Plasticity of fear memory: a search for relapse prevention

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Summary

Fear learning is crucial for survival. It serves as an alarm mechanism by identifying cues that signal impending threat. Just the perception of a threat cue may evoke fear reactions that enable the body to respond rapidly. While it can be highly adaptive to generalize fear to threat cues across different situations, fear generalization becomes maladaptive when fear persists in situations without imminent threat. Indeed, overgeneralization of fear is a core feature of many anxiety disorders.

Most psychological treatments for anxiety disorders involve exposure procedures in which patients are exposed to their feared object in the absence of any overt danger. By consequence, fearful responding to that object declines. Unfortunately, relapses of fear after successful therapy is the rule, rather than the exception. Given that the maintenance of therapeutic change is delicate, an important issue concerns the explanation of these relapses of fear. From a clinical perspective, an even more important question is how such relapses can be prevented.

Over the last decades, laboratory studies in animals have provided major contributions to understanding the rise and fall of fear in humans. Pavlovian fear conditioning is considered to play an important role in the etiology of pathological fear. Fear conditioning refers to the process of pairing an initially neutral conditioned stimulus (CS; e.g., a tone) with an intrinsically aversive unconditioned stimulus (US; e.g., a shock). The learned association between the CS and the occurrence of the US generates a conditioned fear response to the CS on its own (i.e., acquisition effect). Extinction of Pavlovian conditioned fear by repeated presentations of a CS in absence of an aversive event (US) is viewed as the experimental model for exposure therapy.

Animal conditioning studies have also provided explanations for the unstable nature of fear reduction in clinical practice. The most prominent explanation is that extinction is context dependent, whereas fear learning is context *in*dependent. The asymmetry in the contextual control of extinction and fear learning is most obviously unveiled in the studies on renewal. In a typical renewal experiment, animals receive fear conditioning to a CS in one context (Context A) followed by extinction in another context (Context B). Remarkably, the context change after conditioning (from A to B) has little impact on fear responding to the CS; fear learning generalizes well across contexts. By contrast, the same sort of context change after extinction vigorously disrupts extinction performance. That is, a robust return of fear is observed by presenting the CS again in the context of fear acquisition (ABA renewal) or in a novel context (ABC renewal). Hence,

extinction learning generalizes weakly over contexts. Importantly, renewal effects indicate that the originally learned fear association is not erased during extinction. Rather, extinction involves the development of a second association (CS-noUS) that inhibits the initial fear association. It is argued that contexts modulate which association prevails in a certain situation: In all contexts, the initial fear association (CS-US) is on unless the extinction context turns it off. Thus, exposure procedures might extinguish fear reactions without erasing its roots. By implication, the behavioural effects of exposure (i.e., fear reduction) may be lost when the previously feared object is encountered outside the treatment context.

Given that extinction learning is fragile and may easily be forgotten, research on the prevention of renewal has mainly focused on strengthening the extinction memory. Specifically, most studies examined strategies aimed to generalize extinction learning more effectively across contexts. However, such strategies leave the original fear memory intact and due to its robust generalization, return of fear is always possible. In sharp contrast to the traditional strategies, we targeted the original fear memory and designed novel procedures to reduce renewal by weakening of the generalization of (i.e., contextualizing) fear learning. In the present thesis, five experimental studies were conducted that examined contextual renewal and its reduction in humans.

The study in **Chapter 2** challenged the dominant hypothesis that fear learning is context independent. Two experiments were conducted using a fear conditioning paradigm with online expectancy ratings and skin conductance. In a first experiment, the basic renewal effect was replicated. Participants received fear conditioning in one context followed by extinction in another context. Upon a return to the original acquisition context, participants showed renewed shock expectancies (ABA renewal). No renewal was found for skin conductance responding. A second experiment compared the influence of different context changes on renewal. The dominant model of renewal states that only extinction learning depends on the context, such that renewal in the original acquisition context (ABA renewal) should be as strong as in a novel context (ABC renewal). By contrast, we predicted that the context independency of fear learning is possibly less stringent than originally proposed. This idea was inspired by several anomalous findings for the current renewal model. In line with our predictions, participants demonstrated larger renewal of shock expectancies in the acquisition context (ABA renewal) than in a novel context (ABC renewal). The physiological data indirectly showed that renewal effects differed: There was a trend for renewed skin conductance responding in the acquisition context (ABA renewal) but no

evidence of renewal in a novel context (no ABC renewal). Together, these findings suggest that in humans not only extinction learning, but also fear learning is controlled by its context.

