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Plasticity of fear memory: a search for relapse prevention

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General introduction

Introduction

Fear learning is critical for survival. It may serve as an alarm mechanism by identifying cues in the environment that signal impending threat. For example, we all learn that pit-bulls can be dangerous. Accordingly, the perception of a pit-bull may elicit fear sensations like sweating and an increased heart rate. Such fear responses facilitate protective behaviour (e.g., walk away when you see a pit-bull) and dissipate when the pit-bull disappears. From an evolutionary perspective, it is highly adaptive to generalize fear rules across different contexts, rather than relearning the same rule in every situation (e.g., pit-bulls are dangerous in the park, but also in the street). However, fear generalization becomes maladaptive when fear persists in situations in which immediate threat is absent (e.g., avoid to go outside as you may encounter a pit-bull) or when fear generalizes to harmless cues (e.g., puppies). The inability to adequately discriminate between dangerous and safe cues or contexts (overgeneralization of fear) is central to many anxiety disorders. Patients with anxiety disorders often show exaggerated fear responses compared to the level of actual threat (Rosen & Schulkin, 1998).

In the past century, various efficacious psychological treatments for anxiety disorders have been developed. At the core of nearly every treatment are exposure-based interventions that involve in vivo or imaginary confrontation with the feared object (Eysenck, 1981; Marks, 1978). Although effective in reducing fearful responding, many patients experience relapses of fear after successful exposure treatment (Craske, 1999). Apparently, the maintenance of behaviour change is delicate. An important clinical and theoretical question is what causes fear relapse. Of even greater importance is how the recurrence of extinguished fear can be prevented. The present thesis presents several studies on the mechanism of fear relapse and its prevention in humans.

Experimental models of human fears

The next paragraph focuses on behavioural phenomena in the laboratory that serve as experimental models for the etiology, treatment, and relapse of human fears.

Conditioning as a model for the etiology of human fears

Many fears are thought to be learned through experiences. For instance, a dog probably elicits no fear response during its first encounter. It may only evoke a fear

response because it was followed by an unpleasant event (e.g., being bitten). This phenomenon is known as Pavlovian fear conditioning. Since Pavlov (1927), conditioning has been extensively demonstrated in the laboratory, especially in animals. In a prototypical fear conditioning procedure, a rat is exposed to a neutral stimulus (conditioned stimulus, CS; e.g., a tone) that is followed by a biological significant event (unconditioned stimulus, US; e.g., a shock). After a few tone-shock (CS-US) pairings, the tone CS predicts the shock US and presentation of the tone CS alone elicits a vigorous fear response (i.e., acquisition effect). Given that such a response is not elicited by the tone CS prior to the conditioning procedure, it is referred to as a learned or conditioned response (CR). Examples of conditioned fear responses in rats include defensive behaviours (e.g., freezing and suppression of ongoing behaviour) and autonomic responses (e.g., increased blood pressure) (Fanselow, 1994). Although simple conditioning may not account for all aspects of fear, it is considered to play an important role in the development of several anxiety disorders (Mineka & Zinbarg, 2006).

Extinction as a model for the treatment of human fears

Most psychological treatments for anxiety disorders involve exposure procedures. During exposure, a patient is repeatedly and systematically confronted with the object of fear (e.g., dog) in absence of the anticipated disastrous event (e.g., being bitten) (e.g., Öst, 1997). By consequence, the fearful responding to that object declines. The development of exposure therapy is based on findings from extinction experiments in animals (e.g., Wolpe, 1968). In a typical extinction procedure, a stimulus (CS; e.g., a tone) that has acquired the ability to evoke a fear response through conditioning is repeatedly presented in absence of the unpleasant event (noUS). As the tone CS no longer predicts the occurrence of the US, a gradual reduction of fear responding to the tone CS is observed.

Renewal as a model for the relapse of human fears

Exposure therapy has proven to be effective in various anxiety disorders (e.g., Deacon & Arbramowitz, 2004). However, even after complete extinction of fearful responding, fear may re-emerge after some time (e.g., Rachman, 1989). Clinically, the return of extinguished fear is called relapse.

