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Fear extinction in humans: Effects of acquisition–extinction delay and masked stimulus presentations

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ABSTRACT

Fear extinction can be viewed as an inhibitory learning process. This is supported by post-extinction phenomena demonstrating the return of fear, such as reinstatement. Recent work has questioned this account, claiming that extinction initiated immediately after fear acquisition can abolish the return of fear. In the current study, participants were fear conditioned to four different conditioned stimuli (CS) and underwent extinction either immediately or after a 24 h delay. During extinction, we manipulated CS contingency awareness by presenting two of the CSs (one CS+, one CS−) under non-masked conditions and the other two CSs under masked conditions. Compared to delayed extinction, immediate extinction of non-masked CSs promoted less extinction of fear-potentiated startle and shock expectancy ratings and less reinstatement of fear-potentiated startle without affecting shock expectancy ratings. Critically, future research should clarify how the differences between immediate and delayed extinction in within-session extinction modulate the recovery of fear.

1. Introduction

Conditioned fear reflects learning to predict danger, and it is regarded as one of the primary behavioral mechanisms underlying fear-related anxiety disorders (Mineka and Zinbarg, 2006). The principles governing how fears are acquired, stored and suppressed originate from experimental work using Pavlovian conditioning paradigms in which initially neutral stimuli (conditioned stimuli; CSs) acquire behavioral relevance through repeated presentations in a predictive relationship to aversive events (unconditioned stimuli; USs) such as electric shocks (Davis, 1992). The underlying neuroanatomical circuitry has been described in some detail (Davis, 1992; LeDoux, 2000). Briefly, it centers on the amygdala, which houses the basic machinery for forming an association between CSs and USs, and which projects to subcortical structures including the periaqueductal gray (PAG) and other motor control systems in the brainstem commanding overt manifestations of fear. Studies using fear conditioning protocols in human subjects have replicated many of the basic findings in other animals and there is good evidence for common underlying fear circuits across species (Delgado et al., 2006).

Fear extinction is defined as the process whereby the behavioral expression of a previously acquired fear memory is weakened through repeated presentations of a CS in the absence of its associated US. This topic is currently the target of considerable interest because it promises to reveal the mechanisms of action for effective exposure-based treatments of anxiety disorders (Barlow, 2002). The contemporary view of fear extinction is that it represents an inhibitory learning process involving learning of a new association (CS–no US) that competes with the originally learned CS–US association, as opposed to a process of simple erasure of the original memory trace (e.g., Bouton, 1993). This inhibitory-learning theory of extinction is supported mainly by three post-extinction phenomena in which conditioned responses (CR) return: *spontaneous recovery*, which develops with the passage of time (Rescorla, 2004), *reinstatement* following exposure to the US (Bouton and Bolles, 1979b; Rescorla and Heth, 1975; Westbrook et al., 2002), and *renewal* by change of context between extinction and test (Bouton and Bolles, 1979a; Bouton and King, 1983).

Recent work (Myers et al., 2006) has revived interest in the idea of erasure mechanisms by suggesting that different mechanisms mediate extinction depending on the temporal delay between fear acquisition and extinction. Thus, erasure mechanisms might preferentially be invoked when extinction training is initiated shortly after fear acquisition, whereas inhibitory learning accounts for the mediation of extinction once the fear memory has been consolidated (Myers and Davis, 2007). In a series of studies in rodents, Myers et al. (2006) reported that extinction conducted shortly (10 min) after fear acquisition resulted in resistance to reinstatement, renewal, and spontaneous recovery, as measured by the

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fear-potentiated startle reflex, but that these manifestations of the return of fear were present when extinction training was initiated 72 h after acquisition. The apparent difference between immediate and delayed extinction can be understood in the context of consolidation theory, which suggests that memory is more liable to disruption within an hour of encoding (McGaugh, 2000; Schafe et al., 2001).

Initial findings suggesting consolidation-dependent modulation of the behavioral and psychophysiological manifestations of the return of fear have received mixed support. Partial support for a modulatory role of timing comes from other rodent studies using freezing as primary measure (Maren and Chang, 2006) (but see Archbold et al., 2010). Interestingly, Maren and Chang (2006) showed that within-session decrease in CR in rats receiving a standard extinction procedure did not differ from those in a control condition involving the same context as the standard extinction groups, but in which freezing was assessed during sham trials in the absence of CSs. Thus, it was doubtful whether the suppression of CRs in extinguished rats could be attributed to extinction learning per se. In a series of follow-up studies, Chang and Maren (2009) argued that immediate as opposed to delayed extinction yielded a short-lived and context-independent suppression of conditioned freezing, suggesting that immediate extinction might be mediated by habituation mechanisms rather than to rely on learning of a CS–no US contingency during extinction.

In humans, previous studies have reported significant return of fear after immediate extinction. For instance, there are reports of reinstatement following immediate extinction, evidenced by a stronger return of CR to the CS that was previously paired with the US (CS+) than to a control stimulus (CS−), using verbal measures (Hermans et al., 2005) and indirect behavioral (Dirikx et al., 2004), and psychophysiological indices of fear such as reinstatement of skin conductance responses (LaBar and Phelps, 2005; Schiller et al., 2008) and renewal of fear-potentiated startle (Alvarez et al., 2007). However, none of these studies allow inferences regarding quantitative differences in the degree of fear recovery due to the lack of a comparison group receiving delayed extinction training. Such quantitative differences between immediate and delayed extinction may be of both theoretical and clinical interest as they may help to unravel mechanisms affecting the rate of extinction and the return of conditioned fears.