The study in **Chapter 3** examined two possible mechanisms that may explain the contextual control of fear learning observed in Chapter 2. When participants realize that the context during extinction differs from the one during fear learning, they may infer that the acquisition context itself was dangerous (i.e., predicts danger). In associative learning terms, the acquisition context may retrospectively acquire excitatory strength (*retrospective excitation*). Alternatively, when extinction occurs in a different context than fear learning, participants may infer that the threat stimulus only signifies danger in the context of fear acquisition. In learning terms, the acquisition context may retrospectively become an occasion setter indicating that the conditioned stimulus is followed by an aversive event (*retrospective occasion setting*). Using a conditioning suppression paradigm, two experiments were conducted to examine whether an extinction procedure provokes retrospective excitation and retrospective occasion setting in humans. Participants received conditioning training, in which a feature stimulus (X) preceded the conditioning of a target stimulus (A+), followed by extinction training of the target stimulus (A-). In this task, the feature (X) and the target (A) modelled the role of the context and the CS, respectively. The results did not support our hypotheses: Extinction training neither induced retrospective excitation nor retrospective occasion setting of the feature (X). However, we observed another retrospective learning effect. That is, extinction training retrospectively enhanced the ability of the feature (X) to elicit responding to a novel target (B). Nevertheless, these findings make it less plausible that contextual control of renewed fear responding (Chapter 2) could be explained by retrospective revaluation of the acquisition context.

The remaining chapters of the present thesis focused on weakening renewal. The studies in Chapters 4, 5, and 6 were designed to reduce renewal by contextualizing fear learning. Because the history of fear learning can not literally be changed, contextualization should occur *after* a fear memory is established, for instance during extinction training. **Chapter 4** describes a study that used a context discrimination procedure during extinction to contextualize previously acquired fear learning. We employed a fear conditioning paradigm with expectancy ratings, skin conductance responding and startle responding as dependent measures. Participants received fear conditioning in one context followed by extinction training in another context. The control condition received simple extinction

training (CS-noUS). By contrast, the reacquisition condition occasionally received reacquisition trials during extinction training (CS-noUS), in which the CS was again paired with the aversive event (CS-US). Crucially, reacquisition trials were presented in the original acquisition context, while extinction training occurred in the extinction context. Hence, extinction and reacquisition alternated across contexts (*context discrimination training*). Renewal was tested in a novel context. We hypothesized that a context discrimination procedure after acquisition stresses that the context is relevant for fear learning. This may contextualize fear and prevent the generalization of fear to a novel context. Accordingly, we predicted smaller renewal of fear after context discrimination training relative to simple extinction training. The results showed a clear renewal effect after simple extinction (ABC renewal). Contrary to the hypotheses, context discrimination training did not weaken this renewal effect. These findings suggest that the repeated presentation of the fear association in its original context during extinction does not attenuate fear generalization. Despite its failure to disrupt renewal, context discrimination did not *increase* the renewal effect either, suggesting that additional acquisition training does not enhance fear generalization.

The studies presented in Chapters 5 and 6 used a slightly different discrimination procedure in order to weaken renewal. In general, fear learning does not occur in a vacuum, but against a constellation of background cues that make up the context. Rather than increasing the importance of all those cues for fear learning, the studies were designed to enhance the salience of only *one* cue that was part of the acquisition context. It was hypothesized that the remaining context cues from acquisition would loose their ability to retrieve the fear memory and, thereby, reduce renewal. The two experiments that are described in **Chapter 5** tested this hypothesis by employing a predictive learning paradigm with outcome expectancy ratings. In a first experiment, participants were exposed to conditioning in one context (AX) consisting of a coloured screen (A; e.g., red screen) and a sound (X). The control condition then received simple extinction training (CS-noUS) in another context consisting of a different coloured screen (B; e.g., blue screen). The reacquisition condition was also exposed to extinction training (CS-noUS) in this context (B), but, in addition, occasionally received reacquisition trials (CS-US) in the presence of a context cue from acquisition (sound X) (i.e., cued reacquisition). Hence, extinction and cued reacquisition were alternated (*context-cue discrimination training*) in this condition. The results showed that after simple extinction, a return to one contextual feature from acquisition (A; e.g., red screen) produced clear renewal. As expected, context-cue discrimination training reduced this renewal of

responding, although renewal was not eliminated. As expected, both conditions demonstrated full-blown renewal upon a return to the original acquisition context including the cue used for discrimination training (AX; e.g., red screen and sound).

