Fear memory uncovered: Prediction error as the key to memory plasticity
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Chapter 7

General Discussion
To gain insights in the fundamentals of learning and memory and to provide a basis for the development of reconsolidation-based therapy, the current thesis investigated whether the function of reconsolidation of human fear memory is to enable memory updating. Extensive evidence indicated that consolidation mechanisms ensure memory stabilization. However, the mechanisms that underlie the flexible nature of memory are relatively unknown. It is now increasingly acknowledged that memory regains plasticity through the process of reconsolidation. In a series of human fear conditioning experiments we tested whether memory reconsolidation could be identified as an updating mechanism. Additionally, we further investigated the dissociation between the emotional and cognitive components of fear memory expression, as disruption of reconsolidation proved to affect the former but not the latter.

Cognitive and emotional expression of fear learning and memory

Previous studies from our lab demonstrated differential effects of reconsolidation disruption on long-term expression of the startle response on the one hand and US-expectancy ratings and SCR on the other hand (Kindt et al., 2009; Soeter & Kindt, 2010, 2011b, 2011c). Therefore, we aimed to further investigate the different response systems that are involved in fear learning. There is an on-going debate whether cognitive and emotional learning stem from either one common underlying mechanism (single process) or are the results of at least two separate learning systems (dual process). In a replication study (Schultz & Helmstetter, 2010), we presented participants with conditioned stimuli that were either easy or difficult to discriminate (Chapter 2). We found that unaware participants did not show electrodermal conditioning. While contingency awareness was required for electrodermal conditioning, startle conditioning took place in absence of contingency knowledge. The next study (Chapter 3) confirmed previous observations (Chapter 2; Kindt et al., 2009; Soeter & Kindt, 2010, 2011b, 2011c) that the startle response is a specific measure for fear whereas US-expectancy ratings and SCR reflect the predominantly cognitive component of fear memory expression. We found that one day after fear acquisition the simple instruction that the pictures will no longer be followed by the shock completely eliminated both differential US-expectancy ratings and SCR (Chapter 3). The startle reflex, however, remained differentially potentiated at the beginning of extinction. Also, while the instruction prevented reinstatement of both US-expectancy ratings and SCR, return of differential startle responding was observed, in spite of the declarative
knowledge that the pictures would not be reinforced. These findings confirmed the dual process account of fear learning by showing that a cognitive manipulation affects the US-expectancy ratings and SCR while the startle response acts relatively independent from knowledge about the contingencies.

In conclusion, Chapters 2 and 3 support the dual process account of fear learning. Manipulations that influence contingency knowledge showed that the cognitive and emotional component of fear can dissociate, suggesting that at least two learning systems are involved in fear learning. In participants who either were unaware during fear acquisition or received a safety instruction on the CS-US contingencies before extinction, the startle response diverged from the US-expectancies. However, SCR demonstrated a responding pattern very similar to the US-expectancies. In line with previous research (LeDoux, 2000), this suggested that the startle response is indicative of affective learning and expression, while SCR is a non-specific arousal measure mediated by cognitive learning.

**PE-driven learning and memory plasticity**

Chapter 4 describes the first study in a series of experiments on the functional mechanisms of memory reconsolidation. In line with previous studies from our lab (Kindt et al., 2009; Soeter & Kindt, 2010, 2011b, 2011c, 2012), we found that propranolol, contrary to placebo, reduced long term emotional responding (startle response). We showed that propranolol did not have any fear reducing effect when the US-electrodes were not attached to the wrist during memory reactivation. Thus, when we prevented new learning during memory reactivation, memory was not destabilized and propranolol could therefore not interfere with the reconsolidation of the fear memory. These findings point towards a role of prediction error (PE) — the discrepancy between expectations based on previous learning and the actual events — in reconsolidation. If reconsolidation indeed underlies the adaptive function of integrating new learning in an established memory trace, PE would be the ultimate candidate to regulate memory updating. However, with the experimental design used in the study that is described in Chapter 4 we could not directly test whether PE-driven learning induced memory destabilization. As the startle fear potentiation was similar in both conditions, memory destabilization could not be inferred from the fear memory expression itself. Only from the observation of reconsolidation (i.e., reduced fear responding one day later), it was inferred that new learning must have been present during memory reactivation. As discussed in the introduction, to derive the role of PE in
memory destabilization from effective reconsolidation poses a problem for empirical falsifiability.