Over the last decades, animal laboratory studies have provided various findings that may shed light on the unstable nature of fear reduction in clinical practice. One such finding is the *renewal* effect. Renewal refers to the recovery of an

extinguished fear response when animals are tested in a context different from the one in which extinction occurred (e.g., Bouton, 2000). In a typical renewal experiment, rodents receive initial fear conditioning to a CS in one context, Context A. Contexts usually consist of external stimuli (e.g., a cage), but may also include internal stimuli (e.g., drug states) (Bouton, 2000). After acquired conditioned responding, extinction of responding is established by CS alone presentations in another context, Context B. When the CS is subsequently tested in the context of extinction, Context B, no fear is observed. By contrast, presenting the CS in the original acquisition context, Context A, leads to a robust recovery of fear (ABA renewal; e.g., Bouton & King, 1983). Fear recovery is also obtained by testing in a novel context, Context C (ABC renewal; e.g., Bouton & Bolles, 1979), or when acquisition and extinction are conducted in the same context and testing occurs in a novel context (AAB renewal; e.g., Bouton & Ricker, 1994).

Renewal effects indicate that extinction training does not destroy original fear learning (e.g., Bouton, 2004). That is, extinction training may “mask” the cause of fear without erasing the memory of fear learning. Preservation of fear learning is also suggested by other postextinction phenomena. For example, after extinction, the presentation of unsignalled aversive events (USs) (*reinstatement*) or the mere passage of time (*spontaneous recovery*) can cause a return of fear (e.g., Bouton & King, 1983; Pavlov, 1927). Thus, once fear learning has occurred, it seems to be forever.

Renewal effects further illuminate a striking difference in the sensitivity to changes in the background context between fear acquisition and extinction: Whereas extinction performance is easily disrupted by such changes, acquisition performance is not (Bouton, 2000, 2002). A context switch after fear acquisition usually causes no decline in behavioural responding to a CS (e.g., Bouton & King, 1983; Harris, Jones, Bailey, & Westbrook, 2000). Hence, acquisition performance seems to generalize well over contexts. By contrast, extinction performance generalizes poorly over contexts: A change in context after extinction recovers fear responding (e.g., Bouton & Bolles, 1979).

From a clinical perspective, renewal effects serve as an experimental model for relapse after successful anti-anxiety therapy (Bouton, 1988). That is, exposure procedures might extinguish fear reactions without erasing its roots. The behavioural effects of exposure therapy (i.e., fear reduction) may be lost when the previously feared object is encountered outside the therapy context.

Theoretical explanations of renewal

In this paragraph, some of the prevailing explanations of renewal will be outlined. The three explanations reviewed below all assume that fear conditioning results from associative learning. Moreover, they agree that contexts play an important role in fear renewal. They disagree, however, on the precise nature of how contexts influence associative learning and, hence, conditioned responding. As the third explanation (i.e., occasion setting hypothesis) is most relevant to the present thesis, it is described in more detail. Before presenting the explanations of renewal, a short introduction of associative learning principles is provided.

Associative learning

Fear conditioning is assumed to result from the formation of an association between the mental representations of the CS (e.g., a tone) and the US (e.g., a shock) (Rescorla & Wagner, 1972). Subsequent presentation of the tone CS not only activates the mental representation of the CS, but also the representation of the shock US through its association (CS-US). Activation of the shock US representation triggers fear responding. The size of responding depends on the strength of the CS-US association. Changes in associative strength (i.e., learning) are produced by the discrepancy between what is expected about the US and what actually occurs. This implies that learning is greatest when the US (or absence of the US) is surprising. For instance, on early conditioning trials, the US is not predicted by the CS, which results in a strong increase in associative strength between the CS and the US.

Two terms need further clarification. In fear conditioning, the association formed between the CS and the US is excitatory: The CS predicts the occurrence of the US and, therefore, *excites* conditioned responding. Associations can also be inhibitory. In that case, the CS predicts the absence of an otherwise expected US (Rescorla & Wagner, 1972). Imagine a training phase in which a stimulus (e.g., light) is paired with a shock, but is not followed by a shock when presented together with another stimulus (e.g., light + tone). By consequence, the light CS develops an excitatory association, whereas the tone CS forms an inhibitory association with the US; The tone CS predicts the absence of the shock US and, therefore, *inhibits* conditioned responding.

