Erasing fear from memory
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Chapter 8

General Discussion
The objective of this thesis was to develop novel strategies to prevent the return of fear in humans. Though the usual treatment for anxiety disorders (i.e., exposure therapy) is highly effective in reducing fearful responding, a noticeable disadvantage is that it leaves the original fear memory intact (e.g., Bouton, 1993, 2002; LeDoux, 1995), thereby explaining the high percentages of relapse in spite of initial treatment success (Craske, 1999). Recently, it was rediscovered in rats that a permanent reduction of fear may be realized through targeting the process of reconsolidation (Nader et al., 2000; Dębiec & LeDoux, 2004). That is, the protein-synthesis dependent restabilization of a memory upon retrieval enables the modification of the original fear memory representation and thus points to a promising strategy for the treatment of anxiety disorders. In a series of experiments, we tested whether disrupting the process of human fear memory reconsolidation would result in amnesia for the original learning and prevent the return of fear. 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.

Erasing Fear from Memory

Using a differential fear conditioning paradigm in humans, we demonstrated in Chapter 2 that disrupting reconsolidation by the oral administration of the β-adrenergic receptor antagonist propranolol HCl prior to memory reactivation ‘deleted’ the emotional expression of the fear memory 24 hr later (i.e., startle fear responding). The β-adrenergic blocker seemed to be highly effective in eliminating the fear arousing aspects of the memory as the reminder shocks (i.e., reinstatement testing) failed to uncover any startle fear responding. This contrasted sharply with the return of fear that was observed during reinstatement testing in the placebo pill group, demonstrating that traditional extinction learning leaves the original fear memory unaffected (e.g., Bouton, 2002). Given that disrupting reconsolidation prevented the return of fear, the results from Chapter 2 could have important therapeutic implications and thus asked for a solid replication. In addition to replicating our previous findings, we demonstrated in Chapter 3 that the fear erasing effects by the propranolol HCl manipulation ‘persisted’ at one month follow up. 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 (i.e., Chapters 2 and 3). Thus, taken together, given that the oral administration of propranolol HCl as well as memory retrieval seemed to be necessary for ‘persistently’ eliminating the emotional expression of the fear memory (i.e., startle fear responding), the fear reducing effects in Chapters 2 and 3 could not be explained by any anxiolytic effects of the β-adrenergic drug. However, the typical differential fear conditioning paradigm (i.e., CS1-US vs. CS2) in Chapters 2 and 3 did not allow any further inferences about the nature of the fear memory erasure. First, the β-adrenergic receptor antagonist propranolol HCl during reconsolidation could simply have diminished the intrinsically negative valence of the startle probes, which are necessary to elicit startle responses and are typically potentiated during fearful states (e.g., anticipation of the electric stimulus). Second, 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 (i.e., US). 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, disrupting reconsolidation should not be restricted to the feared cue itself when we consider that fear generalization is a main characteristic of anxiety disorder (Lissek et al., 2008).

We addressed these issues in Chapter 4 by using a within-subject differential fear conditioning procedure allowing selective reactivation of one of two categorically distinct fear associations sharing the same aversive outcome and a test of fear generalization. The findings demonstrated that the administration of the β-adrenergic receptor antagonist prior to memory reactivation selectively ‘neutralized’ the fear arousing aspects of the reactivated fear association, as ‘reacquisition’ learning did not reveal any savings of the fear response. This contrasted sharply with the ‘rapid reacquisition’ of the startle fear response to the nonreactivated cue, again demonstrating that extinction learning leaves the original fear memory intact (Bouton, 2002). Remarkably, the fear erasing effect following reconsolidation blockade was not restricted to the reactivated fear association but instead generalized to cues that belong to the same semantic category (i.e., fear network), even though reacquisition learning had recovered the
fear responding before the test of generalization. Given that comparable fear learning in naive participants was sufficient to produce generalized fear responding (i.e., Experiment 1b, Chapter 4), we concluded that relearning following the disruption of reconsolidation may be qualitatively different from original learning. The generalization of fear seems to be dependent on the strength of the memory as operationalized by training intensity (Laxmi et al., 2003). Apparently, the β-adrenergic interference with reconsolidation rendered the core memory trace too weak for fear generalization to occur after successful reacquisition. Thus, the propranolol HCl manipulation may have suppressed the synaptic plasticity instead of solely neutralizing the emotional impact of the memory. Although no objective behavioral test is currently available to answer the question whether disrupting reconsolidation permanently alters memory traces (i.e., storage theory) or just leaves the memory inaccessible as a result of retrieval failure (i.e., retrieval theory) (Tronson & Taylor, 2007), the reacquisition-generalization findings from Chapter 4 strongly support the hypothesis of reconsolidation as a storage mechanism. In any case, the findings from Chapter 4 demonstrated that disrupting reconsolidation by the propranolol HCl manipulation, though selective, undermined the generalization of fear responding.

