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Contextual renewal of cocaine seeking in rats and its attenuation by the conditioned effects of an alternative reinforcer

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Abstract

The present experiment investigated contextual renewal of cocaine seeking and potential methods of attenuating this renewal. Rats were first trained in one context to self-administer cocaine when a discriminative stimulus (tone) was presented. Then, the ABA Group was placed in a second context and responses in tone no longer produced cocaine (extinction). The AAA Group received this extinction in the original context. For two additional groups, responding to the tone was eliminated in a second context by additionally presenting food in tone according to a differential-reinforcement-of-other-behavior (DRO Group) schedule or independently of the rats' behavior on a fixed-time (FT Group) schedule. Renewal of responding to the tone was observed when the ABA Group was returned to the original context for a renewal test, but no renewal was observed in the AAA Group. Renewal also occurred in the DRO and FT Groups upon returning to the original context, but this renewal was significantly less than that of the ABA Group. These results suggest that response elimination techniques that are more active than simple extinction, such as pairing drug-related stimuli with alternative reinforcement, could reduce renewal of drug seeking and thereby help prevent relapse.

Keywords: Context renewal; Cocaine self-administration; Cue exposure; Discriminative stimuli; Operant conditioning; Pavlovian conditioning; Rats

1. Introduction

In the original demonstration of the context renewal effect, Bouton and Bolles (1979) trained rats by pairing a tone conditioned stimulus (CS) with a shock unconditioned stimulus (US) in one context (Context A). Then, the tone was extinguished (i.e., presented without shock) in a discriminably different context (Context B). Extinction in Context B continued until the tone no longer elicited any conditioned responses (CRs). In testing, rats were returned to the original context (A) and, surprisingly, the tone produced a reappearance of responding. The responding observed in this "ABA renewal" Group was comparable to that observed in a group that did not receive any extinction of the tone. In contrast, the tone did not elicit any responding in Context A in a group that received original training as well as extinction in Context A. The context renewal effect is a very robust phenomenon that also exhibits a high degree of generality, having been demonstrated in a variety of experimental preparations including Pavlovian aversive conditioning (Bouton and Bolles, 1979; Bouton and Swartzentruber, 1986, 1989; Bouton and King, 1983, 1986; Bouton and Ricker, 1994; Brooks and Bouton, 1994; Rauhut et al., 2001), Pavlovian appetitive conditioning (Bouton and Peck, 1989; Peck and Bouton, 1990) and operant discriminative appetitive conditioning (Nakajima et al., 2000).

Bouton and his associates have investigated the behavioral mechanisms underlying the context renewal effect and have provided persuasive evidence that the effect is not due to the direct excitatory or inhibitory effects of context on responding (Bouton and Bolles, 1979; Bouton and King, 1983; Bouton and Swartzentruber, 1986). Instead, Bouton (1991, 1993, 2004), Bouton and Swartzentruber (1986) suggests that the context in renewal studies acts like a Pavlovian occasion setter (Holland, 1992) that does not directly control responding, but rather mediates the CS's control over responding. It is postulated that subjects in renewal studies learn that the CS is paired with the US in Context A, but that the CS is not paired with the US in Context B. When returned to Context A, only the original the CS–US association is retrieved and this is why responding to the CS is observed again. Thus, in renewal studies, the context participates in a conditional discrimination involving the CS and US (if Context A, then CS–US; if Context B, then CS–no US),

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rather than in a simple discrimination (Context A–US; Context B–no US).

Recently, several investigators (Bouton, 2002; Collins and Brandon, 2002; Conklin and Tiffany, 2002) have suggested that context renewal might contribute to instances of relapse after extinction-based treatments such as cue-exposure therapy (Drummond et al., 1995). Specifically, it has been suggested that drug-related stimuli (e.g., drug-taking paraphernalia) become associated with the abused drug in one context (e.g., the drug user's normal environment). Then, the effects that these drug cues have over behavior (e.g., elicit craving) are eliminated through extinction treatment (i.e., the drug cues are repeatedly presented without the drug) that is conducted in a context (e.g., a clinic or treatment facility) different from the drug user's normal environment. Because the effects of extinction do not transfer from the treatment context to other environments, these drug-paired stimuli once again exert control over behavior and the individual relapses when the user returns to their normal environment.