Compound conditioning hypothesis

The first explanation of renewal relates to compound conditioning. The context may be assumed as a separate stimulus that is subjective to the same associative learning rules as “distinct” stimuli (CSs) (e.g., Rescorla & Wagner, 1972). During the acquisition phase of an ABA renewal experiment, the context (Context A) and the CS are both assumed to acquire an excitatory association with the US. Hence, conditioned responding is determined by the sum of context-US and CS-US associations. When the context is switched after acquisition, the CS has excitatory associative strength at the start of extinction (i.e., it predicts the US), whereas the extinction context (Context B) has no associative strength (i.e., it was never paired with the US). As the expected US is not presented during extinction, the extinction context is thought to gain inhibitory associative strength (i.e., it predicts the absence of the US), thereby protecting the CS from losing (all of) its excitatory strength (Lovibond, Davis, & O’Flaherty, 2000). When the CS is finally tested in the acquisition context, responding renews because the excitatory associative strength of the acquisition context summates with the residual (excitatory) associative strength of the CS. Hence, the compound conditioning approach accounts for renewal by the formation of direct associations between the context and the US. In this view, after a traumatic experience both the threat object and the *trauma* context may trigger fear reactions. Subsequent exposure therapy involves learning that the *treatment* context is safe, which alleviates fear but simultaneously prevents acquiring that the threat object is no longer dangerous. By consequence, leaving the safe treatment context may unveil the previously acquired fear responding for two reasons: The fear to the threat object itself was not extinguished and/or one returns to the fearful trauma context.

A main problem with the compound conditioning approach is that there is little evidence of direct context-US associations in renewal: Independent tests fail to demonstrate that acquisition contexts are excitatory and that extinction contexts are inhibitory (e.g., Bouton & Swartzentruber, 1986). Another limitation of the context compound conditioning hypothesis is that a context change following initial acquisition has usually no impact on responding (e.g., Bouton & Peck, 1989), whereas the compound conditioning approach predicts such a response loss. As the excitatory acquisition context is absent upon a context change, responding to the CS should reduce.

Configural learning hypothesis

The compound conditioning perspective on renewal considers contexts and CSs as separate stimuli that all acquire an association with the US during conditioning. Alternatively, the configural learning approach (e.g., Pearce, 1987) assumes that the context and the CS combine into a unique representation in memory before acquiring associative strength. Changing the stimulus, for instance by switching the context, results in the formation of a new stimulus representation without any associative strength. Nevertheless, the configural approach assumes that stimulus representations can influence each other by generalization of conditioned responding. The extent of generalization is a function of perceptual similarity. When stimulus representations are more similar, more generalization of responding is expected. In explaining renewal, the configural view states that the acquisition stimulus (Context A-CS) becomes excitatory during fear acquisition. When extinction is carried out in a different context than acquisition, like in ABA renewal, extinction occurs with a stimulus (Context B-CS) that is different from the acquisition stimulus (Context A-CS). Fear is expected to return when the excitatory acquisition stimulus (Context A-CS) is presented again. Thus, the configural approach accounts for renewal by direct associations between a combined context-CS representation and the US. Translated into clinical terms, exposure therapy involves extinction to the “wrong” stimulus. Fear returns when the original fear-evoking stimulus is re-encountered.

Like the compound hypothesis, the configural hypothesis cannot explain that a context change after acquisition has usually no impact on responding to the CS. Following the configural view, a context switch after acquisition implies a stimulus change, thereby preventing full generalization of responding and causing a concomitant response loss. In the conditioning literature, a response loss due to perceptual dissimilarity is called generalization decrement (Pearce, 1987).

Occasion setting hypothesis

To overcome the limitations of the compound conditioning and the configural learning hypotheses, Bouton and his colleagues (e.g., Bouton, 1994a; Bouton & Nelson, 1994; Bouton & Ricker, 1994) postulated an occasion setting model of renewal. In contrast to the former hypotheses, the occasion setting view assumes no development of direct associations between the context and the US. Instead, contexts may indirectly influence behaviour by signalling or retrieving the association between a CS and the US.

