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Behavioral techniques for attenuating the expression of fear associations in an animal model of anxiety

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ABSTRACT

Background and objectives: Recent data indicate that extinguished fear often returns when the testing conditions differ from those of treatment. Several manipulations including extensive extinction training, extinction in multiple contexts, and spacing the extinction trials and sessions reduce the return of fear. Moreover, extensive extinction and extinction in multiple contexts summate in reducing return of fear, and the spacing of the extinction trials and the spacing of extinction sessions summate in reducing return of fear. Here we evaluated whether these techniques also attenuate the context specificity of latent inhibition, and whether they summate to further decrease fear responding at test.
Methods: In two experiments, with rats as subjects in a lick suppression preparation, we assessed the effects of massive CS preexposure, CS preexposure in multiple contexts, and of spacing the CS-preexposure trials and sessions, in reducing the context specificity of latent inhibition.
Results: Fear responding was attenuated by all four manipulations. Moreover, extensive CS preexposure in multiple contexts, and conjoint spacing of the CS-preexposure trials and sessions, were more effective in reducing the context specificity of latent inhibition than each manipulation alone.
Limitations: Our experimental designs evaluated degrees of context specificity of latent inhibition but omitted groups in which latent inhibition was assessed without a context shift away from the context of latent inhibition treatment. This precluded us from drawing conclusions concerning absolute (as opposed to relative) levels of recovery from latent inhibition.
Conclusions: Techniques effective in decreasing the return of conditioned fear following extinction are also effective in decreasing the context specificity of latent inhibition in an animal model of anxiety. Fear and anxiety disorders might be prevented in anxious human participants with the same techniques used here, but that is still an empirical question.

Introduction

In a fear-conditioning preparation a neutral stimulus (conditioned stimulus; CS; e.g., a light) is presented just prior to an aversive event (unconditioned stimulus; US; e.g., a mild footshock) during acquisition training, which gives the CS behavioral control over fear responses elicited previously solely by the US. Presumably a CS–US fear association underlies such learning. Given that fear associations of this kind are believed to be involved in the onset of pathological fear and anxiety disorders in humans (e.g., Field, 2006; Laborda, Miguez, Polack, & Miller, 2012; Mineka & Oehlberg, 2008), studying manipulations that attenuate fear responding in animal models may be informative to clinicians interested in developing better approaches to prevent and/or eliminate fear and anxiety disorders.

Fear responding to a CS is susceptible to reduction through extinction treatment which consists of presentations of the CS alone (e.g., Pavlov, 1927); however, the effect of extinction treatment is labile and extinguished CSs are likely to elicit fear responding once again under a number of circumstances. For example, an extinguished CS elicits more fear responding when, after acquisition training and extinction treatment in two different contexts, it is tested back in the acquisition context or in a third context (ABA and ABC renewal; e.g., Bouton & Bolles, 1979; Bouton & King, 1983; Rosas, García-Gutiérrez, & Callejas-Aguilera, 2007), than when it is tested in the extinction context. Similarly, an extinguished CS elicits more fear responding when it is tested a long time following extinction treatment than when it is tested

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soon following this manipulation (spontaneous recovery; Pavlov, 1927). Thus, fear conditioning models the acquisition of anxiety disorders, fear extinction models exposure therapy, and the return of fear following context changes and/or the passage of time models relapse after exposure therapy (e.g., Bouton, 1988; Bouton & Nelson, 1998; Laborda, McConnell, & Miller, 2011).

Research on extinction has identified some behavioral manipulations that attenuate the return of fear (for reviews, see Bouton, Woods, Moody, Sunsay, & García-Gutiérrez, 2006; Laborda et al., 2011). For example, the return of fear has been attenuated in our fear-conditioning preparation with rats as experimental subjects by: a) using a massive number of extinction trials (Denniston, Chang, & Miller, 2003), b) delivering extinction treatment in multiple contexts (Gunther, Denniston, & Miller, 1998), c) spacing the extinction trials (Urcelay, Wheeler, & Miller, 2009), and d) spacing the extinction sessions (Laborda, Miguez, & Miller, 2014). Moreover, Laborda et al. (2014) provided evidence suggesting that the mechanisms underlying the effects of session spacing are different from those of trial spacing.

Recently, we found that these manipulations not only decrease the return of fear but also that their effects summate to better reduce the reappearance of fear responses. Laborda and Miller (2013) replicated and extended Denniston et al.'s (2003) protective effect of massive numbers of extinction trials and Gunther et al.'s (1998) protective effect of extinction being administered in multiple contexts, in a preparation in which spontaneous recovery and renewal otherwise summated to produce strong return of fear of the CS (see Rosas & Bouton, 1998; Rosas, Vila, Lugo, & López, 2001). They found that extended extinction treatment in multiple contexts was more effective in attenuating the return of fear than each of these techniques by itself. Similarly, Laborda et al. (2014) replicated and extended Urcelay et al.'s (2009) trial spacing effect, also in a preparation in which renewal and spontaneous recovery summated eliciting strong return of fear. More importantly, they found that conjoint spacing of extinction trials and spacing of extinction sessions was more effective in attenuating the return of fear than either treatment alone.