The aim of next study (Chapter 5) was to provide a measure of PE driven learning that is independent from the observation of reconsolidation itself. From previous studies we know that propranolol does not affect the cognitive component of fear learning (Kindt et al., 2009; Soeter & Kindt, 2010, 2011b, 2011c, 2012). Importantly, in Chapters 2 and 3 we confirmed that cognitive (US-expectancy) and emotional responding (startle response) stem from separate underlying mechanisms. As a result, we were able to use the online US-expectancy ratings as a measure of PE-driven learning during reactivation. We designed the acquisition and reactivation procedures in such a way that there was a negative PE (absence of reinforcement), a positive PE (unexpected reinforcement) or no PE (expected reinforcement) during memory retrieval. We observed PE driven learning only in the Negative and Positive PE groups, operationalized as a decrease and an increase respectively in US-expectancy ratings from the end of acquisition to the beginning of extinction on day 3. Learning did not take place in the no PE group, evidenced by no change in US-expectancy ratings. We then observed that propranolol administration after memory reactivation eliminated long-term startle responding only in case PE-driven learning had been present during memory retrieval. In sum, using an index, independent from memory destabilization, we demonstrated that reconsolidation requires PE-driven learning.

In the study described in Chapter 5 we did not take into account that the presentation of new information can also bring about too much new learning, resulting in the formation of an additional memory trace (e.g., extinction learning). Importantly, not only reconsolidation but also extinction learning depends on PE (Rescorla & Wagner, 1972). Extinction training involves the repeated absence of reinforcement, resulting in multiple PEs. Thus, while PE is necessary for reconsolidation, too much PE driven new learning might be counter effective. We know from previous studies that extensive extinction training prevents reconsolidation (Bos et al., 2012; Eisenberg et al., 2003; Lee et al., 2006). However, the transition from reconsolidation to extinction might take place long before the fear expression subsides. If we are to use disruption of reconsolidation as a therapeutic strategy, it is crucial to know when the system decides that new information is different but similar enough to update the original memory, or that the new information is too different from original learning and should be consolidated as a separate entity. In the next study (Chapter 6) we aimed to
investigate the transition from memory updating to new learning. Due to a 50% reinforcement scheme during acquisition, a single unreinforced reminder trial did not generate any new learning and the memory remained intact in spite of propranolol administration. Two unreinforced retrieval trials, however, resulted in a PE and propranolol disrupted the long-term startle fear response. If presentation of unreinforced reminder trials was continued up to four trials, new learning took place, evidenced by a decrease in US-expectancy ratings, whereas the fear response was not yet reduced. We observed that propranolol was no longer effective in reducing the long-term startle response when administered after memory reactivation with four trials. Thus, we show that mismatch decisions result in abrupt transitions from mere memory retrieval, to reconsolidation, to new additional learning. In sum, the three experiments on the functional mechanism of reconsolidation show that memory destabilization indeed depends on PE. The process of reconsolidation is robust, given that studies from our and other labs repeatedly showed the strong effect of reconsolidation disruption on fear memory expression. At the same time, reconsolidation is a subtle process, since it is constrained by the absence and repetition of PE. Small changes such as prolonging stimulus duration or increasing the number of retrieval trials can tip the balance in favour of additional new learning instead of memory updating. Reconsolidation is limited to retrieval conditions that contain PE-driven learning, while absence or repeated PE’s puts a constraint on reconsolidation.