Considering that the generalization of fear lies at the heart of many anxiety disorders (Lissek et al., 2008), the above findings (i.e., 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 ‘reminder duration’ (Eisenberg et al., 2003; Pedreira & Maldonado, 2003) and the ‘strength of training’ (Suzuki et al., 2004; Wang et al., 2009). If we are to target reconsolidation in patients suffering from anxiety disorders such as posttraumatic stress disorder, the strength of the memory should not act as a boundary condition on reconsolidation. Even though ample evidence in animals and humans supports the role of noradrenaline in the formation of emotional memory (McGaugh & Roozendaal, 2009), the effects of stress hormones on human associative fear memory were unknown. Therefore, we first tested in Chapter 5 whether stimulation of the noradrenergic system during memory formation by the administration of yohimbine HCl1 would strengthen the

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1 Yohimbine HCl is a α2-adrenergic antagonist supposed to stimulate central noradrenergic activity (Charney et al., 1987; Peskind et al., 1995).
emotional expression of associative 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. The competition between the original excitatory fear association and the newly formed inhibitory memory trace determines the behavioral outcome of extinction learning (Myers & Davis, 2002). Given that yohimbine HCl was administered during fear conditioning (i.e., 48 hr prior to fear extinction), the noradrenergic manipulation apparently delayed the process of extinction by strengthening the original excitatory fear association. Taken together, these data thus demonstrated that increased noradrenaline release during or shortly after a stressful event strengthened associative fear memory traces and suggest that noradrenaline may play an important role in the aetiology and maintenance of anxiety disorders.

Again using a differential fear conditioning procedure allowing selective reactivation of one of two fear associations, we next tested in Chapter 6 whether the stimulation of the noradrenergic system during memory formation would act as a boundary condition on reconsolidation. Here, the administration of yohimbine HCl contrary to placebo pill delayed the extinction learning process 48 hr later and promoted fear generalization to the non-reactivated fear association. Yet, the β-adrenergic receptor blocker during reconsolidation selectively ‘neutralized’ the startle fear responding to the reactivated fear association along with its category-related information (i.e., fear network). In line with the findings from Chapter 5, these data demonstrated that the noradrenaline level during or shortly after a traumatic experience may be an important determinant in the etiology of anxiety disorders. At the same time, the findings from Chapter 6 could have valuable clinical implications given that the strength of the memory did not act as a boundary condition on reconsolidation. It may be possible that the stimulation of the noradrenergic system during memory formation still rendered the memory trace too weak to prevent reconsolidation from occurring (Suzuki et al., 2004; Wang et al., 2009). On the other hand, the yohimbine HCl manipulation during the formation of memory strongly impaired subsequent extinction learning, whereupon the current treatment of choice for anxiety disorders is based (i.e., ‘exposure therapy’) (Rothbaum & Foa, 2002; Rothbaum & Davis, 2003).