Drug self-administration experiments with rats have produced results that are consistent with the suggestion that context renewal might contribute to drug relapse. In these studies (Crombag et al., 2002; Crombag and Shaham, 2002), rats' lever pressing in one context (A) produced an infusion of cocaine or a cocaine/heroin combination plus the brief illumination of a cue light CS. Then, rats were placed in a second context (B) and lever pressing produced the CS but no drug infusion. Responding declined over these extinction sessions. When, in testing, rats were returned to the original self-administration context (A), there was a reappearance of lever pressing.

Crombag et al. (2002) and Crombag and Shaham (2002) describe their results as instances of context renewal of the type originally demonstrated by Bouton and Bolles (1979). That is, they attribute their results to rats having learned that in Context A the CS was paired with the drug and that in Context B the CS was not paired with the drug. In their test, Context A retrieved the CS–drug association (rather than the CS–no drug association) and this is why rats again responded. Though their results are consistent with this explanation, they are also consistent with the hypothesis that their rats learned only a simple operant discrimination.

In a simple operant discrimination, responses are reinforced in the presence of one stimulus condition (discriminative stimulus; S^D), but not in the presence of another stimulus condition (S^{Δ}). Crombag et al.'s results could be due solely to rats having learned such a simple discrimination because lever presses were reinforced by the drug in Context A (S^D), and not reinforced in Context B (S^{Δ}). In testing, there is a reappearance of responding because they are again presented with the S^D in which responses had never been subjected to extinction. Thus, according to this alternative explanation, the contexts acted as discriminative stimuli that directly controlled lever pressing. Therefore, the Crombag et al. results might not be best described as instances of context renewal. As described above, the context does not directly control responding in cases of context renewal, but instead indirectly controls responding by acting as the cue in a conditional discrimination that tells the animal when a CS (or S^D) signals the US (or response-dependent reinforcement).

Unfortunately, with the Crombag design, it is difficult, if not impossible, to separate the context renewal explanation from the simple operant discrimination explanation. This is because in these studies, responding in the context alone (i.e., in the absence of the CS) preceded and produced the CS. In contrast, in traditional renewal studies, the CS (or S^D; Experiment 2; Nakajima et al., 2000) is presented independently of the subject's behavior and responding produced by this stimulus is measured. This stimulus-produced responding can then be compared to levels of responding when the CS or S^D is absent, either explicitly or implicitly (i.e., through the use of suppression or elevation ratios), to determine the extent to which the context directly controls responding. Because this type of comparison is not possible with the Crombag et al. design, it is not possible to know whether the contexts acted as operant S^Ds that directly controlled responding or whether the context influenced responding by mediating the effects of the CS.

The first objective of the present experiment was to investigate whether contextual renewal of cocaine seeking in rats occurs within a design free from these interpretational difficulties. This was accomplished by using a procedure similar to that of Nakajima et al.'s Experiment 2 (2000) but with cocaine as the reinforcer instead of food. Specifically, in one context (A), rats were trained to self-administer cocaine whenever a tone S^D was present but not absent. In a second phase, responding during the tone no longer produced cocaine. This extinction was conducted in a new context (B) for the ABA Group and in the original context (A) for the AAA Group. On a test for renewal, all rats were returned to the original context (A) and the tone was periodically presented in extinction (i.e., responses were not reinforced during the test). If the context acted as an occasion setter, as it does in traditional renewal studies, then it would be expected that responding would reappear in the ABA Group, but not the AAA Group, and that this renewed responding would be specific to the tone.

One of the most remarkable findings in renewal studies is that robust renewal is still observed in Context A even when extinction training is continued past the point where responding has been completely eliminated in Context B (e.g., Bouton and Swartzentruber, 1989; Rauhut et al., 2001; Tamai and Nakajima, 2000). Some attenuation of renewal is observed only after "massive extinction" training, where 800 extinction trials were conducted in Context B, after only 8 acquisition trials in Context A (Denniston et al., 2003). This demonstrated low effectiveness of extinction in preventing the reappearance of responding does not bode well for extinction-based treatments of drug abuse. Fortunately, there are more active response-elimination techniques than extinction, which simply discontinues the pairing of a CS with a US or a response with a reinforcer.

The second objective of the present experiment was to determine whether one such active response-elimination procedure, differential-reinforcement-of-other-behavior (DRO) training, might reduce any potential renewed cocaine seeking. In DRO training, reinforcement is delivered if and only if the target