



Review article

Understanding the dynamic and destiny of memories

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ABSTRACT

Memory formation enables the retention of life experiences overtime. Based on previously acquired information, organisms can anticipate future events and adjust their behaviors to maximize survival. However, in an ever-changing environment, a memory needs to be malleable to maintain its relevance. In fact, substantial evidence suggests that a consolidated memory can become labile and susceptible to modifications after being reactivated, a process termed *reconsolidation*. When an *extinction* process takes place, a memory can also be temporarily inhibited by a second memory that carries information with opposite meaning. In addition, a memory can fade and lose its significance in a process known as *forgetting*. Thus, following retrieval, new life experiences can be integrated with the original memory trace to maintain its predictive value. In this review, we explore the determining factors that regulate the fate of a memory after its reactivation. We focus on three post-retrieval memory destinies (*reconsolidation*, *extinction*, and *forgetting*) and discuss recent rodent studies investigating the biological functions and neural mechanisms underlying each of these processes.

1. Introduction

Acquiring memories of our life experiences is vital to optimize our future decisions. Based on our memories we can adjust our behavior in response to stimuli that resemble prior experienced situations. For example, returning to your favorite restaurant or avoiding a bumpy road on the way home are situations in which our memories from past events directly guide our decisions. But how does our brain select and store information that is necessary to appropriately shape our behaviors? Although we are constantly exposed to new environmental stimuli, most of the acquired information is lost in a few hours or days. In fact, the majority of our daily mundane experiences are not relevant and remembering them does not bring significant benefits for us as individuals or species. Indeed, our brain has specialized mechanisms that act as filters to select which information should be retained as long-term memory (Richards and Frankland, 2017). Because it is difficult to choose in real time (*i.e.*, during learning) which piece of information is important to be kept, this filtering process occurs *a posteriori*, shortly after the experience has been acquired. There is a consensus that memories are unstable immediately after learning and can be easily modulated until they are consolidated into a more stable form. The time-dependent process of memory stabilization starts with an initial phase known as synaptic consolidation, which lasts for a few hours and allows for the

encoded information to be stored as a memory trace (Asok et al., 2019; Josselyn et al., 2015; McGaugh, 2000). This phase is followed by an enduring phase named systems consolidation, which persists for days to weeks and is believed to be important for the maintenance and reorganization of different types of memories in distinct brain regions (Barry and Maguire, 2019; Dandolo and Schwabe, 2019; DeNardo et al., 2019; Do-Monte et al., 2015b; Do Monte et al., 2016; Frankland and Bontempi, 2005; Moscovitch et al., 2016; Sacco and Sacchetti, 2010; Squire et al., 2015; Todd et al., 2018; Tonegawa et al., 2018; Vahdat et al., 2017; Van den Oever et al., 2013). While the ordinary process of memory stabilization has the biological function of selecting the memories that are potentially beneficial to be maintained in our brain, how it occurs and what sort of information is more prone to be retained as a long-lasting memory trace has been a major object of research in the last years.

Studies in both humans and laboratory animals have shown that memories containing emotional information are better retained than memories with neutral or trivial content (Okuda et al., 2004; Roozendaal and McGaugh, 2011). The underlying mechanisms of emotion seem to be a good candidate to modulate our memory filtering system by favoring the consolidation of emotionally-charged information. But, do memories remain in a steady form once this consolidation process is completed? Because we live in an ever-changing environment, an inflexible memory system would not be adaptive to changes and,

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consequently, would not serve to properly guide our future behaviors. Instead, a system that permits our memories to be constantly updated in accordance with our needs seems to be evolutionarily more advantageous (Lee et al., 2017). Returning to our initial examples, a flexible memory system enables us to stop going to that favorite restaurant if the food doesn't taste good anymore or resume taking that bumpy road on the way home after it gets repaved. Accumulating evidence from the last few decades suggests that, even after being consolidated, our memories can enter a plastic state that allows the incorporation of newly acquired information (Nader et al., 2000b; Wang et al., 2009). This updating process can be initiated when memories are retrieved, making them labile and susceptible to modifications. This post-retrieval mechanism seems to be critical to determine the destiny of our memories, as well as to maintain the efficiency of our memories in predicting future events (De Oliveira Alvares et al., 2013; Lee, 2009).

In this review, we explore the biological mechanisms that regulate the distinct fates of memories after retrieval. We focus mainly on studies using fear and reward conditioning paradigms in rodents, as they represent most of the memory literature that is currently available. First, we describe situations in which the environmental conditions during the retrieval phase resemble the original experience, in this way leading to a memory updating process called *reconsolidation*. Next, we discuss situations in which the current conditions during retrieval have a different meaning compared to the original experience, thereby causing an inhibition of the original memory trace in a process known as *extinction*. Last, we discuss situations in which memories fade away following the acquisition phase. This physiological process, often described as *forgetting*, occurs when a well-established memory is erased or becomes unable to be retrieved.

2. Basic phases of memory formation

Before discussing the post-retrieval destiny of a memory, it is important to revisit the distinct phases of memory. For didactic purposes, we separate memory into three different phases that progress over time. The first phase is called acquisition or encoding and refers to the stage in which the information is initially received and processed in the brain, by changing neuronal excitability and the strength of connections

between neurons (i.e., synaptic plasticity). The second phase, called consolidation, is the dynamic process by which the newly encoded information is gradually stabilized and retained as a memory trace. And the third phase, called retrieval, is the phase in which the previously acquired information is accessed and re-experienced by the subject.