A (fear) memory may become vulnerable to disruption immediately following its retrieval (Nader et al., 2000). In the above chapters on reconsolidation (i.e.,
Chapters 2, 3, 4, and 6), we therefore administered propranolol HCl 90 minutes prior to memory reactivation in view of the peak plasma concentrations (Gilman & Goodman, 1996). Even though the fear erasing effects were only observed during the post reactivation tests (i.e., Chapters 2, 3, 4, and 6), administering pills prior to reactivation does not discard the effect of the drug manipulation on the retrieval of the fear memory itself. However, the reconsolidation window (i.e., the period of instability) is supposed to persist for approximately 6 hr after retrieval (Nader et al., 2000). Indeed, in Chapter 6, we observed a similar reduction in startle fear responding when the β-adrenergic receptor antagonist was administered ‘after’ reactivation of the memory (i.e., Experiment II). Together with the observation that propranolol HCl did not directly affect the expression of the fear memory during retrieval (i.e., Chapters 2, 3, 4, and 6), our findings suggest that the drug manipulation prior to reactivation also specifically affected the processes mediating reconsolidation (Nader et al., 2000).

If disrupting reconsolidation will be of value for clinical practice, it should not only diminish the emotional expression of fear memories (i.e., startle fear responding - Chapters 2, 3, 4, and 6) but also the subjective feelings of anxiety. In our final study (i.e., 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. That is, the participants were instructed which out of two fear-relevant stimuli would at times be followed by a very unpleasant electric stimulus (i.e., US), while the US was never administered. First, the findings from Chapter 7 demonstrated that ‘imagined’ aversive events also undergo reconsolidation. Furthermore, the administration of propranolol HCl contrary to placebo pill not only ‘erased’ the emotional expression of the fear memory but also prevented the ‘renewal’ of fear responding. But most importantly, β-adrenergic blockade after memory retrieval strongly attenuated the subjective feelings of anxiety. Considering that patients with anxiety disorders (1) often fear objects and situations that they have never actually experienced (Rachman, 1977), and (2) primarily suffer from the subjective feelings of anxiety, the findings from Chapter 7 could have important implications for the treatment of anxiety disorders.

In sum, the processes of ‘extinction’ and ‘disrupting reconsolidation’ are two approaches to diminish fear related behavior. In the present thesis, considerable evidence was found that extinction learning leaves the original fear memory intact.
That is, the four hallmark retrieval techniques that we employed (i.e., ‘reinstatement’, ‘reacquisition’, ‘renewal’, and ‘spontaneous recovery’) all revealed a return of fear post extinction learning (i.e., Chapters 2, 3, 4, 5, 6, and 7). Conversely, β-adrenergic receptor blockade during reconsolidation prevented the return of fear, indicating the selective ‘erasure’ of the underlying fear association (i.e., Chapters 2, 3, 4, 6, and 7). Whereas extinction learning seemed to be impaired by noradrenergic modulation (i.e., Chapters 5 and 6), the propranolol HCl manipulation during reconsolidation selectively ‘neutralized’ the fear arousing aspects of the noradrenergic strengthened fear association (i.e., Chapter 6). On top of that, the β-adrenergic interference with reconsolidation undermined the generalization of fear responding (i.e., Chapter 4), even in case when a noradrenergic strengthened (i.e., Yohimbine HCl) fear memory trace triggered broader fear generalization (i.e., Chapter 6). Several lines of evidence suggest that CREB (i.e., cyclic adenosine monophosphate response element binding protein) is one of the transcription factors regulating the synthesis of proteins necessary for the (re)consolidation (Josselyn et al., 2001; Davies et al., 2004) as well as generalization of fear memory (Han et al., 2008). Whereas yohimbine HCl is known to induce the phosphorylation of CREB (Sun et al., 2010), the β-adrenergic receptor antagonist propranolol HCl has been shown to inhibit noradrenaline-stimulated CREB phosphorylation (Jockers et al., 1998; Chaundhry & Granneman, 1999; Thonberg et al., 2002). Together, the findings in the present thesis show the involvement of noradrenergic modulation in the ‘formation’, ‘reconsolidation’ as well as ‘generalization’ of human associative fear memory. Moreover, the findings demonstrate that disrupting reconsolidation may point to a promising alternative strategy in reducing excessive fear responding.