The occasion setting hypothesis asserts that during conditioning an excitatory association develops between the CS (e.g., tone) and the US (e.g., shock) (see Figure 1.1). After conditioning, presenting the tone CS excites the memory of the shock US, thereby producing behavioural responding (CR). During extinction, in which the tone CS is repeatedly presented without the shock US, the excitatory association is not erased. Instead, a new inhibitory tone-shock association (CS-noUS) is formed. By consequence, the meaning of the tone CS is ambiguous as it has now two “conflicting” associations and presentation of the tone CS will elicit both its associations. The inhibitory association suppresses activation of the memory of shock (US) and no behavioural responding is observed (i.e., extinguished CR). Thus, extinction is assumed to involve the formation of a second association, rather than destruction of the first-learned association.

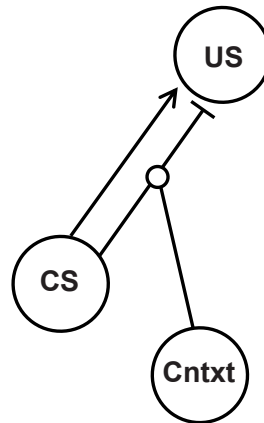


Figure 1.1 Model of extinction. The arrow reflects an excitatory association between the tone (T) CS and the unconditioned stimulus (US). The blocked line reflects a gated inhibitory CS-US association that requires input from both the context and the tone CS for its activation. From “Mechanisms of Feature-Positive and Feature-Negative Discrimination Learning in an Appetitive Conditioning Paradigm,” by M. E. Bouton and J. B. Nelson (2002), in N. A. Schmajuk, P. C. Holland (Eds.), *Occasion Setting: Associative learning and cognition in animals*, p. 72.

The development of a new inhibitory pathway during extinction is also suggested by neurobiological experiments (see LeDoux, 1995, for a review). For instance, lesions of cortical brain areas in rodents impair extinction of conditioned fear responses without affecting fear conditioning itself, indicating different neural pathways underlying extinction and conditioning (LeDoux, Romanski, & Xagoraris, 1989; LeDoux, Sakaguchi, & Reis, 1984). Specifically, studies across

species indicate that the amygdala – a subcortical structure – has a critical function in the acquisition and expression of conditioned fear responding (LeDoux, 2000). Extinction of conditioned responding appears to involve the formation of inhibitory associations by a network of the amygdala, ventromedial prefrontal cortex, and the hippocampus. This network suppresses fear responses elicited by excitatory associations in the amygdala (Sotres-Bayon, Bush, & LeDoux, 2004).

Central to Bouton's theory (e.g., Bouton & Ricker, 1994), the inhibitory association is "gated", meaning that its activation reacquires the joint presence of the CS and the context in which extinction occurred. Hence, inhibitory learning is context dependent. In contrast, the excitatory association is stored independently of its context. Renewal then occurs because absence of the extinction context impairs activation of the inhibitory association, thereby allowing the excitatory association to fully control responding (i.e., CR). To put it another way, renewal effects reflect a failure to retrieve what has been learned in extinction. A change in context after extinction training prevents retrieval of extinction performance in favour of conditioning performance (Bouton, 1993, 1994a, 1994b).

The role of contexts in renewal has also been compared with that of occasion setters (e.g., Bouton & Nelson, 1998). Occasion setting is a phenomenon that is observed in research on discrimination learning (e.g., Holland, 1992). For instance, in a feature-negative discrimination training, a stimulus (the target stimulus; e.g., a light) is followed by a biological significant event (US; e.g., a shock), but not when it is preceded by another stimulus (the feature stimulus; e.g., tone). Crucially, the feature doesn't acquire a direct inhibitory association with the US. Rather, the feature becomes a signal or "sets the occasion" for the target not being followed by a shock. In renewal, contexts are supposed to contain similar properties as occasion setters. That is, contexts are not simply associated with the US (or the absence of the US), but instead selectively activate associations of the CS. Hence, the extinction context activates the CS-noUS association (Bouton & Moody, 2004).