Most of our knowledge about the different phases of memory formation comes from animal models of associative learning (Dickinson, 2012; Hawkins and Byrne, 2015; Pearce and Bouton, 2001). Such models have enabled us to systematically distinguish these three memory phases. This differentiation has been made possible by manipulating the activity of specific brain regions or neurotransmission system before each specific phase and using the animal's response to associated cues as a measure of memory. In contrast, a systematic differentiation between the distinct mechanisms that follows memory retrieval has been more difficult because we have just begun to understand the molecular and temporal processes that separate reconsolidation, extinction, and forgetting, and how each one of these processes contributes to the destiny of a memory (Fig. 1).

3. Memory reconsolidation: mechanisms and biological functions

The mainstream assumption regarding memory formation was based on the dogma that, once consolidated, memories would become stable and protected from further modifications. However, pioneer studies by the middle of the last century started to challenge this view by showing that consolidated memories can undergo modifications after being retrieved (Lewis, 1979; Lewis et al., 1968). Subsequent studies a few decades later demonstrated that reactivation of a well-consolidated memory can trigger cellular events that are critical for memory persistence (Nader et al., 2000b; Przybylski and Sara, 1997). The observation that consolidated memories can enter a labile state and become editable upon retrieval has given origin to the term memory reconsolidation. In the following years, hundreds of studies demonstrated that memory reconsolidation is a ubiquitous process that happens in different species – from worms and fishes to birds and mammals including humans – and can be studied by using distinct memory paradigms (for a review see: Besnard et al., 2012; Dudai, 2012; Haubrich

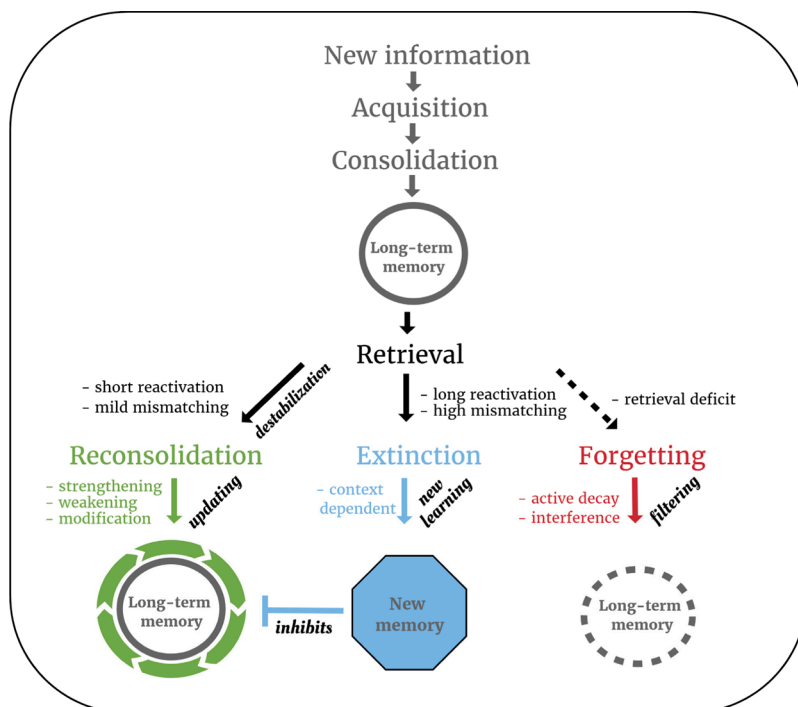


Fig. 1. Schematic of memory destinies following retrieval. During the initial phase of memory formation, new information is acquired and consolidated as a long-term memory. Subsequent retrieval of the consolidated memory may activate three distinct processes: i) **reconsolidation** is triggered after a short period of memory reactivation and a mild degree of mismatching between the original memory and the retrieval session. Reconsolidation involves an initial destabilization of the memory trace followed by memory updating through the strengthening of the original memory and the incorporation of new information; ii) **extinction** is triggered after a long period of memory reactivation and a high degree of mismatching between the original memory and the retrieval session. Extinction involves the formation of a new memory that inhibits the original memory trace; and iii) **forgetting** results from a deficit in the retrieval of the original memory. Forgetting may serve as a filter to remove unnecessary information.

and Nader, 2018; Taujanskaite et al., 2020).

The discovery that memories can be manipulated by interfering with the mechanisms of reconsolidation has generated great excitement and interest in the field because pathological memories are in the heart of many psychiatric disorders including post-traumatic stress disorder (PTSD), phobias and drug addiction (Beckers and Kindt, 2017a; Elsej et al., 2018). Because of the potential clinical relevance of disrupting reconsolidation processes to modulate emotional memories in humans, reconsolidation rapidly became one of the most studied topics in the memory field (Monfils and Holmes, 2018; Phelps and Hofmann, 2019). While many studies have focused on investigating reconsolidation processes in laboratory animals as an attempt to better understanding pathological memories in humans, much less attention has been paid on elucidating the biological functions of memory reconsolidation. Here, we discuss the adaptive role that reconsolidation has on memory updating and the main neuronal mechanisms underlying this process.

3.1. Why is memory updating important and how does it happen?

The long-term maintenance of our significant life experiences is an important adaptive process. Based on past experiences, animals can predict future events and optimize their decisions. Previously formed memories can guide animals to repeat behaviors that have resulted in successful outcomes while avoiding those that have previously failed (Dickinson, 1981, 2012; Rescorla, 1988; Zentall, 2013). However, animals live in a dynamic environment and for this reason memories are normally reactivated in situations that differ from those in which the

original experience has occurred. Therefore, new pieces of information should be integrated with the original memory in order to keep its current significance. This incorporation of new information is believed to be mediated by reconsolidation mechanisms (De Oliveira Alvares et al., 2013; Hupbach et al., 2008; Lee, 2010; Zinn et al., 2020). Memory retrieval triggers a plastic state in which the original memory trace can be modified and subsequently reconsolidated into an updated form (Lee et al., 2017).