**Pharmacological and cognitive manipulations**
In line with previous studies (Kindt et al., 2009; Soeter & Kindt, 2010), we repeatedly showed that propranolol administration in combination with memory reactivation leaves the long term cognitive but not the emotional expression of fear memory (US-expectancy and SCR) intact (Chapters 4, 5, 6). Additionally, we found a double dissociation between the declarative and emotional expression of the memory (Chapter 4). First, similar to the findings in Chapter 3, we observed potentiation of the startle reflex in response to the feared stimulus, in absence of any threat expectancy and SCR. Second, we found elimination of the startle response in spite of threat expectation and differential SCR on day 3. Thus, a cognitive manipulation affected both US-expectancy ratings and SCR but not the startle fear response. Pharmacological manipulation had the opposite effect, leaving US-expectancy ratings and SCR unaffected but reducing the startle response.
Hence, we showed that the cognitive component could be targeted by cognitive manipulations while the emotional component of fear memory is sensitive to pharmacological treatment. In contrast, a previous study from our lab demonstrated an effect of pharmacological manipulation on declarative memory. In that study propranolol was administered before 12 unreinforced reminder trials and did actually impede extinction learning of US-expectancy ratings but not the startle response. This effect persisted one day later on both the extinction retention and reinstatement test (Bos et al., 2012). They observed the direct and delayed effects of propranolol on US-expectancy ratings not on the first trials of extinction and re-extinction but only after multiple unreinforced reminder presentations. Possibly, extensive extinction training, as opposed to the relatively short unreinforced retrieval procedure in our study (4 trials), is responsible for the noradrenergic effect on threat expectancies. Though it is an important observation that propranolol administered before memory reactivation can affect the online expression of threat expectancies, if we aim to use propranolol as a therapeutic drug, it should not interfere with online threat expectancy, since the US-expectancy ratings can guide when the fear memory is open to modification or whether extinction learning is initiated during memory reactivation.

While the four unreinforced reminder trials were sufficient to establish a decrease in US-expectancy ratings, a similar pattern was not observed for the startle response, which remained stable over the course of the 4 unreinforced trials (Chapter 6). Similarly, the startle fear response was potentiated in response to the reminder stimulus (Chapters 4, 5, 6), irrespective of whether reconsolidation was triggered. Hence, the affective expression of fear is not a suitable index of the underlying process that is ultimately engaged by memory reactivation. The mechanisms that generate the fear expression are independent from the mechanisms that underlie memory destabilization (see also Mamou et al., 2006).

It is remarkable that propranolol never interfered with the reconsolidation of declarative memory. This is beneficial from a clinical point of view, since this dissociation provides the possibility to target the emotional impact but not the recollection of the trauma. From a fundamental perspective on memory, the differential effect of propranolol on the response systems raises questions about retrieval-induced plasticity. Theoretically, reconsolidation is a universal property of memory and thus every memory should be able to reconsolidate, provided that the memory is updated. Then, why does a reactivation procedure that is effective in destabilizing the emotional component of fear learning not have the same
effect on declarative memory? The notion that declarative knowledge and affective responding rely on different neural mechanisms might account for the differential effects of propranolol. While declarative memory relies on the hippocampal complex, the amygdala and subcortical areas subserve affective responding (LeDoux, 2000). It is known that the layout of the hippocampus results in reduced interference between hippocampal memory traces (McClelland & Goddard, 1996; O’Reilly & Rudy, 2001). The dentate gyrus and the CA3 region allow for orthogonal encoding of memory representations (pattern separation), even in the case of minimal differences between inputs (Leutgeb & Leutgeb, 2007; Leutgeb, Leutgeb, Moser, & Moser, 2007; Wills, Lever, Cacucci, Burgess, & O’Keefe, 2005). Hence, while the system underlying affective responding is probably not equipped with mechanisms to reduce overlap of representations, the hippocampal structure promotes formation of discrete representations.

Note that while our results suggest that it is difficult to destabilize simple factual memories, reconsolidation of declarative memory for word pairs and objects has been observed in humans (Coccoz, Maldonado, & Delorenzi, 2011; Forcato et al., 2009; Forcato et al., 2007; Hupbach, Gomez, Hardt, & Nadel, 2007). For example, in these tasks participants learn word-pair associations (cue-response). One day later, memory is reactivated by presenting one of the cues followed by the learning of a new list of word-pair associations. Learning the new list on day 2 is supposed to interfere with the reactivated memory, resulting in memory impairment on testing one day later day (Forcato et al., 2009, 2010; Forcato et al., 2007). Learning demands are much higher in these studies than in our conditioning studies, during which participants are only required to learn two simple associations between pictures and (absence of) shock. It is assumed that explicit memories always include both a hippocampal and neocortical component (Hardt, Nader, & Nadel, 2013). Presumably, the high task demands in the declarative memory studies require more involvement of extra-hippocampal areas than in our studies. The more dependent on the extra-hippocampal areas, the more new learning will interfere with the reactivated memory (Hardt et al., 2013).

