Plasticity of fear memory: a search for relapse prevention

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General discussion

Introduction

The objective of this thesis was to develop novel strategies to prevent the renewal of extinguished fear in humans. Animal models explain renewal by a poor generalization of extinction learning over contexts on the one hand and a strong generalization of the original fear learning on the other hand. Increasing the generalization of extinction learning is a well-studied strategy to reduce renewal. An example in clinical practice is to conduct exposure treatment in a variety of real-life situations, which might increase the generalization of what is learned during treatment. Given that the original fear learning is not erased and due to its robust generalization, return of fear is always possible. In sharp contrast to the more traditional strategies, the present thesis aimed to reduce renewal by targeting the fear memory itself instead of the extinction memory. For this objective, we designed novel strategies to study the boundary conditions for renewal. In a series of experiments, we tested whether a discrimination training procedure during extinction learning decreased the generalization of (i.e., contextualized) the original fear memory. In this final chapter, the main findings of our studies are summarized and discussed. In addition, possible clinical implications and suggestions for future research are presented.

Contextual control of fear learning

The occasion setting model states that retrieval of extinction learning, but not fear learning, depends on the context (e.g., Bouton & Ricker, 1994). Accordingly, recovery of extinguished fear in a novel context (ABC renewal) is expected to be as strong as in the original acquisition context (ABA renewal). However, we hypothesized that the context independency of fear learning might be less stringent than proposed and expected smaller ABC than ABA renewal.

In this thesis, conditioned responding renewed upon changing the context after extinction (Chapters 2, 4, 5, and 6). In line with our predictions, renewal in a novel context (ABC) appeared to be smaller than in the context in which fear was originally acquired (ABA), as assessed by cognitive expectancy (Chapter 2). This parallels a recent study of Neumann and Kitlertsirivatana (2010) who, in a similar paradigm, also found less ABC than ABA renewal. The fact that we observed smaller ABC than ABA renewal is important as it may indicate that fear learning is also partially context dependent. The implication is that the context dependency of fear learning may be sensitive for modification.

It should be noted that the ABC renewal in Chapter 2 was not differential. That is, the increase of responding to the fear conditioned stimulus (CS+) and the control stimulus (CS-) was similar. Nondifferential renewal could be the effect of cognitive processes like reasoning. It is likely that human subjects reason while participating in the conditioning experiments. For instance, one may reason that context changes generally imply a switch in contingency (e.g., from stimulus-no shock to stimulus-shock). Such reasoning would lead to a reversal of responding to both stimuli when the context changes after extinction (i.e., increased expectancy). Since a similar reversal effect was not observed upon a context change after initial fear acquisition (i.e., no change or a minimal loss in responding to the CS+) (Chapters 2, 4, 5, and 6), reasoning does not offer a plausible explanation. Alternatively, nondifferential renewal could be due to a general uncertainty about what is going to happen in a novel context. This would result in uncertainty ratings to both stimuli and, therefore, in nondifferential renewal. If novel contexts evoke a general uncertainty, then both stimuli should also elicit uncertainty ratings when the context changes after initial fear acquisition. This was not the case (Chapters 2, 4, 5, and 6). On the other hand, uncertainty may lead to a generalization of learned fear to stimuli that resemble the fear conditioned stimulus, that is, the control stimulus. If so, this would also explain the increase of responding to this stimulus (CS-) by switching the context after acquisition (Chapters 2, 4, 5, and 6). Note that nondifferential return of responding is also observed in other recovery studies (Dirikx, Vansteenwegen, Eelen, & Hermans, 2009) and seems to be related to the use of a control stimulus. In human conditioning studies, the CS- is included to control for nonassociative processes as possible confounders. In the remaining studies of this thesis (Chapters 4 and 6), we instructed participants more explicitly that one stimulus would never be followed by an aversive event in order to ensure that the CS- was actually treated as a control stimulus. Indeed, we found a differential ABC renewal effect in Chapter 4.

