999). Cues associated with drugs also maintain drug-seeking behavior after long periods free of drugs, both in humans and other animals (Gawin and Kleber, 1986; Hellemans et al., 2006; Robinson and Berridge, 2003). More directly related to our study, cues associated with ethanol consumption have also shown to increase appetitive instrumental behaviors without (Krank, 2003) and with demonstrations of associative tolerance (Quezada et al., 2009). For a review on the role of Pavlovian cues in problematic drug use and relapse see Siegel (2001).

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There are several phenomena observed in Pavlovian conditioning that are also present in associative tolerance (e.g., Betancourt et al., 2008b,c; MacRae et al., 1987). One of these is extinction: the reduction of the CR by repeated exposure to CS in the absence of US (Mansfield and Cunningham, 1980; Miguez et al., 2013). Extinction is especially relevant for the treatment of drug abuse disorders (Childress et al., 1988), because through it both drug tolerance and withdrawal symptoms can be reduced, therefore interrupting their role in the maintenance of addictive behavior (Secades-Villa et al., 2007). However, the clinical application of extinction to drug-related disorders has not fulfilled its original expectations (Childress et al., 1988), thus the present research evaluated potential ploys to make extinction-based therapy more effective.

Interestingly, it has been observed that under certain circumstances extinguished responses recover, which indicates that extinction does not erase the original learning but creates a new, possibly inhibitory association that has been shown to be especially context-specific (Bouton, 1993). For example, since the early work of Pavlov it has been reported that extinguished responses recover when a delay is imposed between extinction and testing, a phenomenon known as spontaneous recovery (Pavlov, 1927). In this case, Bouton (1993, 2010) has argued that testing out of the temporal context of extinction is what provokes this type of recovery from extinction. Similarly, recovery from extinction has been reported when testing occurs out of the physical context in which extinction took place, a phenomenon called renewal (Bouton and Bolles, 1979). Additionally, when new CS–US presentations are given after extinction the CR usually develops faster than when such pairings are given to a novel stimulus with US (rapid reacquisition; Ricker and Bouton, 1996); other evidence that suggests the effects of extinction are labile and susceptible to recovery.

These phenomena are fairly robust across a variety of preparations and species (for a review see Bouton, 2002). In the case of associative tolerance, there is evidence for some of the post-extinction response recovery phenomena described above. Brooks et al. (2001) obtained spontaneous recovery of conditioned tolerance to the ataxic effect to ethanol in rats. After successful acquisition and extinction of the tolerance response, subjects were tested with reacquisition CS–US trials after 1, 12, 18, or 24 days from extinction (i.e., retention intervals). Their results showed that tolerance was greater for groups tested 12–24 days following extinction (i.e., it recovered) than for the group tested only 1 day following extinction. This suggests that a relatively long retention interval after extinction spontaneously recovers the extinguished tolerance response. In the case of renewal, the only reported data for associative tolerance to ethanol are those of Betancourt et al. (2008a). Using a similar procedure to the one used by Brooks et al. (2001) and Brooks et al. (2004), they evaluated whether the extinguished tolerance to the ataxic effects of ethanol would recover when acquisition, extinction, and testing occurred in three different contexts. Even though Betancourt et al. found high levels of tolerance to the ataxic effects of ethanol in the context of testing (potential recovery of the extinguished tolerance by testing out of the extinction context), their results should be taken with caution, given that their experiment lacked the critical ABB control group needed to prove this type of renewal (i.e., ABB < ABC).

Various theoretical models have explained both spontaneous recovery and renewal. For example, Bouton's model (1993) proposes that extinction produces an inhibitory memory that interferes with the expression of the acquisition memory. In one version of the model, the extinction memory becomes context-dependent because the CS becomes ambiguous (i.e., it has a history of positive and negative correlation with the US); the association formed during extinction is learned as an exception that can be predicted by contextual cues.

Miller and Laborda (2011) and Laborda and Miller, (2012) extended the ideas of Bouton (1993). For their model, in a given test trial subjects compare the reactivated memory from acquisition and the reactivated memory from extinction. Reactivation of the memories occurs not only due to the strength of the associations learned (i.e., the CS–US memory formed during acquisition and the CS–noUS memory formed during extinction), but also due to the cues from acquisition and/or extinction present at the moment of testing. Therefore, a low response in the test is due to the reactivated memory of extinction being stronger than the reactivated memory of acquisition and vice versa.

Coherently with the previous models, there is evidence supporting the idea that what is learned during extinction is an association with inhibitory characteristics that is easier to express in the spatiotemporal context where extinction occurred than out of that context (Bouton, 1993; Laborda and Miller, 2012). A logical consequence of this is that the differences between the extinction and testing contexts may correlate with the degree of the response recovery found during testing.

In these models summation of the effects of renewal and spontaneous recovery should be expected; changing the physical context and adding a delay from extinction to testing should provoke a greater response recovery than each manipulation by itself. This idea has recently been evaluated by Laborda and Miller (2013) in a fear-conditioned experiment with rats, by Rosas and Bouton (1998) in a taste-aversion preparation with rats, and by Rosas et al. (2001) using a causal judgments paradigm with humans. All reports showed a summative effect of renewal and spontaneous recovery. However, in the case of associative tolerance, the additive effect of spontaneous recovery and renewal has not been explored. Experiment 1 of this report addressed this possibility.

After parameters to evoke high levels of recovery of the extinguished tolerance to the ataxic effect of ethanol were found in Experiment 1, in Experiment 2 we evaluated potential means to disrupt recovery. Recovery from extinction has been established as a model of relapse after exposure treatment for drug-related disorders (Brooks et al., 2004), thus identifying ways to prevent recovery of extinguished tolerance could shed light concerning schemes to prevent lapse and relapse after cue-exposure treatment for alcohol addiction. In Experiment 2 we assessed the effects of giving massive extinction (i.e., a large number of extinction trials) and carrying out extinction in multiple contexts in the recovery of extinguished tolerance. These techniques have previously shown to reduce the recovery of an extinguished response in other preparations (e.g., Chelonis et al., 1999; Denniston et al., 2003; Glautier and Elgueta, 2009; Gunther et al., 1998; Laborda and Miller, 2013), and in other types of associative interference (e.g., Miguez et al., 2014).

2. Experiment 1

Using a similar preparation to that used by Siegel and Larson (1996) to train and assess associative tolerance to the ataxic effect of ethanol, in a 2 (Retention: Short vs. Long) by 2 (Context: Same vs. Different; relative to extinction context) factorial design we manipulated the time elapsed since extinction and the context in which testing was carried out. As shown in Table 1, all subjects had acquisition training where an auditory cue was presented in compound with the effect of an ethanol injection in Context A, followed by an extinction phase where the auditory cue was presented alone in Context B. In the subsequent test, Condition Same was tested in Context B, while Condition Different was tested in a third context, C. In turn, Condition Short (i.e., Groups Short–Same and Short–Different) was tested a day following extinction, whereas Condition Long (i.e., Groups Long–Same and Long–Different) was tested 15 days following extinction. If the effects of both