To be updated in terms of content or strength, a previously consolidated memory that is in a stable state (*i.e.*, inactive state) needs to destabilize and enter a labile state (*i.e.*, active state) (Fig. 2A). This memory destabilization process occurs when there is a certain degree of mismatching (*i.e.*, prediction error) between what is expected and what actually happens during the retrieval period (Popik et al., 2020; Sevenster et al., 2013). Studies in both humans and laboratory animals have shown that in the absence of prediction error, retrieval does not induce destabilization and the original memory remains unmodified, reinforcing the idea that retrieval and memory destabilization are two different processes (Barreiro et al., 2013; Bustos et al., 2009; Extton-McGuinness et al., 2015; Merlo et al., 2015; Milton et al., 2013; Pedreira et al., 2004; Sevenster et al., 2012; Sinclair and Barense, 2018). These experimental observations make sense if we consider the biological role of memory updating because, when the current situation is closely identical to the original experience, there is no need of updating the memory. Using our previous example again, if during a subsequent visit to that same savory restaurant the food continues as tasteful as before, our memory would not be destabilized and our positive judgment about the restaurant

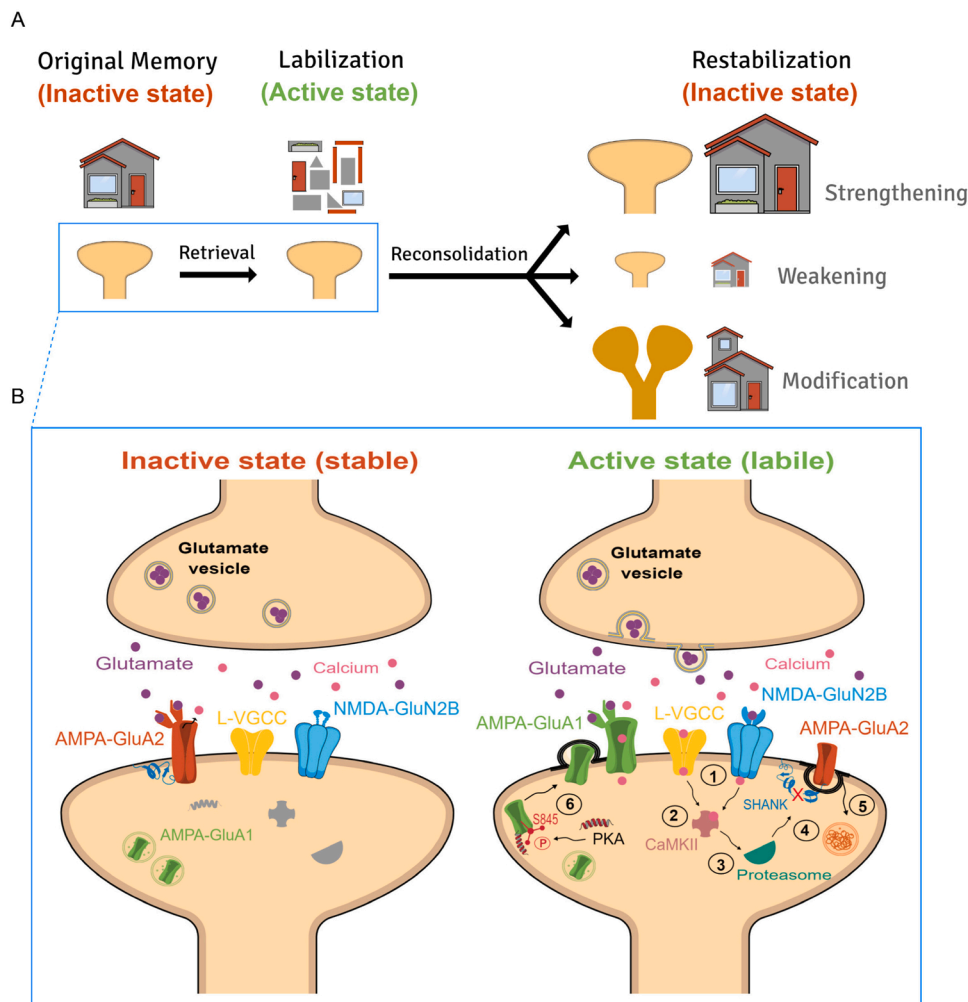


Fig. 2. Representative model and synaptic mechanisms of retrieval-induced memory destabilization. **A)** During memory retrieval, a consolidated memory that is initially in a stable state (inactive state) enters a labile state (active state) if a certain degree of mismatching occurs (*i.e.*, prediction error). Depending on what happens during retrieval, the original memory trace can be updated into distinct forms thereby resulting in a strengthened, weakened, or modified memory. House drawings are used as an analogy for retrieval-induced memory updating. **B)** The transition of the original memory from an inactive to an active state after retrieval involves a series of postsynaptic mechanisms including: 1) Entrance of calcium following activation of GluN2B-containing NMDA receptor and L-type voltage-gated calcium channels (L-VGCC); 2) Activation of protein kinase CaMKII; 3) Activation of proteasomes (e.g., SHANK); 4) Degradation of scaffolding proteins (e.g., SHANK); 5) Endocytosis of calcium impermeable GluA2-containing AMPA receptors from the postsynaptic density (PSD) followed by autophagy; 6) Insertion of calcium permeable GluA1-containing AMPA receptors in the PSD in part due to the phosphorylation of serine 845 (S845) by protein kinase A (PKA).

would continue the same.