Several explanations were provided for the difference in ABA and ABC renewal (Chapter 2). One explanation is that fear learning was already context dependent before extinction started. This possibility received some support from the studies in this thesis – showing a loss of conditioned responding when the context changes after acquisition – (Chapters 2, 5, and 6), but not all (Chapter 4). An alternative explanation is that extinction learning generalized easier to a novel context than to the acquisition context. Two other explanations relate to retrospective learning processes. When participants realize that the context during extinction is different from the one during fear learning, they may retrospectively infer that the acquisition context itself was dangerous (i.e., predicts the aversive event). In associative learning terms, the acquisition context may retrospectively acquire excitatory strength (*retrospective excitation*). Alternatively, when extinction occurs in a different context than fear acquisition, participants may retrospectively infer that the threat stimulus only signalled danger in the context of acquisition. In learning terms, the acquisition context may retrospectively become a positive occasion setter indicating that the conditioned stimulus will be followed by an aversive event (*retrospective occasion setting*). Note that these processes are not mutually exclusive, but may operate next to one another.

Mechanisms of contextual control of fear learning

In Chapter 3, we examined two possible processes that might explain the contextual control of renewed responding observed in Chapter 2: retrospective excitation and retrospective occasion setting. Unravelling mechanisms might be interesting for clinical practice. In case that the acquisition context retrospectively acquires excitatory strength by extinction (*retrospective excitation*), this may point to a paradoxical effect of exposure therapy: Reducing fear by exposure may have the unintended consequence of increasing fear to the situation in which the traumatic experience occurred. In case that the acquisition context retrospectively becomes an occasion setter by extinction (*retrospective occasion setting*), this may imply a beneficial effect of exposure therapy: Through exposure one may not only learn that the threat stimulus is safe, but also learn that the threat stimulus only signalled danger in the traumatic situation. Hence, the anticipation of threat comes to depend on the situation. In contrast to our predictions, an extinction procedure neither induced retrospective excitation nor retrospective occasion setting. This makes it less plausible that contextual control of renewal could be explained by retrospective revaluation of the acquisition context.

Although extinction training neither induced retrospective excitation nor retrospective occasion setting, we observed another retrospective learning effect after extinction (Chapter 3). Extinction training eliminated conditioned responding to a target stimulus that was previously conditioned in the presence of another (feature) stimulus. After extinction, the feature stimulus enhanced responding to a novel stimulus that resembled the original target stimulus. Hence, without being presented itself during extinction, the meaning of the feature stimulus for other stimuli (retrospectively) changed. Translated into clinical terms, while exposure therapy may reduce fear to the threat stimulus, it may simultaneously increase fear to other, perceptual similar stimuli in the trauma situation.

Note that in the study of Chapter 3, we employed a different paradigm (conditioned suppression task) than in the other studies of this thesis (differential conditioning). The reason for this difference is that a conditioned suppression task was more suitable to test the proposed explanations (occasion setting/excitation) (cf. Baeyens, Vansteenwegen, Hermans, Vervliet, & Eelen, 2001) than the differential conditioning paradigm. An obvious disadvantage is that it is difficult to extrapolate these findings to our fear conditioning studies.

Enhancing the contextual control of fear learning

In this thesis, we tested two strategies that aimed to weaken renewal by contextualization of a previously acquired fear association. We attempted to contextualize fear either by *context discrimination training* (Chapter 4) or by *context-cue discrimination training* (Chapters 5 and 6) during extinction. For discrimination training, extinction trials (CS-noUS) in the context of extinction were repeatedly alternated with reacquisition trials (CS-US). Crucially, these reacquisition trials were presented either in the context of initial acquisition (Chapter 4) or featured by a specific context cue from acquisition (i.e., cued reacquisition; Chapters 5 and 6). Repeated alternation between extinction and reacquisition across contexts may indicate that the context is relevant for fear learning, thereby contextualizing fear. Contrary to our predictions, context discrimination training failed to reduce renewal (Chapter 4). At this moment, it is unclear whether context discrimination training *after* fear learning should reduce fear generalization. Nevertheless, context discrimination training can generate context dependent (fear) learning when applied *during initial* fear learning (Bouton & Swartzentruber, 1986; Gawronski, Rydell, Vervliet, & De Houwer, 2010). In line with our predictions, context-cue discrimination reduced renewal (Chapters 5 and 6). After context-cue discrimination, participants showed less renewal of conditioned responding than after simple extinction. Hence, in this thesis we only provided evidence that context-cue discrimination training can weaken renewal. Notably, we tested the effect of context-cue discrimination only in the context of acquisition (i.e., without the cue used for discrimination training; Chapters 5 and 6), whilst the effect of context discrimination was assessed in a novel context (Chapter 4). It is unclear whether context-cue discrimination is also effective at reducing renewal in a novel context, which is clearly the ultimate test of fear generalization.