The model provides an elegant explanation for relapse of fear following successful exposure treatment. The traumatic association may remain intact during exposure therapy, while new learning occurs that is specific to the context in which it was learned. As exposure effects are supposed to be context specific, fear may recur when the previously feared stimulus is encountered outside the therapy context (Bouton, 1988).

In contrast to the compound conditioning and configural hypotheses, the occasion setting model (e.g., Bouton & Nelson, 1994) predicts no loss of

behavioural responding when the context is switched after acquisition. That is, the excitatory association is supposed to be context independent and full elicitation of responding is expected when the fear stimulus (CS) is presented in another context. Moreover, the model can explain observations of renewal in the acquisition context (ABA) as well as in novel contexts (ABC). That is, any switch out of the extinction context should renew conditioned responding to the feared stimulus (CS). Nevertheless, the occasion setting view cannot account for all experimental findings. For instance, renewal in a novel context (ABC) seems to be weaker than in the original acquisition context (ABA) (e.g., Harris et al., 2000). From the view that extinction, but not acquisition, depends on the context, it follows that a return of fear in the original acquisition context (ABA) should be as strong as in a novel context (ABC).

In sum, animal conditioning findings are most compatible with the idea that extinction involves new, context-specific learning that can inhibit original fear learning. Contexts seem to acquire a modulatory role that helps to disambiguate when the original learning (fear learning) or the new learning (extinction learning) is valid. Outside the extinction context, extinction learning is less available and, by consequence, original fear learning regains control over behavioural responding.

Renewal of human conditioned fear

Although renewal effects in rodents have been reported for over the last several decades, evidence for renewal in humans only recently emerged. Renewal was initially observed in anxious individuals who were treated for their fears by exposure therapy. These studies showed that extinguished fear recovers when the previously feared object is encountered in a context different from treatment (Mineka, Mystkowski, Hladek, & Rodriguez, 1999; Mystkowski, Craske, & Echiverri, 2002; Mystkowski, Mineka, Vernon, & Zinbarg, 2003). There is, however, no control over the acquisition history in individuals with anxiety disorders. The circumstances under which fear was acquired are often unknown. Recently, renewal has been demonstrated in humans in whom fear was experimentally induced (Vansteenwegen et al., 2005).

Vansteenwegen and colleagues (2005) showed participants two neutral stimuli (CSs; pictorial faces) of which one stimulus (CS+) was followed by an aversive event (US; a loud noise), whereas the other, control stimulus (CS-) was never followed by the aversive event. Fear acquisition occurred in either a dark or illuminated room (Context A). Extinction of responding was then established by

repeatedly presenting both stimuli (CS+, CS-) alone in the opposite lighting context (Context B). Upon returning to the original acquisition context, responding to the CS+, but not to the CS- recovered (ABA renewal). The studies presented in this thesis used similar procedures to test the hypotheses.

Assessment of human conditioned fear

The expression of human fear is assumed to comprise three components (Lang, 1985): a verbal or cognitive component (e.g., people may report that they are afraid of dogs), a behavioural component (e.g., people may avoid or run away from a dog), and a physiological component (e.g., people may show an increased heart rate when seeing a dog). Conditioned responding in humans is typically assessed for two of these three components: the verbal and the physiological level. An example of a verbal measure is asking participants to what extent they expect a stimulus (CS) to be followed by an aversive event (US) (e.g., Vansteenwegen et al., 2005).

The physiological fear component is usually measured by changes in autonomic responses to a stimulus (CS), such as the skin conductance response and the startle reflex. A skin conductance response involves the increase of the electric conductance of the skin due to activity of the sweat glands (Lykken & Venables, 1971). A stimulus (CS+) that is paired with an aversive US typically elicits increased skin conductance responding. As any stimulus might evoke orienting skin conductance responses, human conditioning studies usually include a control stimulus (CS-) that is equally often presented but never paired with the US. Conditioned responding is reflected by larger skin conductance responses in reaction to the CS+ than to the CS-. A main disadvantage of skin conductance is that it is not selectively sensitive to fear learning. Also stimuli (CSs) that are paired with nonaversive, but arousing events (such as a reaction time task) can evoke increased skin conductance responses (Hamm & Vaitl, 1996). Thus, skin conductance conditioning seems to reflect contingency learning (i.e., knowing that a stimulus is followed by a significant event) rather than emotional learning

