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Current Opinion in Behavioral Sciences

Emotional memory expression is misleading: delineating transitions between memory processes

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The hypothesis that fear memory is not necessarily permanent but can change when retrieved opens avenues to develop revolutionary treatments for emotional memory disorders. Memory reconsolidation is however only one of several mnemonic processes that may be triggered by memory reactivation and subtle environmental differences may cause a transition from a malleable to a stable state. This poses a major challenge to translating the reconsolidation intervention to clinical practice. Here we review recent advances in understanding the transitions between memory processes in animals and humans, and discuss how the cognitive expression (i.e. threat expectancies) of fear memory in humans may serve as read-out to delineate the underlying processes necessary for memory reconsolidation, independent from the emotional expression of fear memory.

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Current Opinion in Behavioral Sciences 2018, **19**:116–122

This review comes from a themed issue on **Emotion–cognition interactions**

Edited by **Mara Mather** and **Michael Fanselow**

https://doi.org/10.1016/j.cobeha.2017.12.018

Introduction

For more than a century a widely accepted view in cognitive science was that memories are only initially labile and sensitive to disruption, after which they become imprinted or consolidated into the physical architecture of the brain. At the turn of this century, a major breakthrough in neuroscience was achieved with the (re) discovery that fear memory is not inevitably permanent, but can change when retrieved [1•,2]. Nader and colleagues [1•] demonstrated in rats that the administration of a protein synthesis blocker (i.e. anisomycin) upon memory reactivation eliminated the expression (i.e. freezing) of a previously formed fear memory. Further observations of post-reactivation amnesia have drastically changed the neuroscience literature on memory by generating a novel and influential conceptual framework — usually referred to as the *memory reconsolidation hypothesis*.

The reconsolidation hypothesis states that memory is an intrinsically dynamic process allowing modification of an established memory trace, should conditions require such adaptation [3]. Upon recall, the memory trace may transfer to a transient destabilized state, requiring time-dependent restabilization to persist further (Box 1). Gene transcription and protein synthesis are necessary for reconsolidation and offer a window of opportunity to fundamentally change the memory trace [1•,4]. The fear-conditioning paradigm is widely used across different species to study the process of memory reconsolidation [5,6]. In the lab, fear memories can be established through Pavlovian fear conditioning, which involves the repeated pairing of an initially neutral cue (e.g. a tone; conditioned stimulus, CS) with an inherently aversive stimulus (e.g. an electrocutaneous shock; unconditioned stimulus, US). As a result, the representation of the CS and US will become connected in the brain, such that a later presentation of the CS will retrieve the US representation and elicit a conditioned fear response. This so-called associative fear memory represents both cognitive and emotional aspects of fear learning: it involves contingency learning between the originally neutral or ambiguous stimulus (CS) and the reinforcer (US), while the CS becomes also imbued with the affective properties of the reinforcers (US) they predict. Upon a reminder trial of the CS, a conditioned fear response (CR) (i.e. freezing) is usually taken as evidence that a CS-US association has been formed, but this behavioral read-out does not distinguish between the cognitive and emotional aspects of fear memory in animals. Yet, this distinction can easily be made in human fear-conditioning studies where the cognitive expression of fear memory is typically assessed by threat expectancies and the emotional expression by the fear-potentiated startle reflex (e.g. [7•,8]).

In order for reconsolidation to occur, memory has to be reactivated (Box 1) and destabilized during a generally brief reminder session. Once the memory is rendered labile, reconsolidation can take place and may be experimentally modified by pharmacological [1•,9,10] or behavioral manipulations [11–13]. In particular, it has been shown that fear memories can be enhanced or weakened,

Box 1 Definitions of core processes and concepts of fear memory.

Memory reactivation: The return of memory from a neurobiologically inactive to an active state in the presence of salient reminder cues. Reactivation of memory may take place without any behavioral output.

Memory retrieval: The complex process by which previously stored information is recalled, which leads to behavioral output.

Match/mismatch: An estimation of how consistent the environment is with previous experience.

Prediction error: For fear conditioning, the magnitude of the outcome or the outcome itself is not being fully predicted.

Memory destabilization: The transient labile state that a memory may return to upon its reactivation.

Memory reconsolidation: The proces of restabilization of memory, once it has been destabilized after memory reactivation.

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depending on the manipulation used [6,14,15]. Since maladaptive memory processing lies at the core of emotional memory disorders (i.e. anxiety disorders, post-traumatic stress disorder, addiction) [8], targeting the process of memory reconsolidation opens avenues to develop a revolutionary treatment. Even though the findings obtained from basic neuroscience are promising, the critical conditions to target complex and pervasive emotional memories typically encountered in clinical practice are still unknown. Very often basic findings from animal literature are translated to clinical trials without a full understanding of the mechanisms of change, leading to disappointing and confusing results. A thorough understanding of the necessary and boundary conditions to trigger and observe memory reconsolidation is essential before we can witness a paradigm shift in clinical practice [6,8,10,16,17].

The reactivation of fear memory is often considered to be synonymous with its behavioral expression, but fear memory may also be reactivated without an observable mnemonic read-out. Hence, a reminder stimulus may return memory to a malleable state necessitating reconsolidation, even when it is not behaviourally expressed [18•,19,20,21•]. Furthermore, there is substantial evidence demonstrating that a memory is not labilized every time it is retrieved [7•,20,22]. If retrieval (Box 1) is *not* sufficient to trigger memory reconsolidation, then the critical question arises: *How do we know whether a particular fear memory actually requires an adaptation?* Memory reactivation is thought to trigger memory reconsolidation when the reminder stimuli are similar but not identical (*match/mismatch*, Box 1) to the original learning environment [5,23]. Yet, a reminder session that is too different from the original learning procedure might not trigger memory reconsolidation, but instead initiate other memory processes such as an intermediate pharmacologically insensitive state of limbo [24•,25,26] or the formation of a new memory, such as in extinction learning [27,28]. Without an independent index of the necessary and sufficient conditions to trigger memory reconsolidation, other than the memory enhancing or amnesic effects of the manipulations themselves, determining the degree of similarity (or dissimilarity) between the original learning and reminder session presents a challenge to empirical falsifiability.

In this review we will discuss different post-reactivation memory processes and illustrate how the transition between these processes depend on subtle changes in the reactivation procedures in interaction with the learning history. Given that there is no single method of memory reactivation that always triggers memory reconsolidation, we claim that an independent read-out is imperative to delineate the underlying processes necessary for memory reconsolidation. In particular, we will briefly review a selection of animal and human studies and describe how memory expression is neither necessary nor sufficient to trigger reconsolidation, but that assessment of a match/mismatch experience (Box 1) may indicate whether a certain reminder trial triggers reconsolidation [6,16,29]. In fear-conditioning studies the match/mismatch between the expected and actual outcome during memory reactivation is operationalized as prediction error, meaning that the magnitude of the aversive outcome or the outcome itself (i.e. US) is not fully predicted (PE, Box 1) [6,16,29]. Furthermore, we will argue that PE is also not a sufficient condition for