An interesting feature of these studies on reconsolidation of declarative memory is the memory reactivation procedure (Coccoz et al., 2011; Forcato et al., 2009; Forcato et al., 2007; Hupbach et al., 2007). In general, the memory reactivation trial (i.e., presenting a cue of the previously learned word-pair associations) is abruptly and unexpectedly ended and the participants are not
allowed to report the associated response. It has been demonstrated that this mismatch between expectations (reporting the response) and real events (interruption of the trial) is required in order to interfere with the original memory (Forcato et al., 2009). Note that this reactivation procedure involves an instrumental prediction error (i.e., unexpected absence of reporting the response). Schultz and Dickinson (2000) pose that prediction error applies not only to Pavlovian but also to instrumental conditioning. During instrumental learning an individual's behaviour is modified by its consequences. A behavioural reaction is executed in the expectation of a certain outcome and a prediction error then takes place when the actual and predicted outcomes differ. Although the response behaviour in the human declarative memory studies is not instrumental conditioning in the strict sense (i.e., there is no direct consequence related to the response), these studies could be an indication that CS-US associations (or at least word-pair associations) can be targeted through reactivation of an instrumental association.

On Prediction Error
As stated in the introduction, a balance between memory stability and plasticity is essential for adaptive responding. A longstanding view on memory consolidation is that it ensures memory stability, but the hypothesis that reconsolidation accounts for memory plasticity was formulated only recently. With the demonstration that new learning is a prerequisite for reconsolidation (Chapters 4, 5, 6), we confirm that memory destabilization allows for the integration of new information in the existing memory trace. Note that it is often suggested that the function of reconsolidation is two-fold: either to update or to strengthen an existing memory trace. However, the two processes are certainly not mutually exclusive, since memory strengthening can be considered as a form of memory updating. After a short conditioning procedure, an additional reinforced trial one day later contains new information about the CS-US contingencies since asymptotic levels of learning are not reached (Chapter 5; Lee, 2008). This new information is integrated in the previously acquired memory trace, resulting in memory strengthening.

Given that PE plays an essential role in reconsolidation, we should consider the learning history when choosing a retrieval procedure. That is, a particular reactivation protocol might destabilize memory trace X but might install extinction learning in addition to memory trace Y. For example, the results in Chapter 5 show that a reinforced reactivation trial leaves the original memory
intact in case of asymptotic learning, but destabilizes the memory when previous learning was non-asymptotic. Similarly, following fully reinforced fear learning (100%) a single unreinforced reminder trial was sufficient to trigger PE and memory destabilization (Chapter 5), whereas such an effect was not observed in case of a partially reinforced (50%) acquisition (Chapter 6). While two unreinforced trials destabilized a memory acquired with a 50% reinforcement rate, it might have resulted in extinction learning in addition to a fully reinforced memory. Thus, the outcome of memory reactivation strongly depends on its interaction with the learning history. This stresses the importance of an independent index that indicates whether retrieval results in memory destabilization.

While it is often assumed that acquisition and extinction learning depend on PE (Rescorla & Wagner, 1972), it seems that the startle response proves an exception to this rule. While contingency learning was required for acquisition of differential US-expectancy ratings and SCR (Chapter 2), acquisition of the startle response could be established in absence of PE. The startle response is an expression of valence (Bradley & Vrana, 1993; Lang, 1995) and, apparently, valence of the US can transfer automatically to the CS, even when participants are unaware of the contingencies (Chapter 2). Note that this unaware acquisition effect is no longer observed on a subsequent post-conditioning test (Weike et al., 2007). Thus, a defensive reflex is produced irrespective of the capability to relate threat to a stimulus in the environment but takes place only in case of imminent threat. The role of PE in startle extinction remains unclear. In contrast to expectancy and SCR, a verbally conveyed PE was not sufficient to extinguish the startle response (Chapter 3). Instead, startle extinction required the actual experience of unreinforced CS presentations.