3.2. What are the molecular/cellular processes involved in memory destabilization/updates?

Several important players have been described to participate in the memory destabilization process (Fig. 2B). For instance, the entrance of calcium ions into the cell through the activation of GluN2B-containing NMDA glutamatergic receptors and L-type voltage-gated calcium channels (L-VGCCs) have been shown to be crucial steps for this process. GluN2B-containing NMDA receptors are glutamate gated ion channels that are centrally involved in neuronal signal transduction and synaptic plasticity (Zhang and Luo, 2013), whereas L-VGCCs are transmembrane calcium channels that play a critical role in neurotransmitter release and gene expression regulation (Berger and Bartsch, 2014; Gomez-Ospina et al., 2006). Systemic or intracerebral injection of the GluN2BR antagonist ifenprodil or the L-VGCC blocker nimodipine before memory reactivation prevents memory updating (Ben Mamou et al., 2006; Haubrich et al., 2015; Suzuki et al., 2008). Studies have shown that calcium influx through GluA1-containing AMPA receptor - a subtype of AMPA-type glutamate receptors that is permeable to calcium - is also required for memory updating (Clem and Hugarir, 2010; Torquatto et al., 2019). Indeed, during memory labilization, GluA1-containing AMPA receptors are inserted into the postsynaptic density, whereas GluA2-containing AMPA receptors, which are known for rendering the channel impermeable to calcium, are in turn endocytosed (Clem and Hugarir, 2010; Hong et al., 2013; Rao-Ruiz et al., 2011b) and degraded through autophagy (Shehata et al., 2018). The postsynaptic density is a specialized region in the membrane of excitatory synapses that is rich in receptors, proteins and signaling molecules, and is known for playing a critical role in synaptic plasticity (Gold, 2012). Increased influx of calcium activates the protein kinase CaMKII, which triggers proteasomes (i.e., large protein complexes) that are responsible for the degradation of synaptic scaffolding proteins (e.g., SHANK), an essential step for memory destabilization. (Jarome et al., 2016, 2011; Lee et al., 2008). Accordingly, inhibiting either CaMKII or proteasomes prevent memory destabilization (Jarome et al., 2016; Lee et al., 2008); and the coordinated regulation of protein synthesis and degradation seems to be a critical process for long-term memory maintenance (Park and Kaang, 2019). Other important players that participate in the process of memory destabilization include dopamine (Merlo et al., 2015), cannabinoid receptors (Lunardi et al., 2020), cholinergic muscarinic receptors (Stiver et al., 2015), and NMDA-induced autophagy (Shehata et al., 2018).

Once memory achieves a labile state, it becomes vulnerable to modification (e.g., enhancement, attenuation, or integration of new information) for a few hours, after which memory is reconsolidated and restabilized. This restabilization process, which is necessary to place memory back into a more steady form, involves RNA synthesis (Sangha et al., 2003), protein synthesis (Nader et al., 2000a), AMPA receptor trafficking (Rao-Ruiz et al., 2011b), and cytoskeleton reorganization (Lunardi et al., 2018). Evidence suggests that the exchange of calcium-impermeable to calcium-permeable AMPA receptors is a hallmark of memory malleability. When high concentrations of calcium-permeable AMPA receptors are located in the postsynaptic density, memory becomes destabilized. Replacement of calcium-permeable by calcium-impermeable AMPA receptors shifts memory back to a stable form (Clem and Hugarir, 2010; Torquatto et al., 2019). This switch in memory malleability is accompanied by structural changes mediated by actin remodeling, which results in alterations in the number and morphology of dendritic spines (Roy et al., 2017). Accordingly, actin remodeling in dendritic spines has been described following distinct forms of synaptic plasticity including long-term potentiation (LTP) and long-term depression (Fonseca, 2012; Ramachandran and Frey, 2009; Szabo et al., 2016). We propose that together with the AMPA receptor trafficking, there is an orchestrated reorganization of actin in which mature dendritic spines become structurally

labile through actin depolymerization. Thus, dendritic spines can be rebuilt in an updated form depending on what happens after retrieval: becoming larger in the case of memory enhancement or smaller in the case of memory impairment. Future experiments using two-photon microscopy will test this prediction by longitudinally tracking individual dendritic spines during the time window of memory reconsolidation.

Previous studies have demonstrated that memories with intense emotional content are more resistant to destabilization, and consequently, less susceptible to interference (Bustos et al., 2010; Suzuki et al., 2004; Wang et al., 2009). In short, memory strength is a boundary condition that limits memory from undergoing reconsolidation. For example, during a strong fear conditioning training, activation of locus coeruleus neurons increase the release of noradrenaline in the amygdala, thereby reinforcing the memory trace (Haubrich et al., 2020). Subsequent to retrieval, activation of beta-adrenergic receptors in the amygdala halts AMPA trafficking and down regulates GluN2B-NMDAR, which prevents memory restabilization (Haubrich et al., 2020; Wang et al., 2009). Thus, strong emotional experiences seem to be more resistant to undergoing reconsolidation and as a result less vulnerable to modifications. Nevertheless, studies in rodents and humans have demonstrated that even emotionally-charged memories can be modified through reconsolidation mechanisms under certain conditions that involve the correct length of reactivation, the ideal memory mismatching, and/or the use of drugs to enhance memory labilization (Elsej and Kindt, 2017; Soeter and Kindt, 2012; Zhang et al., 2018a).

3.3. How can memory be updated through reconsolidation mechanisms?

As we have discussed above, memory updating is a critical process that helps to maintain the predictive value of previously acquired information and consequently to avoid inappropriate behavioral responses. Such updating is mediated by reconsolidation mechanisms and may serve as an opportunity for modifying the strength and the content of memories. Memory updating is observed in many species and may have evolved in some organisms to assure that information about resources (e.g. food, water, and mate) and potential threats (e.g., risk of predation) are always up to date. In this section, we explore how reconsolidation can lead to distinct forms of memory updating including: i) the modulation of memory strength, ii) the modification of the original memory content, iii) the formation of false representations, iv) the incorporation of state-dependency into the memory trace, and finally v) the shift of memory valence through counterconditioning.

