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Extinction in multiple virtual reality contexts diminishes fear reinstatement in humans

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ABSTRACT

Although conditioned fear can be effectively extinguished by unreinforced exposure to a threat cue, fear responses tend to return when the cue is encountered some time after extinction (spontaneous recovery), in a novel environment (renewal), or following presentation of an aversive stimulus (reinstatement). As extinction represents a context-dependent form of new learning, one possible strategy to circumvent the return of fear is to conduct extinction across several environments. Here, we tested the effectiveness of multiple context extinction in a two-day fear conditioning experiment using 3-D virtual reality technology to create immersive, ecologically-valid context changes. Fear-potentiated startle served as the dependent measure. All three experimental groups initially acquired fear in a single context. A multiple extinction group then underwent extinction in three contexts, while a second group underwent extinction in the acquisition context and a third group underwent extinction in a single different context. All groups returned 24 h later to test for return of fear in the extinction context (spontaneous recovery) and a novel context (renewal and reinstatement/test). Extinction in multiple contexts attenuated reinstatement of fear but did not reduce spontaneous recovery. Results from fear renewal were tendential. Our findings suggest that multi-context extinction can reduce fear relapse following an aversive event – an event that often induces return of fear in real-world settings – and provides empirical support for conducting exposure-based clinical treatments across a variety of environments.

1. Introduction

The ability to predict aversive events from environmental cues serves a clear adaptive function. Nonetheless, it is also adaptive to override this acquired knowledge about fearful relationships with new learning once a cue no longer signals any danger, as this information allows an individual to disregard nonthreatening cues and thus spare energy resources. In laboratory studies, this new learning is referred to as *extinction* (Pavlov, 1927) and occurs through presentation of the previously learned threat cue (i.e. conditioned stimulus, CS) in the absence of an aversive unconditioned stimulus (US). Extinction procedures form the basis of exposure therapies (Milad & Quirk, 2012), which have proven effective in the treatment of anxiety disorders (Nemeroff et al., 2006). It is well known, however, that extinction learning is more fragile than initial fear learning. As evidence, conditioned fear expression tends to return over time, whether extinguished in laboratory experiments or treated by pharmacological and behavioral therapy in anxiety disorders. An important goal of clinical translational research is thus to understand what conditions reduce the return of extinguished fear in humans.

Laboratory studies of fear conditioning have identified three predominant ways in which conditioned fear returns (Bouton, 2004): *spontaneous recovery*, *renewal*, and *reinstatement*. Spontaneous recovery refers to the return of conditioned fear responding after some amount of time has elapsed since extinction; fear renewal refers to the return of conditioned fear observed when the threat cue is encountered outside the extinction context; and reinstatement refers to the return of conditioned fear following presentation of the aversive US or a related stressor. The role of spatiotemporal contexts is particularly relevant to understand many facets of these fear recovery phenomena. Human and nonhuman animal research has routinely demonstrated that extinction learning is typically bound to the context in which extinction occurred (Bouton, 2002). In clinical practice, the extinction context is the treatment environment (e.g. therapist's office) where a patient is exposed to a fear-inducing stimulus or situation in the absence of an aversive consequence. While fear expression is reduced within the confines of the treatment context during exposure

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training, this inhibition often fails to generalize outside the treatment context, consistent with the laboratory models of extinction learning (Craske et al., 2008). A theoretical interpretation for the specificity of extinction learning is that it is the second thing the animal learns regarding the CS (the first being that it predicts the US), and is thus an exception to an established rule (Bouton, 2004). In this regard, the context becomes highly relevant to this new information, as it may be a factor that determines why the CS no longer predicts the US. If, however, the animal is provided the opportunity to learn that the CS is safe across multiple different environments, then it may help break the context-specific grip of extinction learning.

Potential explanations for why multiple-context extinction may promote generalization of extinction have been proposed by Bouton, Garcia-Gutierrez, Zilski, and Moody (2006). First, this procedure increases the chance that contextual cues (i.e. features in the environment) related to the extinction context will be present when the CS is later encountered in a new context, which would help retrieve the extinction memory. Another possibility is that context switches during extinction maintain a heightened level of responding due to renewal. Higher levels of responding during extinction may be tied to better extinction learning, as emphasized by clinical models of exposure therapy (Foa & Kozak, 1986). Finally, extinction in a single context may promote the formation of an inhibitory association between the extinction context and the US, which "protects" the CS from receiving full extinction (Rescorla, 2003); in other words, the absence of the US is attributed primarily to the context and not to a change in the associative value of the CS. Switching between different contexts during extinction may consequently remove this inhibitory control, leading to better extinction that is less context-dependent.

