Summary
Since the dawn of psychology at the end of the nineteenth century, psychologists and psychiatrists have tried with dozens of treatments to change undesired emotional memory. Though some progress has been made, even a successful treatment such as ‘exposure therapy’ leaves the emotional memory intact, as is substantiated by the high percentages of relapse in spite of initial treatment success. Once emotional memory has been established, it is held to be forever. From an evolutionary perspective, it is extremely functional to never forget the most important events in life. However, the putative indelibility of emotional memory may also become harmful and maladaptive, such as in patients suffering from anxiety disorders. If emotional memory could be weakened or even erased, then we might be able to eliminate the root of many psychiatric disorders, such as posttraumatic stress disorder.

Recently, it was rediscovered in rats that fear memory is not necessarily permanent but can change when retrieved. Upon their retrieval, items in long-term memory enter a labile, protein synthesis dependent state, in which they might become sensitive to disruption. This process, called ‘reconsolidation’, thus offers the opportunity to manipulate memory after it is formed and may therefore point to a promising alternative strategy in the treatment of anxiety disorders. Reconsolidation of fear memory can be influenced by neurobiological manipulations during or shortly after the reactivation period. Propranolol HCl, a noradrenergic β-blocker, supposedly blocks the protein synthesis required for reconsolidation. As a result, disrupting reconsolidation by administering propranolol HCl ‘before’ or ‘after’ memory reactivation may lead to ‘permanent’ changes in the expression of human fear memory.

Pavlovian fear conditioning is a well-controlled experimental model to unravel the processes and mechanisms underlying fear memory in humans. In a typical fear conditioning procedure in the laboratory, a neutral or ambiguous stimulus (i.e., CS; e.g., tone) acquires the capacity to elicit fear responses after the pairing with an intrinsically aversive event (i.e., US; e.g., electric stimulus). Even though Pavlovian fear conditioning is not necessarily the means through which human fear originates, it offers an excellent model of ‘associative learning’, which is considered to play an important role in the aetiology of anxiety disorders. Extinction of Pavlovian conditioned fear by repeated presentations of the CS in the absence of the aversive event (i.e., US) is viewed as the experimental model for
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‘exposure therapy’. Notably, rather than ‘erasure’, fear extinction solely involves the formation of a new inhibitory memory trace that acts to inhibit or competes with the original fear association. Animal and human studies indeed show that a variety of post extinction processes can uncover the original fear memory, including the presentation of unsigned USs (i.e., reinstatement), a context change (i.e., renewal), simply allowing time to pass (i.e. spontaneous recovery) or fear recreation. From a clinical perspective, post extinction retrieval effects may provide the mechanisms of relapse after successful ‘exposure therapy’. At the same time, post extinction retrieval techniques offer a potent means to trigger the original fear memory in the experimental setting. Accordingly, the Pavlovian fear conditioning paradigm is well suited to investigate whether targeting the process of reconsolidation results in a ‘permanent’ reduction of fear responding.

Using such a differential fear conditioning procedure with fear-relevant stimuli (i.e., pictures of spiders), we tested in Chapter 2 whether disrupting reconsolidation by the oral administration of propranolol HCl prior to memory reactivation would diminish fear responding and prevent the return of fear relative to placebo pill. We employed fear-relevant stimuli because they lead to a superior conditioning of aversive associations and are especially resistant to extinction learning compared with fear-irrelevant cues. Moreover, given that most anxiety disorders are associated with these categories of stimuli, we are specifically interested in targeting stronger fear memory. Testing included different phases across three consecutive days each separated by 24 hr. During acquisition (i.e., day 1), one of the slides (i.e., CS1+) was repeatedly paired with an aversive electric stimulus (i.e., US), while the other slide (i.e., CS2-) was not. Participants received double-blind an oral dose of 40 mg of propranolol HCl or placebo pill 90 minutes prior to memory reactivation (i.e., day 2). To determine whether the effect of propranolol HCl requires the active retrieval of the fear memory, the propranolol HCl drug was administered to another fear conditioned group without reactivation of the memory. Memory retention was tested 24 hr later (i.e., day 3). In order to maximize the likelihood of fear memory expression, ‘reminder shocks’ were administered following extinction learning (i.e., day 3). Expression of fear memory was measured using startle fear potentiation. Declarative knowledge of the fear association was measured through online US expectancy ratings. Here, we demonstrated that disrupting reconsolidation by administering propranolol HCl prior to memory reactivation resulted in ‘amnesia’ for the emotional expression of
the fear memory 24 hr later (i.e., startle fear responding). This reduction in startle fear responding was critically dependent on the active retrieval of the fear memory as the omission of memory reactivation after propranolol HCl intake yielded normal fear responding. Interestingly, the propranolol HCl manipulation left the declarative memory for the learned fear association (i.e., US expectancy ratings) intact, but this knowledge no longer produced any emotional effects. Hence, the pharmacological agent prior to memory reactivation specifically targeted the emotional expression of the memory (i.e., startle fear responding), thereby emphasizing the concept of multiple memory systems.