A limitation is that no conclusions could be drawn for the effect of context-cue discrimination on physiological responding (Chapter 6). Therefore, it may be possible that reducing renewal by context-cue discrimination was only realized on a cognitive level (expectancy), but not on a physiological level of fear learning (startle and skin conductance). Recent evidence suggests that contingency knowledge (expectancy) can be separately manipulated from physiological fear responding (Sevenster, Beckers, & Kindt, submitted). Currently, it is unclear whether or not context-cue discrimination training affected the physiological expression of fear learning.

Speculations on the (in)effectiveness of discrimination training

Several explanations were given for the lack of an effect of context discrimination training on renewal (Chapter 4). Firstly, the failure to weaken renewal may be due to an increased context specificity of extinction learning. We assumed that context discrimination would confine a previously acquired fear association to its context. However, increasing the relevance of the context for fear learning might unintentionally also enhance the context relevance for extinction learning. Thus, extinction learning may have become even more context dependent after context discrimination than after simple extinction. If our procedure enhanced the context dependency of both fear and extinction learning, this may have impaired the generalization of fear learning from acquisition to test (reducing renewal in a novel context) as well as any possible generalization of extinction learning from extinction to test (increasing renewal in a novel context). Then, the net effect is no change in renewal. Secondly, the failure to downshift renewal could be explained by enhanced negative stimulus connotation. Context discrimination training had the unintended consequence of increasing negative valence ratings to the fear conditioned stimulus (CS+) as compared to simple extinction training, presumably due to additional pairings with the shock. It is known that negative stimulus valence after extinction predicts return of fear (Dirikx, Hermans, Vansteenwegen, Baeyens, & Eelen, 2007; Hermans et al., 2005). Although a negative stimulus connotation possibly precluded the reduction of renewal in Chapter 4, it did not prevent renewal reduction in Chapter 6. Rather, context discrimination training (Chapter 4) and context-cue discrimination training (Chapters 5 and 6) may have resulted in different learning processes.

We hypothesized that context-cue discrimination training might enable previously acquired (context-free) fear learning to become context dependent. This implies updating of an existing fear memory in that new information about the context is integrated into that memory. Recent work indicates that consolidated (i.e., existing) memories are not necessarily permanent, but open to change when retrieved (Kindt, Soeter, & Vervliet, 2009; Nader, Schafe, & LeDoux, 2000; Soeter & Kindt, 2010). When a memory is reactivated, it appears labile and vulnerable to change before it is reconsolidated again. Hence, reconsolidation may provide an opportunity to modify or update an existing memory (Lee, 2009), that is, to become context dependent. However, one may question whether the current protocol allowed for reconsolidation to occur. Memory reconsolidation is subject to several boundary conditions, for instance, the timing between memory reactivation and presentation of the to-be integrated information (e.g., Schiller et al., 2010).