Dissociating Response Systems

Even though the β-adrenergic receptor blocker during memory reactivation was highly effective in ‘eliminating’ the emotional expression of the fear memory (i.e., startle fear responding, subjective feelings of distress), we did not observe any effects on the US expectancy ratings and skin conductance discrimination (i.e., Chapters 2, 3, 4, 6, and 7). Human startle potentiation is considered to be a reliable and specific index of fear (Hamm & Weike, 2005), directly connected with, and modulated by, the amygdala (Davis, 2006). Amygdala activation is also
reported in association with electrodermal activity (i.e., SCR) either evoked by fear conditioning or the processing of threat cues (Büchel et al., 1998; Phelps et al., 2001; Williams et al., 2001). However, one difficulty in interpreting SCR-related brain activity in behavioral studies is that the experimental paradigm does not permit dissociating secondary induced SCR-related neural activity from activity related to psychological stimulus processing (Critchley et al., 2001, 2002; Nagai et al., 2004). Irrespective of this difficulty, other fMRI studies signify that the amygdala is one among a set of modulatory regions (e.g., vmPFC, thalamus, hypothalamus), influencing but not uniquely generating skin conductance responding (Frederikson et al., 1998; Critchley et al., 2001, 2002; Nagai et al., 2004). Although skin conductance responding is traditionally considered to reflect the emotional expression of fear conditioning, several findings also suggest that SCR primarily reflects the anticipation of threat (Bechara et al., 1996; Critchley et al., 2000; Weike et al., 2007). In the present thesis, the SCR indeed closely mirrored the US expectancy ratings, whereas the startle fear responding strongly diverged from the electrodermal activity, a finding in line with several other studies on human fear conditioning (Hamm & Vaitl, 1996; Hamm & Weike, 2005; Weike et al., 2007). These data thus demonstrated that memories may undergo reconsolidation at one level (i.e., amygdalar fear memory), while leaving the anticipation of threat untouched, both at a cognitive (i.e., US expectancy ratings) and a physiological level (i.e., skin conductance discrimination) (i.e., Chapters 2, 3, 4, 6, and 7). Apparently, the processes of reconsolidation for the various expressions of a single learned fear association do not necessarily act in concert.

It should be noted that these findings do not imply that reconsolidation is restricted to the emotional expression of fear memory (i.e., startle fear responding, subjective feelings of distress). In principle, all memory systems should be subject to disrupting reconsolidation given the appropriate situations (Lee, 2009). Indeed, post-retrieval lability has been found with numerous memory tasks including declarative memory in humans (Hupbach et al., 2007; Forcato et al., 2007, 2009; Strange et al., 2010). However, reconsolidation may be viewed as a fundamental process in the ongoing modification and storage of memories, which seems potentially adaptive in terms of maintaining a memory’s relevance in guiding future behavior (Dudai, 2006; Lee, 2009). As a result, labilization and reconsolidation do not necessarily occur when a memory is being reactivated, but only when there is something to be learned during retrieval (i.e., ‘informational
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value’) (Pedreira et al., 2004; Forcato et al., 2009; Lee, 2009; Sevenster et al., Unpublished Data). A violation based upon prior learning is supposed to be a necessary condition for reconsolidation, meaning that the magnitude of the outcome or the outcome itself is not being fully predicted (i.e., ‘prediction error’) (Pedreira et al., 2004; Forcato et al., 2009; Lee, 2009). In the present thesis, the partial reinforcement scheme during acquisition may therefore have prevented the single unreinforced reactivation trial from memory updating at the ‘propositional’ level (i.e., Chapters 2, 3, 4, and 6). Recently, a behavioral approach targeting the reconsolidation of fear memory in fact demonstrated that multiple unreinforced presentations allowed for the updating of threat anticipation in humans (Schiller et al., 2010). That is, an extinction procedure performed within the window of reconsolidation resulted in the persistent erasure of skin conductance discrimination. Even though animal studies showed a destabilization of the fear memory trace in the lateral amygdala by behaviorally disrupting reconsolidation (Monfils et al., 2009; Clem & Huganir, 2010), the effects on the emotional expression of fear memory in humans remained unknown. Given that a behavioral procedure is obviously preferred over pharmacological manipulations, we tested in Chapter 4 (i.e., Experiment II) whether the behavioral disruption of reconsolidation would not only affect skin conductance responding but also the US expectancy ratings as well as startle fear responding.