The studies on reconsolidation in the present thesis (Chapters 4, 5, 6) suggested that both cognitive and experience-based learning are required for memory destabilization. Cognitive knowledge without the experience that the CS will not be followed by the US during reactivation did not induce reconsolidation (Chapter 4). Given the crucial role of PE-driven learning in memory destabilization it seems unlikely that propranolol-induced disruption of the startle fear response can be established with CS presentations that lack cognitive learning. Nevertheless, we did not test whether, similar to acquisition learning, memory can be destabilized by a reactivation trial that contains experience-dependent but not cognitive learning. A speculative hypothesis would be that in contrast to extinction learning, memory destabilization could occur without cognitive
knowledge as long as the reminder trial contains experience based new learning. From an evolutionary point of view it is adaptive that fear acquisition is easily acquired while the system is conservative about new inhibitory learning (extinction). For example, while fear responses easily generalize to different contexts after acquisition, extinction learning is much more context specific (Bouton & Bolles, 1979; Bouton, 2002). Also, acquisition requires subcortical brain areas (LeDoux, 2000), whereas extinction learning additionally involves the ventromedial prefrontal cortex (Herry & Garcia, 2002; Morgan et al., 1993). Thus, given the adaptive constraints and involvement of cortical areas, establishing an extinction circuit might require cognitive learning, in addition to experience-based learning. Since reconsolidation concerns updating of the original memory, the conditions that apply to acquisition could also be valid for reconsolidation.

Note that in previous reconsolidation studies (Kindt et al., 2009; Soeter & Kindt, 2010, 2011b, 2011c, 2012) and the study described in Chapter 4, memory destabilization was triggered in absence of a statistically significant change in US-expectancy ratings. In the studies in which cognitive learning did take place during memory reactivation (Chapters 5 and 6), we designed the acquisition and reactivation procedure in such a way that cognitive learning could clearly be observed. For example, in case of fully reinforced acquisition it was even pointed out to the participants which picture would be followed by a shock and which picture was safe (Chapter 5). Consequently, an unreinforced reactivation trial produced significant and observable cognitive learning. However, absence of a significant change in threat expectancy does not automatically mean that cognitive learning did not have a role in memory updating. In contrast to the significant change induced by an unreinforced trial following fully reinforced asymptotic learning, a similar reminder trial does not generate this effect on the expectancy ratings in the case of partial reinforced non-asymptotic learning, while this does not preclude a memory destabilization. Supposedly, a small (statistically non-significant) change in threat expectancy might already be enough to induce memory destabilization.

**Pattern completion and pattern separation**

Computational models suggest that memory relies on both the ability to complete partial or similar patterns of activity into a single common representation (pattern completion) and the ability to separate overlapping patterns of activation in distinct representations (pattern separation) (Blumenfeld, Preminger, Sagi, &
The hippocampal CA1 region has been proposed as a key structure in assessing whether the current sensory input that arrives directly from the cortex matches with the internal memory representation projected from the CA3 region (Lisman & Grace, 2005; Vinogradova, 2001). Thus, CA1 functions as a ‘comparator’, assessing whether current sensory input (representation of the reactivation session) matches or mismatches expectation derived from previous experiences (representation of the original fear memory trace). Small differences between representations will be compensated and incorporated in the original representation resulting in memory updating. Since memory updating depends on mismatch learning, it is surprising that little attention has been paid to how the concept of pattern completion relates to the phenomenon of reconsolidation. The process of reconsolidation could underlie the ability to ‘clean up’ similar representations in one single pattern. Up to some point the system accepts mismatches between the inputs as reflecting nothing more than variations of a single representation. Beyond that point, the expectations and current events differ to such a degree that it renders pattern completion impossible and memory updating does not occur. An additional new representation is formed instead and thus pattern separation could be fundamental to the realization of extinction memory. The dentate gyrus, together with the CA3 region, is supposed to underlie the orthogonalization of representations (Leutgeb & Leutgeb, 2007; Leutgeb et al., 2007). Crucially, this suggests that changes in sensory input can trigger sudden transitions from mere memory retrieval, to updating, to formation of a new memory. In Chapters 5 and 6 we provided evidence that small alterations in the fear memory retrieval procedure can have major effects on memory and subsequent behaviour. It would be very exciting to further investigate the neurobiological mechanisms underlying memory updating and new learning.