3.3.1. Memory strength

The first direct evidence that memories can be strengthened through reconsolidation mechanisms was the demonstration that a weak learning event can be reinforced by additional training until it achieves an asymptotic level (Fukushima et al., 2014; Lee, 2008, 2009). In one of these studies, laboratory rats were fear conditioned with foot shocks to achieve a freezing level of around 40 % (freezing was used as a measure of memory retrieval). When the same animals were conditioned again, freezing levels went up to ~70 %. However, different molecular cascades were necessary during these two phases: knocking down the expression of brain-derived neurotrophic factor (BDNF, a critical protein for memory acquisition) before the initial conditioning phase disrupted memory formation, whereas knocking down the expression of zif268 (a critical protein for memory reconsolidation (but see Zalcman et al., 2015)) before the second conditioning session impaired memory strengthening; suggesting that reconsolidation rather than new learning is the main mechanism underlying memory strengthening (Lee, 2008). Other studies using similar experimental designs have drawn the same conclusion by demonstrating that reactivation-induced reconsolidation strengthens the original memory trace (De Oliveira Alvares et al., 2013; Forcato et al., 2014; Inda et al., 2011). Together, these studies indicate that retrieval-induced memory destabilization is an essential step in the strengthening of previously acquired memories, most likely through

reconsolidation mechanisms.

3.3.2. Memory content

In addition to modifying memory strength, another possible function of reconsolidation is to modify memory content. That is, to permit the integration of new information into an existing memory trace during the malleable period that succeeds retrieval (Fernandez et al., 2016; Morris et al., 2006; Winters et al., 2009). For instance, prior studies have shown that rats that were fear conditioned in one context (e.g., context A) showed low levels of freezing when tested in a distinct context (e.g., context B). However, when the conditioned memory was reactivated in a hybrid context that resembled both context A and context B, animals started to exhibit high levels of freezing when tested in context B, suggesting that during the reactivation session the information from context B was inserted into the memory trace previously associated with context A (De Oliveira Alvares et al., 2013; Zinn et al., 2020).

3.3.3. False memory

The brain's capacity to modify memories opens up the possibility of creating a false memory, a process that consists in either changing the representation of previous events by implanting false information upon an existing memory trace or making up a completely inaccurate memory trace by incorporating exogenous misinformation (Loftus and Davis, 2006). The phenomenon of false memory takes place when the information inserted into an existing memory trace is altered until the point that the updated form no longer fit into the original memory (Schacter et al., 2011). This distorted or even fabricated recollection of events is believed to be a side effect of memory malleability that occurs during the time window of reconsolidation.

Memories are known to be formed following the association between biologically salient events and sensory stimuli. Nevertheless, a recent study has demonstrated that mice can create a fully artificial memory without being exposed to a sensory experience (Vetere et al., 2019). In this study, optogenetic activation of olfactory sensory neurons expressing the odorant receptor for acetophenone was paired with optogenetic activation of lateral habenula projections to the ventral tegmental area (VTA), a circuit known to mediate aversive responses. In a separate group of mice, optogenetic activation of the same olfactory sensory neurons was paired with optogenetic activation of laterodorsal tegmental nucleus projections to the VTA, a circuit known to mediate rewarding responses. After pairings, mice receiving optogenetic activation of the aversive or rewarding circuits spent less or more time in the side of a chamber containing the acetophenone odorant, respectively, despite the animals never having smelled the acetophenone odorant before (Vetere et al., 2019). These findings suggest that memories can be artificially formed by entirely bypassing a sensory experience. Although this study demonstrates the genesis of an artificial memory through the modulation of acquisition/consolidation mechanisms, a similar process involving the insertion of false information into a previously existing memory trace has been described in other studies (Ramirez et al., 2013; Redondo et al., 2014).

Previous studies using activity-dependent neural tagging have shown that manipulation of neural populations that were active during learning can enable previously acquired experiences to become associated with new stimuli (Ramirez et al., 2013; Redondo et al., 2014). In one of these studies, mice hippocampal neurons that were activated by exposure to a neutral context (context A) were subsequently labeled with the light-sensitive cation channel channelrhodopsin (ChR2) (Ramirez et al., 2013). Animals were then exposed to a different context (context B) and the neurons labeled in context A were optogenetically reactivated during a fear conditioning training with foot shocks. In the following day, animals displayed increased freezing responses in context A, even though they had never experienced a foot shock in that context, suggesting that the encoded information about context A was updated and combined with the foot shock information (Ramirez et al., 2013).

3.3.4. State-dependent memory

Besides the inclusion of external cues, reconsolidation also enables the inclusion of internal cues into the mental representation of the environment, which may result in memory updating. Examples of internal cues include the distinct mental states that are experienced by the subject during the retrieval session (e.g., specific mood states, particular arousal situations, or the influence of drugs). In other words, the mental state prevailing during memory reactivation can be incorporated into the neural substrate of the memory (henceforth called engram), thereby making the original memory state-dependent. Afterwards, subsequent memory retrieval will be better achieved if the same internal state is presented again (Gisquet-Verrier et al., 2015; Sierra et al., 2013). A similar state-dependent induction has been also reported during extinction training (Rosa et al., 2014), suggesting that state-dependency is a general memory process that may be established when the memory is in a labile/plastic state (e.g., after acquisition or reactivation), hence incorporating the internal state into the memory engram (for a review see: Gisquet-Verrier and Riccio, 2018).