Unlike skin conductance responding, potentiation of startle responding appears to be a more specific index of fear learning since it is only observed when an aversive event (US) is paired with a CS (Hamm & Vaitl, 1996). The startle response is a reflexive response in reaction to the sudden onset of an intense stimulus, for instance a loud noise (Grillon, Ameli, Woods, Merikangas, & Davis, 1991). Human startle responses are usually measured by the eyeblink reflex produced by a rapid contraction of muscles around the eye. The loud noise, or

startle probe, is presented either during a stimulus (CS) or in the interval between two stimulus presentations (intertrial interval). Eyeblink reflexes elicited during aversive states, for instance in the anticipation of an aversive event, are potentiated as compared to responses evoked during neutral states (Lang, Bradley, & Cuthbert, 1990). Conditioned responding is indexed by larger eyeblinks to probes presented during a fear conditioned stimulus (CS+) relative to a control stimulus (CS-) or an intertrial interval (Grillon, Cordova, Morgan, Charney, & Davis, 2004).

Prevention of renewal

The general implication of renewal studies is that once a fear memory is established, it is forever. A fear memory persists even after extinction training removed the behavioural response. If exposure treatments do not eliminate fear learning, then relapses are always possible. Treatments may be optimized by methods that prevent occasions of relapse. Most strategies aimed to prevent renewal encompass the strengthening of extinction learning, either by directly strengthening the formation of the extinction memory or by generalizing extinction learning more effectively across contexts. Some examples are described.

Several studies showed beneficial effects of extinction in different contexts on renewal. Chelonis, Calton, Hart, and Schachtman (1999) and Gunther, Denniston, and Miller (1998), for example, demonstrated that conducting extinction in multiple contexts reduces renewal relative to extinction in a single context. From the view that contexts are composed of many cues, extinction in multiple contexts might connect extinction learning to a wide variety of contextual cues. This increases the likelihood that the renewal test context shares cues with the extinction contexts, thereby facilitating retrieval of extinction learning and weakening renewal of fear (Chelonis et al., 1999; Gunther et al., 1998). Important to note is that Gunther et al. also showed that extinction in multiple contexts was not effective in weakening renewal when fear conditioning had also been conducted in (other) multiple contexts. This indicates that extinction in different contexts does not erase original fear learning and that this strategy may remain vulnerable for relapse.

From the view that renewal reflects a failure to retrieve extinction, it follows that renewal should be reduced if extinction is retrieved just before test (Bouton, 1994b). Several studies confirmed this prediction. In a series of experiments, Brooks and Bouton (1994) conditioned rats in one context before subjecting them to extinction training in another context. During extinction, a discrete cue

preceded most of the trials. Renewal occurred when rats returned to the context of conditioning. In contrast, presenting the extinction cue at test weakened renewal. The extinction cue, or retrieval cue, may remind the subject that the extinction association is valid, thereby offsetting renewal of fear.

An exciting, new finding is that administration of the drug D-cycloserine (DCS) can boost the effects of extinction training in animals (Ledgerwood, Richardson, & Cranney, 2003; Walker, Ressler, Lu, & Davis, 2002) and exposure treatment in anxiety patients (Hoffman et al., 2004; Ressler et al., 2004). Walker et al., for instance, showed that administering DCS before extinction training facilitated extinction learning as compared to administering saline (a control). Nevertheless, it is currently known that DCS does not protect extinction learning against recovery phenomena like renewal (Bouton, Vurbic, & Woods, 2008).

In sum, generalizing extinction learning beyond the context of extinction may be effective in counteracting renewal. Original fear learning is, however, not erased. Fear learning may be suppressed by extinction learning but its robust generalization remains a serious risk for relapse. Therefore, strategies aimed at preventing renewal may benefit more from decreasing the generalization (i.e., contextualization) of fear learning rather than exclusively increasing the generalization (i.e., decontextualization) of extinction learning. Obviously, the history of fear learning cannot be changed literally in patients with anxiety disorders. Therefore, contextualization of fear learning should occur *after* a fear memory has been established, thus retrospectively, in order to be of clinical value.