Future research
In addition to the unresolved questions that arose in the previous sections, several directions for future research with particular interest to the field of reconsolidation will be considered. The first issue concerns the molecular mechanisms of memory destabilization and extinction. Reconsolidation and extinction learning have often been considered as competing processes during memory retrieval and to be mutually exclusive (trace dominance) (Eisenberg et al., 2003). However, in our study (Chapter 6) we could not rule out that the 4 trial memory reactivation
procedure, which prevented reconsolidation, did not initially engage reconsolidation. It would therefore be crucial to be able to dissociate reconsolidation from extinction learning on the molecular level. For example, it would be very interesting to determine whether reconsolidation is immediately triggered by the second unreinforced reminder trial (Chapter 6) but later suppressed when PE reduces. Inhibition of reconsolidation by new learning might involve the suppression of transcription nuclear factor-κB (NF-κB) (de la Fuente, Freudenthal, & Romano, 2011; Merlo, Freudenthal, Maldonado, & Romano, 2005; Merlo & Romano, 2008). In a contextual fear paradigm it was shown that short context re-exposure enhances expression of NF-κB, which is essential for induction of reconsolidation. In case of longer context exposure NF-κB activation, measured at various time points during and after re-exposure, was blocked by the phosphatase calcineurin (CaN) that is essential for extinction. Importantly, during prolonged exposure no significant increase in NF-κB activity was observed on the time point that coincides with a peak of NF-κB activity during the short reactivation procedure (de la Fuente et al., 2011). Note that most studies on the differential mechanisms underlying reconsolidation and extinction learning use single trial reactivation of either short or long duration, respectively. The results described above (de la Fuente et al., 2011) and others (Pedreira et al., 2004) suggest that either reconsolidation or extinction is triggered only upon CS termination. Thus, in case of a long single trial reactivation session reconsolidation could never be engaged and extinction consolidation starts only upon CS-offset. However, it is unknown whether during repeated short memory reactivation trials reconsolidation is initially engaged or not. Therefore, it would be interesting to investigate the molecular mechanisms in a multi trial reactivation procedure in a reversed translational study (i.e., from human to rodent) of the experiment described in Chapter 6. Hypothetically, termination of the second unreinforced reminder trial might trigger reconsolidation (increase in NF-κB), which is suppressed by CaN as the number of unreinforced trials increase.

The current thesis did not address individual differences in effective reconsolidation induction. Fear learning varies widely among individuals and, critically, only some individuals experience the excessive fear, worry and disruption to everyday function following trauma (Bishop, 2007). Similarly, realization of memory destabilization could differ considerably between individuals. Successful induction of reconsolidation may be associated with differences resulting from epigenetic alterations. Epigenetics refers to a functional change in gene
expression that can be induced by environmental events but does not involve an alteration of the underlying DNA sequence (Novik et al., 2002). Such mechanisms offer the possibility of defining concrete molecular pathways by which environmental factors might directly alter gene expression. Thus, hypotheses for individual differences relating to gene expression and, possibly, susceptibility to retrieval-induced plasticity can be formulated. For example, it has been suggested that early life stress results in long lasting epigenetic-mediated reduction of NMDA receptor subunits (Roceri, Hendriks, Racagni, Ellenbroek, & Riva, 2002). NMDA receptors are critically involved in the destabilization of a consolidated fear memory (Mamou et al., 2006). It could be speculated that trauma early in life has a detrimental effect on cellular plasticity, resulting in a reduced ability to destabilize memory. It would be very interesting to see whether such an epigenetic-mediated vulnerability to retrieval induced plasticity exists and whether pharmacological manipulation can reverse the inability to trigger reconsolidation.