3.3.5. Counterconditioning

Another way to update a memory during the labile state induced by retrieval is through counterconditioning, a process in which the original memory is modified by the integration of new information containing opposite emotional valence. During counterconditioning, a fearful memory can be updated by presenting hedonic information during the period of reactivation, so that the original negative valence is "replaced" by a positive/less aversive one. This emotional remodeling has been demonstrated in a series of studies in which a conditioned stimulus (CS) previously associated with a foot shock became less aversive after being re-associated with an appetitive stimulus such as chocolate (Haubrich et al., 2015), caffeine (Pedraza et al., 2018), methylphenidate (Arellano Perez et al., 2020) or amphetamine (Toledano and Gisquet-Verrier, 2014). The observation that counterconditioning updating is prevented by the infusion of memory destabilization inhibitors (e.g., GluN2B-NMDA antagonists or L-VGCC blockers) suggests that memory updating during counterconditioning is mediated by reconsolidation mechanisms rather than new learning (Haubrich et al., 2015).

While significant progress has been made in elucidating the neural mechanisms involved in memory updating, there are still several open questions that need to be addressed to clarify how additional information is inserted into an existing memory trace. Are new neurons incorporated into the engram? Are neurons that do not carry relevant information anymore removed from the engram? Which patterns of neuronal activity regulate these processes? Future experiments using activity-dependent neuronal tagging or calcium imaging recordings of neuronal dynamics during memory acquisition vs. reconsolidation are likely to yield more information about how a memory engram activity is modified following reconsolidation; and by what means the insertion or removal of cells from the engram correlates with behavioral changes. Another important question regarding memory reconsolidation is the possibility of translating basic research findings to clinical practice. While some studies have successfully manipulated reconsolidation mechanisms in human patients with the purpose of attenuating emotional memories, others have failed (for a review see: Beckers and Kindt, 2017b; Elsey et al., 2018). This inconsistency of results may be explained by differences in the boundary conditions (e.g., the strength and age of the memories) or in the degrees of prediction error observed in each of these studies, which are important limiting factors for memory to undergo destabilization/reconsolidation (Elsey and Kindt, 2017; Sevenster et al., 2012; Sinclair and Barense, 2018, 2019). Further studies focused on investigating the mechanisms that govern these limiting factors in laboratory animals may provide better insights to elucidate memory destabilization/reconsolidation in humans.

4. Memory extinction: mechanisms and biological functions

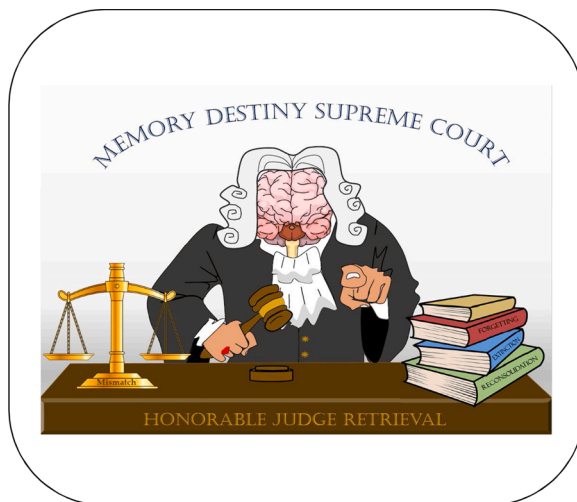
In the previous section, we described how memories can undergo a reconsolidation phase after being retrieved, a process by which the encoded information can be updated and re-established. Here, we discuss a different process called extinction, which takes place to attenuate/inhibit the original memory (Bouton, 1993; Pavlov, 1927). Extinction mechanisms are triggered when the retrieval phase surpasses a critical period, and the presence of a previously learned CS does not predict the same outcome anymore (i.e., high prediction error) (Merlo et al., 2014; Salinas-Hernandez et al., 2018) (Box 1). In such cases, multiple exposures to the same CS in the absence of consequences (i.e., unconditioned stimulus) lead to an attenuation of the conditioned response (Quirk and Mueller, 2008). Although the extinction phenomenon has resisted a brief and simple explanation, there is a consensus that extinction is not the same as forgetting or habituation, where habituation is defined as a response decrement to a repeated stimulus (Furlong et al., 2016; Thompson and Spencer, 1966). Extinction can also not be explained by synaptic depotentiation (Hong et al., 2009; Kim et al., 2007), as synaptic inputs that were facilitated during memory acquisition remain potentiated following extinction training (Clem and Haganir, 2010; Kim and Cho, 2017; but see: Park and Choi, 2010). Instead, increasing evidence supports the idea that extinction is a new learning that competes with the initial association (for a review see: Bouton, 2004; Dunsmoor et al., 2015; Luchkina and Bolshakov, 2019; Maren and Quirk, 2004). For example, an extinguished memory can resurge with the passage of time after the extinction training (spontaneous recovery) (Rescorla, 2004), as well as when the subject is tested in a context other than that in which the extinction training occurred (renewal) (Bouton et al., 2006; Goode and Maren, 2014). In addition, an

extinguished memory may also reappear when the subject is presented to a simple reminder of the original memory after the extinction training is completed (reinstatement) (Bouton and Bolles, 1979). While many features about the extinction process have been unveiled recently, many basic questions still remain unsolved. For example, why does extinction memory weaken with time? Why is extinction memory context-dependent? How does the single presentation of an unconditioned stimulus retrigger a conditioned response?