In contrast to changing the original fear memory, discrimination training may have triggered new learning. Learning theories (e.g., Rescorla & Wagner, 1972) state that the amount of learning on a trial depends on violation of expectations, that is, the discrepancy between what is expected and what happens. This implies that more learning occurs when an event is surprising. Based on visual inspection of the expectancy ratings, we speculate that occurrence of the aversive event (US) on reacquisition trials (CS-US) was more surprising in the context-*cue* discrimination training (Chapters 5 and 6) than in the context discrimination training (Chapter 4). That is, on the first reacquisition trial in the *context discrimination training*, participants almost completely expected the aversive event to occur. Given that the aversive event was actually delivered, there was little violation of expectation. By contrast, on the first reacquisition trial in the *context-cue discrimination training*, participants were uncertain whether the aversive event (US) would occur. Hence, subsequent delivery of the aversive event substantially violated their expectation. Accordingly, context-*cue* discrimination training, but not context discrimination training, may have triggered a new fear memory that also comprised information about the context (cue X: CS-US).

In line with an explanation of additional learning, context-cue discrimination training (Chapters 5 and 6) may have endowed the specific context cue with (positive) occasion setting properties. Positive occasion setters appear to control responding to other stimuli independently of their own associative strength (e.g., Holland, 1992). Rather, they signal that other stimuli will be followed by an aversive outcome. An explanation in terms of occasion setting predicts that the presence of the context cue is necessary for eliciting conditioned responding. This interpretation was supported by our findings. Outcome expectancies at test were larger in the *presence* than in the *absence* of the context cue used for discrimination training (Chapters 5 and 6).

The occasion setting hypothesis may be consistent with safety-signal learning (Seligman, 1968). The explicit discrimination procedure may not only specify conditions in which the aversive event occurs, but also provide information about the absence of threat. That is, by administering the aversive event only in the presence of a specific cue, the absence of that cue indicates the absence of danger (i.e., safety). Moreover, by presenting a discrete cue (Chapters 5 and 6), as opposed to an entire context (Chapter 4) for signalling the aversive event, the occurrence of danger may become specific to this cue. This may restrict the range of cues or situations that trigger fear responding when the context is changed after extinction (i.e., reduction of renewal). Our strategy of reducing renewal by specifying the conditions of danger may parallel with studies presenting signalling cues to reduce chronic anxiety. Increasing the predictability of a threatening event has shown to reduce contextual anxiety (Fonteyne, Vervliet, Hermans, Baeyens, & Vansteenwegen, 2009, 2010). Together, these findings may indicate that rendering an aversive event more predictable or specific to certain situations might restrict the unrestrained elicitation of fear.

Finally, we found no evidence for the hypothesis that attenuation of renewal was caused by backward blocking (Chapter 5). Learning that only one context cue from acquisition reliably signalled the aversive outcome (US) may retrospectively have blocked (i.e., reduced) the signalling properties of the remaining context cues from acquisition. Theoretical accounts of retrospective learning state that cues must have been previously associated for later backward blocking to occur (e.g., Dickinson & Burke, 1996). By implication, reduction of renewal was only expected by using a context cue from acquisition, but not by using a novel cue for context-cue discrimination training. However, the reduction of renewal appeared to be independent of the cue used for discrimination training. One might argue that participants failed to discriminate between the novel cue (sound Y) and the cue originally presented during acquisition (sound X). If so, it follows that the novel cue condition was not appropriate to test for backward blocking. To avoid a potential discrimination failure, we are currently planning an experiment in which discrimination training with an acquisition context cue (sound X) is compared with discrimination training with a novel cue of a different modality (i.e., visual cue Y).

Context manipulations

A methodological issue concerns the operational definition of contexts in the present thesis. Contexts were defined quite diverse, ranging from simple coloured computer screens and sounds, through more complex pictures of rooms, to illumination of three-dimensional rooms. This restricted use of unimodal or bimodal contexts (i.e., visual and auditory stimuli) in our human studies (see also Kalisch et al., 2006; Neumann & Kitlertsirivatana, 2010; Vansteenwegen et al., 2005) differs from the multimodal contexts used in animal conditioning research (e.g., Bouton & King, 1983; Thomas, Larsen, & Ayres, 2003). In animal studies, contexts are usually manipulated by varying odour, floor texture, sound level, illumination, and sizes of three-dimensional boxes. Moreover, stimuli that served as contextual features in the present thesis (e.g., a lamp) were used as conditioned stimuli (CSs) in other studies (Milad, Orr, Pitman, & Rauch, 2005). Finally, the simple contexts used in the present thesis do not comprise the multifaceted situations in which traumatic conditioning experiences occur and may therefore lack ecological validity (i.e., the ability to generalize findings to real-life situations). Nevertheless, the use of simple contexts in the present thesis allowed us to demonstrate similar effects of context specificity of extinction learning like in animal research.