Overall, the findings from Experiment II, Chapter 4 stand in sharp contrast to those reported by Schiller et al. (2010). That is, we did not observe any effects of the behavioral procedure presented within the reconsolidation window on conditioned (fear) responding (i.e., Chapter 4; Kindt & Soeter, 2011). Animal studies show that subtle procedural variations may render reconsolidation procedures unsuccessful in generating fear erasing effects (e.g., Nader, 2003; Chan et al., 2010). There are indeed a number of procedural differences that may explain why the behavioral procedure (i.e., ‘extinction learning’) did not allow for the updating of fear memory in our studies (i.e., Chapter 4; Kindt & Soeter, 2011). Thus, even though disrupting reconsolidation may point to a promising strategy in the permanent reduction of fear, subtle procedural differences seem to be crucial for the phenomenon. Specifically, whether a retrieval trial triggers reconsolidation appears to depend on a complex interaction between initial learning and the available information at the time of memory retrieval (i.e., ‘prediction error’) (Lee et al., 2006, Lee, 2009). This may also explain why we did not observe any fear
reducing effects on the *subjective feelings of anxiety* in Chapter 4 of this thesis. That is, as the repeated pairing of the CS with the ‘experience’ of a relatively mild noxious event (e.g., electric stimulus) makes the aversiveness of the US very ‘predictable’, the traditional human fear conditioning paradigm in Chapter 4 may not have been suitable for targeting the *subjective component* of fear memory (i.e., Chapter 4). In Chapter 7, when the aversiveness of the US was anticipated but never actually experienced (i.e., instructed fear learning), the β-adrenergic blocker during reconsolidation in fact strongly diminished the previously acquired *subjective feelings of anxiety*. Although these findings may thus stress the role of a ‘prediction error’ in transforming fear memories from a fixed state to one that is amenable to change (Lee, 2009), we cannot be certain what caused the attenuation of the *subjective feelings of anxiety* in Chapter 7. First, we also modified the ‘online distress ratings’ itself in Chapter 7 relative to Chapter 4 by adding a body chart in order to focus the participants’ attention on their bodily sensations of distress. Second, in Chapter 7, we further disentangled the subjective distress from the expectancy of the US by explaining that the mere expectation of the electric stimulus could, but did not necessarily have to cause feelings of distress. Nevertheless, the point to be made is that the mere retrieval of a fear memory is not sufficient for inducing reconsolidation. A better understanding of the necessary conditions for labilization and reconsolidation is critical if we are to target reconsolidation in patients suffering from anxiety disorders. Yet, under the ‘appropriate’ conditions, targeting the process of reconsolidation allows for the *permanent* attenuation of the emotional expression of fear memories in humans (i.e., startle fear responding, *subjective feelings of anxiety*) (i.e., Chapter 7).