Despite the temporary nature of extinction (Vervliet et al., 2013), cognitive behavioral therapies based on extinction learning (e.g., exposure therapy) continue to be considered the gold standard intervention to suppress the expression of emotional memories in humans (e.g., anxiety disorders, substance abuse) (Foa and McLean, 2016; Hollandt et al., 2020; Kiefer and Dinter, 2013). The identification of potential cognitive enhancers (also called nootropic drugs) to improve extinction learning, and consequently attenuate fear or substance use disorders, has been the focus of many studies in the last decades (for a review see: Carpenter et al., 2019; Singewald et al., 2015). Additional insights on understanding the mechanisms of extinction have emerged from recent studies centered on investigating both the molecular/cellular processes and the neural circuits underlying extinction learning. Below we describe the main molecular/cellular mechanisms underlying extinction and explore the central determining factors that control the switch between reconsolidation and extinction processes following memory retrieval. Next, we discuss some rodent studies focused on elucidating the neural circuits that regulate the extinction of fear- or reward-associated memories. We draw some parallels between classical studies using lesions/pharmacological approaches and recent studies using optogenetic/chemogenetic tools to investigate extinction circuitry.

Box 1

The “Retrieval Judge” of memory destinies



To better understand how the destiny of a consolidated memory is determined, here we use a metaphor to compare the process of memory retrieval with a judicial trial court. In this analogy, the judge (*memory system*) evaluates many aspects of the defendant's sentence (*original memory*) and compares it with the new evidence presented during the appeal (*retrieval session*) in order to offer a new verdict (*memory destiny*). If a minor degree of mismatching between the new proofs and the original evidence is observed during the appeal (*lack of memory destabilization*), the judge will resentence the defendant to the same penal conviction (*memory persists unaltered*). However, when the new pieces of evidence (*cues*) presented during the appeal differ significantly from the original evidence (*mild prediction error*), bigger are the chances that the judge will adjust the sentence (*memory destabilization*) by extending, reducing or modifying the verdict (*reconsolidation with enhancement, attenuation, or modification of the memory content*). In other cases, when the defense attorney presents new evidence that strongly differ from the original evidence (*high prediction error*), the judge will temporarily acquit the defendant and a completely different verdict will be pronounced (*extinction memory*). Finally, if the defendant's request for an appeal is not sufficient to persuade the court (lack of retrieval), the appeal will be denied and the case closed (forgetting).

4.1. What are the molecular/cellular processes involved in memory extinction?

A large number of molecular and cellular processes are required for extinction memory formation, many of which resemble those required for memory reconsolidation. For instance, the acquisition of both extinction and reconsolidation requires protein synthesis (Milekic and Alberini, 2002; Suzuki et al., 2004) and the activation of several systems of neurotransmission and intracellular messengers in distinct brain areas including the amygdala, the hippocampus, and the medial prefrontal cortex (mPFC) (Baldi and Bucherelli, 2015; Kida, 2019; Lee et al., 2006; Merlo et al., 2014; Wideman et al., 2018). It has been shown that glutamate plays a critical role in extinction learning through the activation of AMPA (Yamada et al., 2009), NMDA (Kwapis et al., 2014), and mGluR1 receptors (Simonyi et al., 2007). The inhibitory neurotransmitter GABA is also important for extinction formation. Systemic or intracerebral infusions of GABA-A receptor agonists impairs extinction memory (Hart et al., 2009; Laurent and Westbrook, 2009), whereas infusions of GABA-A receptor antagonists facilitates it (Berlau and McGaugh, 2006). In addition, catecholamines such as noradrenaline are important modulators of extinction processes. Augmented noradrenergic transmission has been shown to potentiate the extinction of fear memories (Berlau and McGaugh, 2006; Mueller et al., 2008; Uematsu et al., 2017), whereas the blockade of either alpha-1- or beta-adrenergic receptors has been associated with extinction learning impairment (Bernardi and Lattal, 2010; Cain et al., 2004; Do-Monte et al., 2010a, b; Fitzgerald et al., 2015; Mueller et al., 2008).

Moreover, the endocannabinoid system plays a critical role in fear extinction with increased levels of endocannabinoids being detected following extinction training (Marsicano et al., 2002). Activation of endocannabinoid receptors type 1 (CB1) is indispensable for fear extinction formation as CB1 knockout mice or animals treated with either systemic or intracerebral infusion of CB1 antagonists show a robust impairment in extinction memory (Lisboa et al., 2019; Lutz, 2007; Marsicano et al., 2002; Sachser et al., 2015; Varvel et al., 2005), whereas animals treated with CB1 receptor agonists or inhibitors of endocannabinoid uptake/metabolism show extinction facilitation (Bisby et al., 2020; Bitencourt et al., 2008; de Oliveira Alvares et al., 2008; Do Monte et al., 2013; Gunduz-Cinar et al., 2013; Morena et al., 2018; Segev et al., 2018). In contrast to fear extinction, the extinction of drug-associated memories is rather facilitated by the infusion of antagonists/inverse agonists of CB1 receptors (Colombo et al., 2004; Gessa et al., 2005; Hu et al., 2015; Khaleghzadeh-Ahangar and Haghparast, 2015), suggesting that CB1 receptors may have different effects on extinction processes depending on the emotional valence of the original memory.

The activation of the abovementioned receptors and others not described here triggers intracellular signaling processes that play an important role in extinction memory formation. For example, calcium influx through NMDA receptors activates the phosphatase calcineurin (Lieberman and Mody, 1994), and its pharmacological or genetic inhibition impairs extinction memory (de la Fuente et al., 2011; Havekes et al., 2008). Equally implicated in extinction memory formation are a number of protein kinases including ERK1/2 (Herry et al., 2006; Merlo et al., 2018), MAPK (Lu et al., 2001), PI3-K (Kritman and Maroun, 2013), and CaMKII (Szapiro et al., 2003), as well as a series of intracellular pathways that control remodeling of dendritic spines and structural plasticity (Lai et al., 2012; Sananbenesi et al., 2007). For further understanding about the molecular and cellular mechanisms underlying extinction formation, we refer the readers to some comprehensive reviews that have been recently published in this topic (Baldi and Bucherelli, 2015; Pagani and Merlo, 2019).