Previous studies explicitly manipulating acquisition-to-extinction timing in humans have however yielded contradictory results. One study, measuring differential skin conductance responses, reported that delayed compared to immediate extinction attenuated conditioned fear renewal and spontaneous recovery (Huff et al., 2009). Another study measuring fear-potentiated startle, however, reported larger spontaneous recovery in the delayed extinction group compared to the immediate group in a differential conditioning paradigm but not in a single-cue paradigm (Norrholm et al., 2008). Interpretation of the latter results are complicated by the fact that the original rodent studies reporting recovery effects that were specific to the delayed extinction procedure were based on a single-cue conditioning paradigm (Myers et al., 2006).

In summary, although it has previously been shown that CR can recover after immediate extinction in humans (i.e., Alvarez et al., 2007; Dirikx et al., 2004; Hermans et al., 2005; LaBar and Phelps, 2005; Schiller et al., 2008), there is mixed support for whether there are quantitative differences in fear recovery between immediate and delayed extinction (Norrholm et al., 2008; Huff et al., 2009). Also, it remains unclear whether the effects of immediate extinction are mediated by habituation-like processes rather than to rely on learning of a CS–no US association (Chang and Maren, 2009).

The main objective of the current study was to directly assess the effect of varying the acquisition-to-extinction-interval on reinstatement of fear-potentiated startle. More specifically, we hypothesized that immediate compared to delayed extinction would result in less reinstatement of fear-potentiated startle. Also, to explore whether varying the acquisition-to-extinction interval would have an effect on reinstatement in the absence of CS–US contingency learning during extinction, we manipulated explicit CS–US contingency learning by including masked CS trials. Backward masking is a procedure in which a brief presentation of a target picture is followed by a masking picture, resulting in participants reporting that they only see the masking picture but not the preceding target (Enns and Di Lollo, 2000; Wiens and Öhman, 2007). Previous research has shown that conditioned fear to fear-relevant stimuli can survive masking (Morris et al., 1998; Öhman and Soares, 1993), implying that, under some circumstances (i.e., when stimuli are fear-relevant), explicit awareness of the CS–US contingencies is not necessary for the expression of conditioned fear (Esteves et al., 1994). Thus, we reasoned that a differential decrease in CR during masked extinction conditions could be attributed to habituation of the CR rather than to explicit CS–no US contingency learning.

To address these issues, participants were randomly assigned to an immediate or a delayed extinction group and fear conditioned to four different fear-relevant CSs (two CS+ and two CS−). During extinction, we manipulated contingency awareness within-subjects by repeatedly presenting one CS+ and one CS− under non-masked conditions that allowed for explicit CS–US contingency learning while the other two CSs (one CS+ and one CS−) were presented under masking conditions that precluded CS–US contingency learning during extinction. Immediately after extinction training, all participants received three unsignaled US presentations followed by a reinstatement test. Based on previous results (Myers et al., 2006; Norrholm et al., 2008), we hypothesized that immediate extinction following non-masked CSs would elicit less reinstatement of fear-potentiated startle than delayed extinction without altering reinstatement of shock expectancy ratings. Moreover, we predicted that in the absence of CS−US contingency learning during extinction, reinstatement would be unaffected by the acquisition-to-extinction interval, i.e., we expected that both the immediate and the delayed group would show significant reinstatement of fear-potentiated startle and shock expectancy ratings to the previously masked CSs.

2. Materials and methods

2.1. Participants

Thirty-three students at Karolinska Institutet participated in the study after signing an informed consent form (approved by the ethics committees at Karolinska Institutet) and donating saliva sample for DNA extraction and genotyping (data not reported). All participants were screened for lifetime psychiatric disease and medication. Four participants were excluded from the final analysis due to technical problems, and two participants were excluded because of voluntary interruption, leaving a final sample of 27 (8 men) healthy participants with a mean age of 24.9 years (SD = 5.3). Participants were randomly assigned to two groups; immediate extinction ($N = 13$) or delayed extinction ($N = 14$). All participants were given two cinema vouchers for their participation.

2.2. Stimulus material

Four different pictures depicting fearful male faces from the Karolinska Directed Emotional Faces (Lundqvist et al., 1998) served as CSs (model nr: AM14AFS, AM23AFS, AM34AFS, AM35AFS) and two additional neutral faces served as masks (model nr: AM04NES, AM29NES). For each picture, the background was removed and color was converted to grey-scale. A white fixation cross was shown on a black background during the inter-trial intervals (ITI), the duration of which varied between 12 s and 15 s throughout all experimental sessions (acquisition, extinction and reinstatement test). The experiment was run in a sound-attenuated chamber on a desktop PC with a standard 21-in. cathode ray tube (CRT) monitor. Screen resolution was 800 × 600 pixels and the refresh rate was set to 60 Hz. The experiment was programmed in Presentation 13.1 (Neurobehavioral Systems, www.neurobs.com). Participants viewed pictures at a distance of about 1 m. The US