**Limitations of the Present Thesis**

The findings of the present thesis should be interpreted with, at least, the following limitations in mind. First, we only collected behavioral data in this thesis (i.e., on a subjective and physiological level). Although behavioral effects can provide insights into the mechanisms of learning and memory, they do not unveil the underlying neurobiological mechanisms. We could therefore only speculate on how ‘noradrenaline’ affects the ‘formation’, ‘reconsolidation’ as well as ‘generalization’ of human fear memory. A second limitation of this thesis is that
the retrieval techniques (i.e., ‘reinstatement’, ‘spontaneous recovery’, ‘renewal’, and ‘reacquisition’) were all implemented following fear extinction (i.e., day 3). As a result, we cannot be certain whether the absence of a return of fear in the propranolol HCl conditions (i.e., Chapters 2, 3, 4, 6, and 7) was exclusively due to targeting the process of reconsolidation or to the combination with fear extinction (i.e., day 3). Yet, given that we could not observe a behavioral effect of extinction learning as the startle fear responding was already eliminated on the first trials of the extinction procedure (i.e., Chapters 2, 3, 4, 6, and 7), it may be suggested that extinction learning did not play a role in preventing the return of fear in the propranolol HCl groups. Obviously, future research should test whether the administration of retrieval techniques without fear extinction also prevents the return of fear (i.e., day 3). A third limitation of the present thesis has to do with the time elapsed between extinction learning and the retrieval techniques that we used (i.e., ‘reinstatement’, ‘spontaneous recovery’, ‘renewal’, and ‘reacquisition’). As mentioned above, the retrieval techniques were all implemented directly following fear extinction. Hence, there was no ‘consolidation’ of the extinction memory, which requires - just like consolidation processes in general - an extended period to be completed (Dudai, 2004). In the placebo pill groups (i.e., Chapters 2, 3, 6, and 7), the newly formed extinction memory may therefore have been ‘better’ in inhibiting the original fear association if we had inserted the retrieval techniques for instance 24 hr after extinction learning. Note, however, that in Chapter 4, Experiment II, the extinction learning on day 2 did not prevent the return of fear 24 hr later. Other limitations of the present thesis, including the ‘simple’ nature of the fear association (i.e., CS-US), the ‘strength’ as well as the ‘age’ of the fear memory and the ‘population’ that was under investigation, will be discussed in more detail in the section on clinical implications.

Clinical Implications, Future Research and Concluding Remarks

Anxiety disorders are thought to originate from a learned association between a previously neutral or ambiguous event (i.e., CS) and an anticipated disaster (i.e., US). In the present thesis, we demonstrated that disrupting reconsolidation allows for the modification of this underlying fear association (i.e., CS-US), which not only results in a permanent reduction of fear but also undermines the generalization of fear responding, a main characteristic of anxiety
disorders. Considering that traditional extinction learning leaves the original fear memory intact, as is substantiated by the high percentages of relapse after apparently successful treatment (Craske, 1999), disrupting reconsolidation may have important implications for the treatment of anxiety disorders such as phobias and posttraumatic stress disorder. Furthermore, targeting the process of reconsolidation may also be a successful treatment strategy for other psychiatric disorders such as substance abuse (Lee et al., 2005, 2006; Taylor et al., 2009), given that drug-associated cues are known to be a major cause of relapse to addictive behavior (Taylor et al., 2009).

In considering clinical implications, there are, however, several issues that need to be addressed. First of all, given that the present studies were only conducted in healthy participants, we do not know whether disrupting reconsolidation will be as effective in patient populations. Individual differences in for instance temperament are known to play an important role in the aetiology of anxiety disorders (e.g., Mineka & Zinbarg, 2006). Such vulnerability traits may also be a determining factor in the effectiveness of disrupting reconsolidation. Furthermore, as mentioned above, there are a number of experimental conditions under which reconsolidation does not seem to occur, such as the ‘strength of training’ and ‘memory age’ (Suzuki et al., 2004; Wang et al., 2009). Even though stimulation of the noradrenergic system during memory formation did not act as a ‘boundary condition’ on reconsolidation (i.e., Chapter 6), a crucial question is whether ‘strong’ and ‘old’ memories in patients with anxiety disorders will also be sensitive to disrupting reconsolidation. For now, preliminary evidence in trauma patients showing reduced trauma-relevant physiological responding is promising (Brunet et al., 2008). Second, the experimental paradigm in the present thesis (i.e., fear conditioning) only allowed for investigating ‘simple’ fear associations in which a stimulus was related to a single aversive event (i.e., CS-US). However, traumatic events are thought to result into especially large and complex associative fear networks (Foa & Kozak, 1986; Foa et al., 1989), such that activation of one element of the network leads to activation of related elements (Anderson & Bower, 1974). In this thesis, we demonstrated that the fear erasing effects following reconsolidation blockade spread to information from the same category that was not previously associated with the originally feared stimulus (i.e., Chapters 4 and 6). Moreover, in rats, it has already been demonstrated that higher-order (i.e., associated) memories undergo reconsolidation when reactivated by the primary
(i.e., first-order) fear association (Dębiec et al., 2006). Nevertheless, whether disrupting reconsolidation does alter the entire network of associative fear memories currently remains unknown. germane to this issue is whether reactivation of more abstract but related information will also render the primary (i.e., first-order) fear association sensitive to disruption. Here, we only demonstrated the effects of disrupting reconsolidation by reactivating the ‘core’ fear association (i.e., CS1-US). However, this ‘core’ fear memory may be difficult to uncover in clinical practice.