A second experiment examined whether the reduction of renewal was caused by backward blocking. Increasing the relevance of one cue from the acquisition context for fear learning may have reduced (i.e., blocked) the relevance of the other context cues, such that they become less able to elicit renewal. Current learning theories state that cues must have been previously presented together for later blocking to occur. By implication, reduction of renewal is only expected when a cue from acquisition, but not when a novel cue is used for context-cue discrimination training. A similar experiment as the previous experiment was conducted with the difference that reacquisition occurred either in the presence of a context cue from acquisition (sound X) or a novel context cue (sound Y). The results showed that context-cue discrimination training with an acquisition context cue (sound X), again, reduced renewal of responding relative to simple extinction training. Unexpectedly, context-cue discrimination training with a novel context cue (sound Y) also weakened renewal, suggesting that backward blocking played no role in reducing renewal. Instead, the findings suggest that conditioned responding became under the control of a discrete context cue irrespective of its origin. This may enlarge clinical implications as patients do not always remember the exact context features that surrounded a traumatic event.

Chapter 6 presents a study that is similar to the first experiment described in Chapter 5. This time, however, the effects of *context-cue discrimination training* were examined in a fear conditioning paradigm that allowed for assessing physiological fear indices (skin conductance and startle responding) besides subjective ratings. Furthermore, we employed more complex contexts (room pictures) than the context cues in Chapter 5 (coloured screens and sounds). All participants were exposed to fear conditioning in one context (AX; e.g., living room including a lamp) and extinction in another context (B, e.g., office). Participants in the control condition received simple extinction training (CS-noUS). In contrast, participants in the experimental condition occasionally received reacquisition trials (CS-US) during extinction training (CS-noUS). Crucially, reacquisition occurred in the joint presence of the extinction context (B; office) and a discrete cue from the acquisition context (X; a lamp). Hence, extinction and cued reacquisition occurred in alternation (*context-cue discrimination training*). Context-cue discrimination training appeared, again, effective in reducing renewal of subjective expectancies when tested in a subset of the acquisition context (A; e.g., living room). Unexpectedly,

context-cue discrimination increased renewal in the original acquisition context (AX; e.g., living room and lamp). Given that no acquisition effect was obtained for skin conductance responding and startle responding, no conclusions could be drawn for the physiological data. Thus, we only showed that context-cue discrimination training reduces renewal for the subjective level of fear expression. This study supports again the conclusion that conditioned responding became under the control of a specific context cue.

In the general discussion, presented in **Chapter 7**, the main findings of the studies in this thesis are discussed. First, we concluded that not only extinction learning, but also fear learning may depend on the context. It seems not plausible that retrospective learning effects caused this contextual control of fear learning. Second, we provided some evidence that a context-cue discrimination procedure reduces renewal of extinguished fear, at least for declarative knowledge (i.e., the conscious recollection about events). Nevertheless, reduction of renewal was only observed when tested in (a part of) the acquisition context. Whether context-cue discrimination training also attenuates renewal in a novel context remains to be tested. Third, we found no evidence that backward blocking contributed to renewal reduction by discrimination training. Instead, we assume that context-cue discrimination training provides the specific context cue with occasion setting properties. That is, the presence of the specific context cue may be necessary to elicit conditioned responding (to the CS), while absence of this cue might hamper conditioned responding, thereby weakening renewal. This indicates that it may be possible to bring fear learning under contextual control. Whether this indeed implies updating of an existing fear memory with information about the context (plasticity of fear memory) or triggering of new learning is a question for future research. The chapter closes with possible applications of discrimination training in clinical practice and suggestions for future research.