It has been argued that contexts can be defined in a structural and a functional way (Balsam & Tomie, 1985). A structural definition refers to all the features of an experimental situation that surround the conditioned stimuli and are irrelevant to the task that has to been learned (i.e., CS-US). This may include external features, like a room or background stimuli, but also internal features, such as hormonal states or the passage of time (Bouton, 2000). A functional definition of contexts refers to the modulatory role a stimulus can have over the control exerted by other stimuli. For instance, contexts may signal when a particular relationship between a CS and US is in effect. We believe that both aspects are important for the operational definition of contexts in renewal research. That is, contexts may surround conditioned stimuli perceptually (background stimuli) and temporally (longer duration), but may also gain functional control over performance when the situation becomes ambiguous like in extinction training.

Clinical implications

In the present thesis, only modest evidence was provided that a discrimination procedure during extinction reduces renewal. Renewal reduction was only observed after context-cue discrimination training, but not after context discrimination training. Moreover, we found only support for the attenuating effect of context-cue discrimination on renewal on a subjective fear level. Furthermore, although context-cue discrimination training weakened renewal, the return of fear was not abolished. Also, discrimination training undesirably enhanced the negative connotation of the fear conditioned stimulus. Finally, the present thesis lacks data on whether context-cue discrimination training would also be beneficial in anxious individuals. Altogether, this raises serious questions about the clinical applications of discrimination training in the prevention of relapse.

Nevertheless, although more research is warranted, we may speculate about possible clinical applications. If context-cue discrimination training is effective in contextualizing fear, we suggest that it should specifically be applied in fears that include a realistic component. That is, when a realistic threat to the patient's well-being underlies the development of an anxiety disorder, such as a history of bullying in social phobia, being bitten by a dog in specific phobia, or an assault in posttraumatic stress disorder (PTSD). This does not imply that the threatening event should be directly experienced. Also observing others experiencing a trauma (*vicarious learning*) or simple provision of information about a trauma may lead to the development of strong fear memories (Rachman, 1977). In therapy, one may focus on contextualizing the traumatic memory, for instance by imagination. That is, one may learn that situational features that are related to the traumatic experience differ from current situational features. For instance, consider a person with social phobia and a history of bullying and humiliation. Explicitly focusing on features that were specific for the traumatic experience (e.g., a specific boy or girl that bullied) may help to contextualize fear. Such contextualization may prevent the recurrence of threat expectancies in situations that lack these features.

Although contextualization of fear memories might be a novel approach in experimental conditioning research, similar approaches are already applied in clinical practice. For instance, contextualization is one of the key components of effective cognitive therapy for reducing re-experiencing symptoms in patients with PTSD (e.g., Ehlers, Clark, Hackmann, McManus, & Fennell, 2005; Ehlers et al., 2003). Patients with PTSD often report re-experiencing brief moments from the trauma such as "hearing footsteps behind me" or "seeing the perpetrator stand before me with a knife" (Ehlers et al., 2002). According to Ehlers and colleagues (2002), these intrusions reflect sensory stimuli that predict the worst moments of the trauma ("hotspots"). In this sense, the functional significance of intrusions can be compared to the signalling value of conditioned stimuli (CSs) in predicting aversive events (USs). Intrusions are thought to result from a disjointed trauma memory, in that the traumatic experience is not remembered as an integrated event, but rather as isolated parts (Ehlers & Clark, 2000). The disjointedness of memories is addressed in therapy by reconstructing the memory of the traumatic event (Ehlers et al., 2005). By various techniques such as imaginal reliving, writing narratives, and revisiting the trauma site, patients reconstruct the trauma memory and try to identify cues (CSs) that trigger the memories of the worst moments of the trauma (US). By stimulus discrimination training, patients learn that those cues (CSs) can have different meanings in different contexts. Patients focus on the differences between the trigger (CS) in the present (safe) context and the trigger that occurred in the trauma context (Ehlers et al., 2005). In other words, patients learn to distinguish the safe context from the trauma context. Although such interventions are based on a theoretical model (Ehlers & Clark, 2000), the exact mechanisms by which behaviour change is realized remains unclear. Conditioning studies may provide an excellent experimental framework in which these predictions can be tested.

