



Fear Memory Uncovered: Prediction Error as the Key to Memory Plasticity
D. Sevenster

Summary

Anxiety disorders rank among the most prevalent and chronic forms of psychopathology. While commonly used therapeutic techniques, such as exposure therapy, are effective in reducing fear, there are high rates of relapse. Experimental models can account for the return of fear following initially successful fear reduction. During the repeated exposure to a feared object or situation a new inhibitory memory is formed that suppresses but leaves the original fear memory intact. The original fear memory is inhibited but not eliminated by the new exposure memory. Subsequently, when inhibition of the fear memory fails, fear will return.

According to the traditional view on memory, once an emotional memory has been stored in the brain through the process of consolidation, the memory remains as a permanent trace. However, exciting insights from neuroscience showed that through re-exposure, a consolidated fear memory can return to a plastic state. From this plastic state the memory has to reconsolidate in order to endure, depending on new protein synthesis. Spectacularly, blocking protein synthesis after memory retrieval in rodents disrupted the process of reconsolidation, resulting in fear amnesia. Also, the first series of studies on reconsolidation disruption in humans showed that the noradrenergic β -blocker propranolol could eliminate learned fear, while leaving the factual knowledge of the fear-learning event intact. Several well-known techniques were not capable of recovering the fear response, indicating a far more permanent elimination of fear than conventional fear-reducing techniques can establish. Thus, disrupting reconsolidation may offer the unique possibility to directly target the excessive emotional memory that comes with anxiety disorders.

Since its rediscovery in 2000, there has been a surge of interest in the phenomenon of reconsolidation. However, the conditions under which reconsolidation does and does not take place remain to be elucidated. It has been hypothesized that reconsolidation serves the adaptive function of updating the previously consolidated memories with new information. Yet, evidence for this hypothesis is rare in the animal literature and lacking when it comes to human fear memory. If we are to use disruption of reconsolidation as a therapeutic tool, it is crucial to gain further understanding of the conditions that allow and prevent reconsolidation. The aim of the current thesis was to unravel the mechanisms that determine whether memory reactivation effectively induces reconsolidation.

In order to investigate the mechanisms underlying fear learning we used the experimental model of Pavlovian conditioning. During a typical conditioning session used in the studies described in the current thesis, participants learned to associate an initially neutral conditioned stimulus (CS; a picture) with an intrinsically aversive consequence, the unconditioned stimulus (US; electrical stimulation). Another CS, the safe stimulus, was never paired with the aversive stimulus. At the end of the conditioning session participants demonstrated both heightened threat expectancy (i.e., expectation that the picture will be followed by the US) and fear-induced physiological responding (fear potentiated startle) for

the picture that was coupled with the electrical stimulation compared to the safe stimulus. In the studies on reconsolidation the memory was reactivated one day later by presentation of the picture that was previously followed by the aversive stimulus and propranolol or placebo was administered. On day 3 the effects of pill administration on the reactivated memory were tested. First, participants underwent an extinction procedure (i.e., repeated unreinforced presentation of the CS). Next, three unsignaled USs were presented, a well-known technique to recover the extinguished conditioned response.

Before addressing the functional role of reconsolidation we investigated the dissociation between threat expectancy and physiological fear responding in **Chapters 2 and 3**. Given that previous studies from our lab revealed differential effects of propranolol on threat expectancy and physiological fear responding, it is especially important to understand the response systems involved in fear learning. In **Chapter 2** we manipulated awareness of the CS-US contingencies by presenting difficult to discriminate conditioned stimuli to investigate whether fear responding can take place in unaware participants. Indeed, participants were unable to learn the relation between the CS and the US, but these unaware participants did develop a conditioned fear response. Next, in **Chapter 3** we investigated the effect of instructing the participants before extinction that the CS would no longer be followed by the US. This simple verbal instruction eliminated threat expectancy. In spite of the knowledge that the CS would not be reinforced, fear responding could still be observed. Also, while unsignaled presentation of the US did not recover threat expectation, the fear response did reinstate. Together, we demonstrated that being unaware of the contingencies or receiving a safety instruction dissociated threat expectancy and fear responding. Thus, these findings demonstrate that threat expectancy and physiological fear responding stem from different underlying response systems and can be differentially affected.

The functional mechanisms of reconsolidation were addressed in a series of experiments described in **Chapters 4, 5, and 6**. Learning theories pose that associative learning depends on prediction error (PE) – a discrepancy between expectation based on previous learning and actual events. If reconsolidation were to function as an update mechanism its induction should depend on PE-driven learning during memory reactivation. In **Chapter 4** we demonstrated that in absence of any learning during memory reactivation – by removing the US-electrodes – propranolol could not sort any effect. Thus, when participants were completely certain of the outcome of CS presentation, nothing could be learned and reconsolidation did not take place. However, while we showed that absence of learning prevented reconsolidation, it remained to be demonstrated that PE-driven learning was essential for memory destabilization.

In **Chapter 5** we established an index of PE. Previous studies from our lab already demonstrated that propranolol eliminates fearful responding but does not affect declarative memory. In **Chapters 2 and 3** we confirmed – that threat expectancy and fear responding stem from separate underlying mechanisms. Hence, we used the declarative knowledge

about the CS-US contingencies as a measure of PE-driven learning during memory reactivation. Propranolol eliminated the fear response only when the reactivation trial induced a change in threat expectancy from the end of acquisition to the beginning of extinction. In contrast, propranolol did not affect the fear response when threat expectancy remained stable. Thus, PE-driven learning – measured by means of changes in threat expectancy – proved essential for memory destabilization. However, while we demonstrated that PE was a necessary condition for reconsolidation to occur, it might not be sufficient, given that PE can also give rise to the formation of a new memory trace. For example, during extinction learning repeated unreinforced re-exposure (multiple PEs) eventually reduces both threat expectancy and fear responding. It has already been demonstrated that extinction prevents memory destabilisation. Nevertheless, the transition from updating of the original memory trace to the formation of a new extinction memory trace may occur long before the expression of the extinction memory (i.e., reduced fear responding) can be observed. In **Chapter 6** we investigated the transition from memory reconsolidation to extinction. Post-retrieval changes in threat expectancy as an index for PE served as a read-out for the underlying processes engaged by memory reactivation. Again, we demonstrated that PE was essential for triggering reconsolidation. However, multiple PEs reduced US-expectancy but not fear responding during memory reactivation and prevented reconsolidation. These findings suggest that a reduction in US-expectancy during memory retrieval may indicate the initiation of a new memory trace long before the fear expression itself diminishes.

Chapter 7 provides a discussion of the results and addresses limitations and future research. The studies described in the current thesis provided evidence that reconsolidation indeed enables the updating of a consolidated memory. The main conclusions that can be derived from the thesis were that 1) expression of learned contingencies and fear responding stem from separate underlying mechanisms, 2) PE-driven learning is a necessary but not a sufficient condition for memory reconsolidation to occur, 3) reconsolidation is preceded and followed by phases that prevent modification of the original memory trace and, 4) changes in threat expectancy but not fear responding can serve as a read-out for the underlying memory process that is ultimately engaged by reactivation. These findings are of relevance for the mechanisms underlying learning and memory by demonstrating the unique role reconsolidation holds in memory plasticity. Finally, clinical practice will hopefully benefit from these insights in the development of new reconsolidation-based therapies for those who suffer from anxiety disorders and PTSD.