Since disrupting reconsolidation prevented the return of fear, the results from Chapter 2 could have important clinical implications and thus asked for a solid replication. Moreover, given the constructive nature of memories, the intact recollection of the fear association (i.e., declarative knowledge) could eventually ‘rebuild’ the fear memory, resulting in the ‘spontaneous recovery’ of the startle fear responding. Yet, if disrupting reconsolidation will be of value for clinical practice, perseverance of the amnesic effects is desired. In Chapter 3, we replicated our previous findings by showing that the administration of propranolol HCl prior to memory reactivation ‘deleted’ the emotional expression of the fear memory 24 hr later (i.e., startle fear responding). But most importantly, this effect persisted at one month follow-up. Notably, the propranolol HCl manipulation not only left the declarative memory for the acquired contingency (i.e., US expectancy ratings) untouched, but also skin conductance discrimination. In addition, a close association between declarative knowledge and skin conductance responding was found. These findings are in line with the supposed double dissociation of fear conditioning and declarative knowledge relative to the amygdala and hippocampus in humans. They support the view that skin conductance responding primarily reflects contingency learning, whereas startle fear responding is a rather specific measure of fear. Furthermore, the results indicate the absence of a causal link between the actual knowledge of a fear association and its fear response, even though they often operate in parallel. Together, these data demonstrated that memories may undergo reconsolidation at one level (i.e., amygdala fear memory), while leaving the hippocampal-dependent declarative memory untouched.

Although the findings from Chapters 2 and 3 could point to promising interventions persistently erasing fear responses from trauma memory without
affecting the actual recollection, the typical differential fear conditioning paradigm (i.e., CS1⁺ vs. CS2⁻) did not allow any inference about the nature of the fear memory ‘erasure’. That is, due to the systemic drug administration, the attenuation of the startle fear responding could also have resulted from a more diffuse effect of the propranolol HCl manipulation by reducing the fear-provoking aspects of the aversive consequence itself. In considering clinical implications, disrupting reconsolidation should not radically alter functional reactions to potentially dangerous situations (i.e., US), but ‘selectively’ weaken the underlying maladaptive fear association (i.e., CS1-US). At the same time, the fear reducing effects should not be restricted to the feared cue itself considering that fear generalization is a main characteristic of anxiety disorders. In Chapter 4, Experiment I and Experiment Ib, we addressed these issues by using a within-subject differential fear conditioning paradigm allowing selective reactivation of one of two categorically distinct fear associations sharing the same aversive outcome and a test of fear generalization. In Experiment IIb, we tested whether a behavioral approach targeting the reconsolidation through extinction learning was also effective in weakening the original fear memory. A behavioral procedure is evidently preferred over drug manipulations provided that similar effects can be obtained. Here, the extinction procedure subsequent to retrieval did not ‘eliminate’ the emotional expression of the fear memory as the retrieval techniques (i.e., reminder shocks, reacquisition) unveiled a return in startle fear responding. In contrast, the propranolol HCl manipulation during reconsolidation selectively ‘neutralized’ the fear-arousing aspects of the memory (i.e., startle fear responding) along with its category-related information. Furthermore, the pharmacological manipulation rendered the core memory trace too weak to observe fear generalization after successful reacquisition. Given that three-trial fear acquisition in naïve participants was sufficient to produce a generalized fear response (i.e., Experiment Ib), relearning following the disruption of reconsolidation seemed to be qualitatively different from initial learning (i.e., Experiment I). Together, the findings from Chapter 4 demonstrated that disrupting reconsolidation by the propranolol HCl drug, although selective, undermined the generalization of fear responding.