A search for new strategies in preventing renewal

It has long been suggested that once memories are consolidated, they are indelible and fixed (McGaugh, 1966). This would suggest that once a fear memory is stored independent of its context, it is immune to the storage of additional information about the context in which fear learning occurred. In other words, it would not be possible to transform an existing fear memory that is context independent into a context-dependent fear memory. Animal studies suggest, however, that consolidated fear memories are not necessarily permanent, but open to change upon retrieval (e.g., Nader, Schafe, & LeDoux, 2000). Reactivation of a consolidated fear memory appears to return it temporarily into a labile state, from which it needs reconsolidation in order to persist (Sara, 2000). During this labile state, fear memories can be weakened, for instance by drug manipulations (Nader et al., 2000). Hence, also established fear memories may be sensitive to change.

The question is whether the context independency of existing fear memories can also be influenced. If an initially context-free fear memory could be made context dependent, this may be useful in the prevention of renewal.

The present thesis aimed to provide novel strategies to counteract renewal of fear. Instead of enhancing the generalization of extinction learning, we developed procedures that are meant to weaken the generalization of fear learning. Animal conditioning findings may provide some important clues in this regard. One finding is that fear learning is sometimes less context independent than assumed by the occasion setting model (e.g., Harris et al., 2000). If fear learning can be partially context dependent, then it is more likely that we can influence (i.e., enhance) the context dependency of fear learning in order to reduce renewal. Another finding is that context discrimination procedures can generate fear learning that is specific to the context in which it was acquired (Bouton & Swartzentruber, 1986). In context discrimination training, fear learning (CS-US) in one context is repeatedly alternated with inhibition training with the same stimulus (CS-noUS) in another context. Hence, the context explicitly signals whether the stimulus is followed by an aversive event. Therefore, context discrimination training may be a key to contextualizing fear learning: It may help to discern dangerous contexts from safe contexts. In the study of Bouton and Swartzentruber (1986), however, context-dependent responding was found for *newly* formed fear memories. Given that upon retrieval fear memories can be modified after they are acquired (Nader et al., 2000), we hypothesize that context discrimination training after fear acquisition (i.e., during extinction training) will contextualize *previously* learned fear memories.

Outline of the present thesis

The aim of the present thesis was to develop novel strategies to weaken renewal of extinguished fear in humans. In contrast to prevailing strategies, we aimed to reduce renewal by decreasing the generalization of the original fear learning.

The present thesis encloses three sections. The first section (Chapter 2) addresses the contextual control of fear learning. We tested the hypothesis that fear learning is more context dependent than is proposed by the occasion setting model. For this purpose, renewal in the acquisition context (ABA) was compared with renewal in a novel context (ABC). The second section (Chapter 3) deals with possible mechanisms for the contextual control of fear learning observed in the first section. By simultaneously changing the context (from A to B) and the

Chapter 1

contingency (from acquisition to extinction), subjects may have inferred that the acquisition context was relevant for fear learning, while the extinction context is relevant for extinction learning. This would imply retrospective learning about the acquisition context. In Chapter 3, we used a conditioned suppression task to test whether an extinction procedure can indeed induce retrospective learning. The third section (Chapters 4, 5, and 6) focuses on enhancing the contextual control of fear learning in order to weaken renewal. Chapter 4 describes a study that used a context discrimination procedure during extinction training to contextualize fear learning. The context discrimination procedure stresses that the (acquisition) context is relevant for fear learning. In Chapters 5 and 6, we used a different discrimination procedure to weaken renewal. Instead of the entire context (Chapter 4), a discrete context cue was made relevant for fear learning. The effect of context-cue discrimination training on renewal was examined both in a predictive learning paradigm (i.e., assessing only the cognitive component of fear) (Chapter 5) and a fear conditioning paradigm (Chapter 6). Finally, in Chapter 7, the main findings of the studies presented in this thesis are summarized and discussed.