Future research

Several areas are of interest for future research. A first suggestion for future research relates to test contexts. In the present thesis, we only demonstrated that context-cue discrimination training weakened renewal in a subset of the initial acquisition context (Chapters 5 and 6). Whether context-cue discrimination can also reduce renewal in a novel context remains to be studied. Although a subset of the acquisition context could be viewed as a context that was never seen before, testing in an entire novel context is obviously the ultimate test for fear generalization. It may be possible that novel situations create a sense of ambiguity that override the previously acquired rule of discrimination training (i.e., *in absence of the specific cue the aversive event does not occur*). Future studies on the beneficial effects of discrimination training should therefore include novel renewal test contexts.

A second consideration for future research is related to individual differences. Although the present thesis provides a first step in that discriminating training may reduce fear generalization, the present studies were only conducted in healthy subjects. Future research may elucidate whether anxious individuals also show beneficial effects of discrimination training on renewal of extinguished fear. This is important as learning about contexts may be impaired in patients with anxiety disorders (Pohlack, Liebscher, Ridder, Lipinski, & Flor, 2009). This impairment would explain the overgeneralization of fear in patients suffering from anxiety disorders and may impede adequately differentiating between dangerous and safe contexts in discrimination training. Moreover, people with anxiety disorders tend to interpret ambiguous stimuli and situations as threatening (Clark et al., 2007), which may also preclude advantageous effects of discrimination training.

Future research may also examine the challenging interaction of decreasing the generalization of fear learning and increasing the generalization of extinction learning in order to reduce renewal. As noted before, one way of countering the context dependency of extinction learning is conducting extinction in multiple contexts. A reduction of renewal by extinction in multiple contexts has recently been shown in spider anxious people (Vansteenwegen et al., 2007). Nevertheless, overall, the reducing effects of extinction in multiple contexts on renewal are inconsistent, with some studies demonstrating positive effects (Chelonis, Calton, Hart, & Schachtman, 1999; Gunther, Denniston, & Miller, 1998; Thomas, Vurbic, & Novak, 2009, Exp 3), while other studies fail to do so (Bouton, García-Gutiérrez, Zilski, & Moody, 2006; Thomas et al., 2009, Exp 1 and 2). Therefore, it would be interesting to examine whether simultaneously decontextualizing extinction learning and contextualizing fear learning may produce more robust attenuating effects. A novel experiment could be designed in which extinction training in multiple contexts is combined with context-cue discrimination training. Such a procedure might reverse the rules for extinction and fear learning. That is, contexts may become irrelevant for extinction learning, but important for fear learning. In other words, fear learning may become the contextual exception to the general rule: The threat stimulus means only danger when accompanied by the context-cue, but is safe anywhere else.

Another area for future research is whether discrimination training is also effective in reducing renewal by exposure to imagery instead of real aversive events in discrimination training. In clinical practice, re-exposing patients to their original traumatic experience would obviously be unethical. Therefore, an interesting question is whether it is sufficient to instruct participants to think about the past experience with the shock and its predictive salient context features.

A final area of interest for future research may be identifying the neural circuitry underlying the attenuating effects of discrimination training on renewal. In the present thesis, only behavioural (i.e., subjective and physiological) data were collected. Although behavioural effects can provide insight in mechanisms, they do not unveil the underlying neurobiological pathways. As understanding how the brain controls fear is relevant for the treatment of unrestrained fear, some suggestions are proposed for neural circuits that may be important for fear contextualization. Given the limited effects in the present thesis, these suggestions are highly speculative.