A further consideration for clinical implications is that the specific reactivation conditions to transform fear memories from a fixed state to one that is amenable to change seem to differ for the various aspects of fear memories. In the present thesis, the reactivation conditions allowed for the updating of the emotional expression of fear (i.e., startle fear responding, subjective feelings of anxiety) (i.e., Chapter 7). On the other hand, given that there was nothing to be learned about the ‘contingency’ at the time of memory retrieval, the propranolol HCl manipulation did not affect the anticipation of threat (i.e., skin conductance responding, US expectancy ratings). Since anxiety disorders may be characterized by irrational beliefs, such as an overestimation of danger, it can also be desirable to affect the anticipation of threat. Even though all memory aspects should be subject to disrupting reconsolidation (Lee, 2009), an understanding of the optimal conditions for updating the different aspects of fear memory is critical if we are to consider reconsolidation blockade as a novel therapeutic strategy for treating people suffering from emotional disorders.

Another thought for the application of reconsolidation in clinical practice is the differentiation between reconsolidation and extinction (Eisenberg et al., 2003; Pedreira & Maldonado, 2003; Suzuki et al., 2004). That is, if repetitive or prolonged retrieval of an acquired fear memory promotes the formation of a novel extinction memory trace, pharmacological manipulations intended to impair reconsolidation may instead or additionally interfere with the consolidation of fear extinction (Ouyang & Thomas, 2005; Mueller et al., 2008; Bos et al., Unpublished Data). Thus, to the degree that reconsolidation procedures generate extinction learning, β-adrenergic interference may be counterproductive. If we are to target reconsolidation with pharmacological agents, careful selection of the timing parameters is crucial in ensuring that extinction learning does not occur. Although the propranolol HCl manipulation can be administered ‘after’ reactivation of the
memory (i.e., Chapter 6), it should be noted that the demarcation between reactivation and extinction is less controllable in clinical practice than in the experimental setting.

Finally, behavioral procedures are evidently preferred over drug manipulations provided that similar effects can be obtained. Even though in Chapter 4 the behavioral procedure (i.e., fear extinction) did not allow for the updating of a relatively strong fear memory, it would be interesting to know whether other behavioral approaches targeting the process of reconsolidation will be effective in weakening the original fear memory. Indeed, some cognitive behavioral interventions (e.g., behavioral experiments or rescripting) may already capitalize on disrupting reconsolidation of the underlying fear memories. Although restrictive in itself, translational research may contribute to unravel the optimal and boundary conditions for updating fear memory through behavioral manipulations.

In sum, we demonstrated that a permanent reduction of fear can be realized through targeting the process of reconsolidation. Of course, experimental models of human fear (i.e., Pavlovian fear conditioning) are an oversimplification of the complexity of pathological fear and its related disorders. At the same time, Pavlovian fear conditioning is an excellent model to unravel the processes and mechanisms underlying human fear memory, which may eventually culminate in strategies to improve the effectiveness of therapies for anxiety 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 and other psychiatric disorders.

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