Clinical implications

The demonstration that reconsolidation serves the crucial adaptive function of incorporating new information in an already established memory trace to keep memories up to date advances our understanding of the mechanisms that underlie memory reconsolidation. However, the simple fear association learned in a laboratory setting is not equivalent to the excessive emotional memory that comes with anxiety disorders. While it is believed that CS-US associations lie at the core of fear memory, traumatic memory is embedded in a network that is as complex as it is extensive. However, preliminary evidence in PTSD patients suggests that propranolol administered before or after reactivation of the traumatic memory decreased trauma related physiological responding (Brunet et al., 2008) and PTSD symptoms, with most patients no longer meeting diagnostic criteria for PTSD (Brunet et al., 2011). Although promising, these studies lacked the necessary control conditions to conclude that fear reduction was the result of reconsolidation blockade. That is, control conditions that received propranolol in the absence of traumatic memory reactivation were not included. Hence, non-specific effects of propranolol cannot be ruled out. Of great therapeutic promise is a recent pre-clinical trial with spider phobic individuals. Propranolol/placebo controlled administered after fear memory reactivation resulted in a dramatic drop of avoidance behaviour on later tests (Soeter & Kindt, in prep), while
propranolol in the absence of memory reactivation did not sort any fear reducing effects.

The current thesis stresses that the interaction between the learning history and memory reactivation plays a crucial role in memory destabilization. The learning history cannot be similarly controlled in clinical practice as we did in the experimental setting. Sometimes patients do not seem to have had any direct history of fear learning, since simply observing others behaving fearfully or experiencing a trauma can already result in the development of anxiety disorders (Mineka & Zinbarg, 2006). It can be questioned whether this poses a problem for clinical practice. A pre-reactivation baseline of threat expectancy might actually be unnecessary in the clinical setting. The excessive fear experienced by patients suffering from anxiety disorders makes high threat expectancies likely. Therefore, absence of the expected threat during exposure should trigger memory destabilization, which enables interference with the reconsolidation of the fear memory. But when these procedures are translated to clinical practice, it is very important to control the amount of exposure, since a slight reduction of threat expectancy during exposure might already prevent memory destabilization and render the memory insensitive to manipulation (Chapter 6).

Contextual influences may be critical in deciding whether new information during exposure destabilize the old memory trace or is stored as an additional memory trace. We hypothesize that in the experimental setting any event that occurs within an unfamiliar context will more rapidly be linked to this new context and not to the old one in which fear learning took place. This should especially be the case when threat expectancy is high; when the predicted outcome unexpectedly fails to occur this will be easily attributed to the new context. Similarly, the patient might ascribe the absence of the predicted feared event during exposure to the safe therapeutic context, which facilitates extinction learning over memory destabilization. Further research on the context influences on the outcome of memory retrieval is vital for the success of reconsolidation-based therapy.

Concluding remarks
Memory has such a significant and omnipresent role in our daily lives that we usually do not pay much attention to it. This changes dramatically when an experience is so dreadful that the memory of it haunts us. Indeed, patients suffering from anxiety often struggle with the excessive strength, persistence, and
inflexibility of the fear memory. According to the traditional view on memory there was little hope for patients whose fear memory had evolved in excessive anxiety, since it was believed that once a memory had been consolidated it remained as a permanent trace. The current thesis contributes evidence that fear memory is more dynamic than was previously believed. We show that prediction error during memory reactivation controls memory plasticity. Hence, the results presented here confirm the hypothesis that the functional nature of the phenomenon of reconsolidation is to keep memories up to date with new relevant information. The insights in memory updating provide an application of tremendous clinical importance. We showed that reconsolidation-mediated memory updating could be disrupted by noradrenergic β-blocker propranolol, eliminating the emotional component of fear learning while leaving the conscious recollection of the fear learning episode intact. We are just starting to unravel the mechanisms that underlie memory reconsolidation. Research on reconsolidation is done in multiple disciplines, ranging from the molecular to the behavioural level, to the development of a clinical application. An integration of these disciplines is essential to advance the understanding of the basic mechanisms underlying memory plasticity and the development of new tools for clinical practice.