The amygdala is stated to be critically involved in the acquisition and expression of conditioned fear (see Hartley & Phelps, 2010; LeDoux, 2000, for reviews). By consequence, presentation of the fear stimulus (CS) activates the amygdala among several other brain areas, which in turn drives fear behaviour (e.g., autonomic and avoidance responses). A neural circuit that includes the amygdala, the ventral medial prefrontal cortex (vmPFC), and the hippocampus is thought to support the acquisition, retrieval and contextual modulation of extinction learning (Quirk & Mueller, 2008). The amygdala seems a critical site for the formation of extinction memories (CS-noUS), while the ventromedial prefrontal cortex (vmPFC) appears to be important for the consolidation and retrieval of extinction memory. During extinction retrieval, the vmPFC inhibits the amygdala, so that the fear stimulus (CS) is prevented from eliciting a conditioned fear response. The hippocampus is thought to play a central role in the context-dependent retrieval of extinction learning. The hippocampus has been implicated with the formation of contextual memory representations (Holland & Bouton, 1999). One hypothesis is that the vmPFC uses contextual information from the hippocampus to determine the retrieval of extinction (e.g., Hobin, Goosens, & Maren, 2003): Within the extinction context, the vmPFC inhibits the amygdala resulting in reduced fear (i.e., suppression of CR). Outside the extinction context, the vmPFC is prevented to inhibit the amygdala, which allows fear responding to recover. Thus, retrieval of extinction memories by the vmPFC may be hippocampal dependent.

Assuming that the hippocampus is involved in the context-dependent recall of extinction, a similar hippocampal involvement may be achieved in the retrieval of initial fear memories. That is, fear may be contextualized by turning the amygdala-dependent retrieval of fear memories hippocampal dependent, for instance by using reconsolidation updating mechanisms. As noted before, reconsolidation processes may allow for the modification of existing memories when retrieved. Accordingly, when a traumatic memory (CS-US) is reactivated, focusing on situational features associated with the traumatic event may result in a hippocampal dependent recall of fear memories. Since the time window of reconsolidation appears to be rather limited (e.g., Nader et al., 2000), contextualization of fear memories may involve a subtle timing process.

Conclusion

Without any doubt, experimental models of fear acquisition, its extinction, and recurrence are an oversimplification of the complexity of real-life fear and its related disorders. Nevertheless, scientific efforts to unravel the mechanisms of fear relapse may eventually culminate in strategies to improve the long-term effectiveness of anti-anxiety therapies. The dominant theoretical model states that fear relapse results from *context-dependent* extinction learning and *context-independent* fear learning. In line with this model, the present thesis demonstrated that extinction learning is specific to its context. Contrary to the prevailing account, we showed that fear learning can also become context dependent in humans. The contextual control of fear was a starting point for the development of novel strategies to prevent occasions of relapse due to renewal. More specifically, we tested strategies aimed to increase the context dependency of fear learning through discrimination training. We demonstrated that context-*cue* discrimination training during extinction weakens renewal. By contrast, context discrimination training failed to attenuate renewal. This may point to the robustness of renewal effects in general, which is also indicated by previous failures to counter renewal. For instance, renewal has been shown to be resistant to extinction in multiple contexts (e.g., Bouton, García-Gutiérrez et al., 2006; Thomas et al., 2009), instructions that devalue the role of contextual cues (Neumann, 2007), extensive extinction (Rauhut, Thomas, & Ayres, 2001), and to drug facilitation of extinction (Woods & Bouton, 2006). Given the severity of anxiety disorders, continued efforts should be undertaken to develop new procedures that boost the efficacy of anti-anxiety treatment on the long term. In the same way that continued efforts are undertaken to bridge extinction learning over contexts, we hope that the current thesis will inspire researchers to target the root of anxiety disorders, that is, the unrestrained generalization of fear.