Just as fear responding is reduced by presentations of the CS alone after acquisition training (i.e., extinction; e.g., Pavlov, 1927), presentations of the CS alone before acquisition training also reduce fear responding (i.e., latent inhibition, also known as the CS-preexposure effect; e.g., Lubow, 1973a; Lubow & Moore, 1959). Moreover, just as extinction seems to be specific to the context in which it occurs, responding to a latently inhibited CS seems to be minimized when testing occurs in the context of preexposure. The context specificity of latent inhibition is also evidenced when subjects receive preexposure treatment and acquisition training in two different contexts and are tested back in the acquisition context or in a novel context, relative to subjects tested in the context of latent inhibition treatment (e.g., Bailey & Westbrook, 2008; Maes, 2002). The observed context specificity of latent inhibition is consistent with the view that CS preexposure creates a memory of the nonreinforced CS that later competes with the memory of the CS being reinforced (i.e., the CS–US association) and contradicts the initial view of latent inhibition that CS preexposure simply retards subsequent acquisition of the CS–US association (for a theoretical review, see Escobar & Miller, 2012).

Just as extinction of fear conditioning models exposure therapy, latent inhibition of fear conditioning can be viewed as a technique that prevents the development and/or the expression of conditioned fear, and it potentially models a means of preventing anxiety disorders (e.g., Lubow, 1973b, 1998). For instance, cues apt to be presented in the presence of expected traumatic events could be preexposed to attenuate the formation of aversive associations, which might reduce the likelihood of developing pathological fear reactions to these events or at least reduce the strength of the expression of such reactions (e.g., prevention of posttraumatic stress disorder in soldiers). At least in certain circumstances, one might want latent inhibition to generalize to contexts and times other that those of latent inhibition treatment; hence, as with the return of fear, the context specificity of latent inhibition is an effect we might want to thwart in applied settings.

Can the context specificity of latent inhibition be prevented or at least attenuated through the use of techniques similar to those that have proven successful in attenuating the return of fear after extinction treatment? The small existing literature concerning this suggests these manipulations might prove effective in making latent inhibition more enduring. For example, Wheeler, Chang, and Miller (2003) found that both massive CS-preexposure treatment and CS preexposure in multiple contexts attenuated the contextual specificity of latent inhibition. In the present research, we evaluated whether techniques that summate to reduce the return of fear after extinction, massive nonreinforcement in multiple contexts, and conjoint spacing of nonreinforcement trials and sessions, also summate to prevent or at least attenuate the context specificity of latent inhibition.

Experiment 1

The purpose of the present series of experiments was to evaluate whether some behavioral manipulations that attenuate the return of conditioned fear produced by a change in context from that of extinction can also reduce the context specificity of latent inhibition, potentially identifying a number of new parallels between extinction phenomena and latent inhibition phenomena. More specifically, Experiment 1 (see Table 1 for the experimental design) was intended to evaluate whether massive CS-preexposure trials in multiple contexts attenuate the context specificity of CS preexposure, just as massive extinction trials in multiple contexts has shown to reduce the return of fear (Laborda & Miller, 2013). All subjects were exposed to a procedure with CS–US pairings occurring in a context different from the context(s) in which CS preexposure had occurred, and testing occurring in an additional distinctly different context. No control for latent inhibition (i.e., a group in which latent inhibition is assessed without a context shift away from the context of CS preexposure) was included because our goal was not to demonstrate an absolute latent inhibition effect, but to assess differences in degrees of latent inhibition. A 2 × 2 factorial design was used with the two variables being CS preexposure in one or multiple different contexts and the number of preexposure trials being moderate or massive (i.e., many).

Table 1
Design summary of Experiment 1.

Groups	Preexposure			Acquisition	Test
Single/Moderate	30 X– (A) (B) (C)	30 X– (A) (B) (C)	30 X– (A) (B) (C)	3 X+ (D)	X (E)
Single/Massive	150 X– (A) (B) (C)	150 X– (A) (B) (C)	150 X– (A) (B) (C)	3 X+ (D)	X (E)
Multiple/Moderate	30 X– (A) (B) (C)	(A) 30 X– (B) (C)	(A) (B) 30 X– (C)	3 X+ (D)	X (E)
Multiple/Massive	150 X– (A) (B) (C)	(A) 150 X– (B) (C)	(A) (B) 150 X– (C)	3 X+ (D)	X (E)

Note: X was a 10-s click train. "+" denotes reinforcement with a mild footshock. "–" denotes no reinforcement. Letters in parenthesis indicate contexts. Context A, B, and C were counterbalanced. Numbers preceding letters indicate number of trials in that phase.