Considering that fear generalization lies at the heart of many anxiety disorder, the findings from Chapter 4 could have important clinical implications. However, there are a number of experimental conditions (i.e., boundary conditions) that
may prevent reconsolidation from occurring, such as the ‘strength of training’. If we are to target reconsolidation in patients suffering from posttraumatic stress disorder, the strength of the memory should evidently not act as a boundary condition on reconsolidation. Although ample evidence in animals and humans supports the role of ‘noradrenaline’ in the formation of emotional memory, the effects of stress hormones on human ‘associative’ fear memory previously remained unknown. Therefore, we first tested in Chapter 5 whether stimulation of the noradrenergic system during memory formation by the administration of yohimbine HCl would strengthen the emotional expression of fear memory in humans. Here, the administration of yohimbine HCl contrary to placebo pill extensively delayed the process of extinction learning and generated a superior recovery of fear (i.e., reinstatement, reacquisition) 48 hr later. On the other hand, the yohimbine HCl manipulation did not affect the skin conductance responding and US expectancy ratings, again emphasizing the concept of multiple memory systems. Together, these data demonstrated that increased noradrenaline release during or shortly after a stressful event strengthens the emotional expression of human ‘associative’ fear memory and suggest that noradrenaline may play an important role in the aetiology and maintenance of anxiety disorders.

Next, in Chapter 6, we tested whether the noradrenergic strengthening of fear memory would impair the disruption of reconsolidation by again using a within-subject differential fear conditioning procedure allowing selective reactivation of one of two fear associations. In Experiment I, participants received double-blind an oral dose of yohimbine HCl or placebo pill prior to fear acquisition (i.e., day 1). Reconsolidation of one of the fear associations was manipulated by the administration of propranolol HCl prior to its selective reactivation (i.e., day 2). In Experiment II, we administered the β-blocker after reactivation of the memory in order to discard the effect of the propranolol HCl manipulation on the memory retrieval itself. Here, the excessive release of noradrenaline during ‘memory formation’ not only delayed the process of extinction 48 hr later but also triggered broader fear generalization. Yet, the propranolol HCl manipulation during reconsolidation selectively ‘neutralized’ the fear-arousing aspects of the noradrenergic strengthened memory and undermined the generalization of fear responding. We observed a similar reduction in fear responding when propranolol HCl was administered after reactivation of the memory. Together, the results demonstrated the involvement of noradrenergic modulation in the formation as
well as generalization of human fear memory. Given that the noradrenergic strengthening of fear memory impaired extinction learning but not the disruption of reconsolidation, the findings from Chapter 6 could further have important implications for the treatment of anxiety disorders.

In the above chapters on reconsolidation (i.e., Chapters 2, 3, 4, and 6), we provided ample evidence that disrupting reconsolidation attenuates the emotional expression of fear memories (i.e., startle fear responding). However, for the feasibility of reconsolidation in psychotherapy, disrupting reconsolidation should also diminish the subjective feelings of anxiety. In Chapter 7, we addressed this issue by using an ‘instructed’ fear learning paradigm in which a noxious event (i.e., ‘electric stimulus’) is anticipated but never actually experienced. Here, β-adrenergic receptor blockade during reconsolidation strongly diminished the emotional expression of the ‘instructed’ fear memory (i.e., startle fear responding) as well as the subjective feelings of anxiety 24 hr later, yet without affecting both the ‘physiological’ and ‘cognitive’ component of the anticipation of threat (i.e., skin conductance responding, US expectancy ratings). Together, these findings suggest that the various memory expressions of a single learned fear association not necessarily undergo reconsolidation in harmony. Considering that patients with anxiety disorders often fear objects and situations that they have never actually experienced, and primarily suffer from the subjective feelings of anxiety, it seems that disrupting reconsolidation is on the verge of clinical application.

In the general discussion, presented in Chapter 8, the main findings of the studies in this thesis are discussed. We end by stating that disrupting reconsolidation allows for the modification of the underlying fear association, which not only results in a permanent reduction of fear but also undermines the generalization of fear responding, a main characteristic of anxiety disorders. Yet, while in the present thesis the propranolol HCl manipulation during reconsolidation targeted the emotional expression of fear memories (i.e., startle fear responding) as well as the subjective feelings of anxiety, the anticipation of threat remained untouched (i.e., skin conductance responding, US expectancy ratings). First, this dissociation clearly emphasizes the concept of multiple memory systems. Second, it indicates that the specific reactivation conditions to transform fear memories from a fixed state to one that is amenable to change differ for the various aspects of fear memories. Undeniably, experimental models of human fear (i.e., Pavlovian fear conditioning) are an oversimplification of the complexity of
pathological fear and its related disorders. Acknowledging that disrupting reconsolidation is only a proof of principle, at least, we may conclude that it clearly outperformed the traditional extinction learning. Hence, disrupting reconsolidation may point to a novel therapeutic strategy for treating patients suffering from anxiety disorders. Chapter 8 closes with possible applications of disrupting reconsolidation in clinical practice and suggestions for future research.