A limited number of studies have tested the effects of extinction under multiple contexts on return of fear in humans or non-human animals (reviewed in Vervliet, Craske, & Hermans, 2013). These investigations have focused on fear renewal, as it pertains most directly to fear relapse following a change in the physical context between extinction and test. Relative to extinction in a single context, extinction in multiple contexts in rats attenuates the return of fear when the CS is later encountered in a novel context (Laborda & Miller, 2013; Thomas, Vurbic, & Novak, 2009) (but see Bouton et al., 2006). This finding has been extended to humans in a small number of fear conditioning studies (Balooch & Neumann, 2011; Balooch, Neumann, & Boschen, 2012) as well as clinical (Shiban, Pauli, & Muhlberger, 2013) and preclinical (Vansteenwegen et al., 2007) investigations that do not use fear conditioning procedures per se. However, other human studies have not shown a reduction in fear renewal (Neumann, Lipp, & Cory, 2007) or only a modest reduction in renewal (Lang & Craske, 2000; Rodriguez, Craske, Mineka, & Hladek, 1999) following extinction in multiple contexts. One critique of the limited human conditioning literature on multiple context extinction is that return of fear has been assessed on the same day as fear acquisition. Thus, it is not clear whether these effects extend over a longer period of memory consolidation. Also, some studies have reported only explicit ratings of shock expectancy but have not reported psychophysiological markers of conditioned learning (Neumann et al., 2007). Finally, context manipulations have been limited thus far to changing only some key features (lights or sounds) within a testing room environment (Neumann et al., 2007) or a 2-D background image on a computer monitor (Balooch et al., 2012). As described below, these changes may not constitute effective contextual manipulations for human research subjects. Due to these methodological issues and inconsistency in the literature, more research is needed to determine the conditions under which multi-context extinction is effective in mitigating fear renewal.

In contrast to fear renewal studies, little human research has examined the factors that mitigate the other fear recovery paradigms. Although some studies have shown that spontaneous recovery can be modified by the delay intervals between acquisition and extinction testing (e.g. Huff, Hernandez, Blanding, & LaBar, 2009; Norrholm et al., 2008; Schiller et al., 2008), it is unknown whether multiple-context extinction has any effect on spontaneous fear recovery. Spontaneous recovery is typically tested in the extinction context following a delay (i.e. "extinction recall"). Recovery is context-dependent in the sense that the passage of time very likely changes the internal context of the animal between the time of extinction and the time of test, even if the physical features of the context are the same. Thus, if the time frame between extinction and test is held constant, then it is not clear that multiple-context extinction should afford any benefit over extinction in a single context on fear recovery in a previously encountered environment. Alternatively, if multiple-context extinction improves extinction learning by removing background inhibition, then this should be reflected in all forms of return of fear, including spontaneous recovery.

Reinstatement, on the other hand, is a context-dependent extinction effect that is subject to changes in the physical environment; reinstatement only occurs if the CS is tested in the same environment as the reinstatement US (e.g. LaBar & Phelps, 2005) (for related studies, see Bouton, 2002; Bouton & King, 1983). Bouton (2004) has proposed that reinstatement relies on contextual conditioning induced by the reinstatement US. Reinstatement increases the associative strength of the context, which then summates with residual fear from the extinguished CS to promote fear recovery. Importantly, reinstatement effects are not confined to the acquisition or extinction context, and can extend to novel contexts when the US and CS are both presented in that context (Westbrook, Iordanova, McNally, Richardson, & Harris, 2002). This feature makes reinstatement a clinically relevant phenomenon, as anxious individuals often experience strong return of fear when confronted directly with triggers or reminders in myriad environments after initial exposure. While it is unknown whether multi-context extinction attenuates fear reinstatement in a novel context in humans, reexposure to shock would provide a strong test of the effectiveness of this technique. That is, if, as a result of multiple context extinction, residual fear of the CS is low in the novel environment, then context conditioning induced by shock reexposure should afford little or no fear recovery.

One challenge in multiple-context extinction research is how to experimentally manipulate features of a human laboratory environment to provide impactful contextual changes. Prior efforts have largely used single unimodal cues (such as a visual change on a single feature of a static 2-D computer background) to manipulate contexts (e.g. Armony & Dolan, 2001; Kalisch et al., 2006; Pace-Schott et al., 2009). However, such single-cue manipulations may produce weak context effects that do not invoke spatial contextual encoding mechanisms (see discussion in Huff et al., 2011). Moreover, they may not qualify as providing a genuinely new context, since other contextual cues in the laboratory are still present. Other studies have attempted to resolve this limitation by conducting different phases of the experiment in separate testing rooms (Huff et al., 2009; LaBar & Phelps, 2005); however, this approach limits the number of physical environments that can be used in multi-context extinction studies, and certain features of the context will undoubtedly overlap. To overcome these constraints, we used 3-D virtual reality technology to create ecologically-valid scenarios in order to enhance the sense that subjects were encountering the CSs while navigating through unique environments across the different stages of learning. Moreover, by presenting these virtual scenarios in a head-mounted display, participants are completely removed from the physical features