4.2. How does retrieval trigger extinction?

As described above, retrieval-induced memory destabilization can

drive memory in two opposite directions: reconsolidation or extinction. In the former case, memory strength or its content may be updated. In the latter, a new inhibitory memory is created to compete with the original one. Experimentally, the only procedural difference that will determine whether a memory will undergo reconsolidation or extinction processes is the duration of the memory reactivation session. Several studies have shown that increasing the duration of the retrieval session interrupts reconsolidation and activates extinction formation. Whereas a brief exposure to the CS leads to memory reconsolidation, longer exposures trigger mechanisms of extinction (Bustos et al., 2009; Pedreira and Maldonado, 2003; Suzuki et al., 2004), suggesting that the fate of the retrieved memory depends on the length of the retrieval session. However, the specific temporal boundaries and the molecular mechanisms that determine the transition between these two processes remain largely unsolved. The first insight into this topic came from a mice study showing that the post-retrieval course of memory depends on a switch of transcription factors in the hippocampus (de la Fuente et al., 2011). In this study, the authors demonstrated that nuclear factor Kappa B (NFkB) is required for reconsolidation but, during the transition to extinction, calcineurin phosphatase inhibits NFkB expression thereby facilitating extinction memory formation.

Subsequent studies using a fear conditioning paradigm in rats have proposed that reconsolidation and extinction are mutually exclusive processes separated by a transition state in which neither process is recruited (Merlo et al., 2018, 2014). In the first study, the authors demonstrate that manipulating the activity of NMDA glutamate receptors following a reconsolidation (1 CS) or an extinction (10 CSs) protocol affected the original fear memory, but the same manipulation following a transitional state (4 CSs) had no effect (Merlo et al., 2014). Similarly, the second study showed that exposure to either 1 CS or 10 CSs during the retrieval session resulted in increased expression of ERK1/2 in the amygdala, but exposure to an intermediate retrieval session of 4 CSs failed to activate ERK1/2 in this same region (Merlo et al., 2018). Together these findings suggest that, at some point between the first and the fourth CS presentation, the activity of NMDA receptors and the expression of ERK1/2 are arrested to terminate the labilization/reconsolidation period. As the retrieval session progressed and more CSs were presented to the animals (7–10 CSs), both NMDA receptor activation and a second wave of ERK1/2 expression were reestablished and extinction mechanisms were recruited (Merlo et al., 2018, 2014). Increasing the number of CS presentations during the retrieval session also augmented the expression of calcineurin in the amygdala; and blocking calcineurin expression following the extinction protocol, but not following the reconsolidation protocol, impaired extinction formation, suggesting that reconsolidation and extinction recruit mutually exclusive processes (de la Fuente et al., 2011; Merlo et al., 2014). It is worth mentioning that this transition state between reconsolidation and extinction processes has been also demonstrated in other paradigms such as contextual fear conditioning in rodents (Cassini et al., 2017) and differential fear conditioning in humans (Sevenster et al., 2014).

Inspired by the observation that pharmacological manipulations during the reconsolidation window affect the updating of a destabilized memory trace (Alberini and Ledoux, 2013; Meir Drexler and Wolf, 2017; Nader, 2015; Otis et al., 2015), some laboratories have investigated the effects of post-retrieval extinction training on the persistence of the reactivated memory. In these studies, fear conditioned rodents that were exposed to an extinction training session after a single unreinforced CS presentation (i.e., memory reactivation) did not show any return of fear at later retrieval tests, suggesting that the extinction information incorporated during the reconsolidation window was sufficient to permanently attenuate the original memory trace (Graff et al., 2014; Monfils et al., 2009; Pineyro et al., 2013; Rao-Ruiz et al., 2011a). This reactivation-extinction effect seems to be independent of prediction error or memory destabilization, as behavioral or pharmacological interventions that either reduce prediction error or block memory

destabilization are not sufficient to prevent the effect (Cahill et al., 2019). In contrast, other studies using a similar reactivation-extinction paradigm have failed to demonstrate a permanent attenuation of the original memory trace (Chalkia et al., 2020a, b; Chan et al., 2010; Costanzi et al., 2011; Goode et al., 2017; Ishii et al., 2012). While these mixed findings may have resulted from specific boundary conditions that in some experiments impeded memory destabilization during the reactivation session, they indicate that there are limits to the efficacy of the reactivation-extinction paradigm in disrupting the original memory trace. Future studies will help to answer unsolved questions: how can small changes in the length of the retrieval session result in enormous differences in behavioral outcome? Do the strength and age of the original memory interfere with the temporal boundaries between reconsolidation and extinction? Which molecular mechanisms dictate the transition from reconsolidation to extinction processes?

4.3. Which neural circuits mediate the extinction of emotional memories?

The recent advent of new techniques to investigate neural circuit function in laboratory animals have led to a significant increase in the number of studies aimed at elucidating the neural circuits of extinction. A better understanding of the neural mechanisms that regulate extinction memory may help to identify: i) genetic markers that are particularly expressed in extinction circuits, ii) distinct patterns of brain activity that are correlated with successful extinction and reduced risk of relapse, and iii) pharmacological targets that may guide the development of new therapies in patients undergoing extinction-based therapies.

It is well accepted that the neural circuit that underlies extinction memory is regulated by a distributed network of brain regions that partially overlap with those recruited during memory acquisition (Fig. 3). Support for this idea comes from several rodent studies demonstrating that manipulation of brain areas that are essential for fear and reward conditioning also interferes with extinction processes. For example, lesions or pharmacological manipulation of the basolateral amygdala (BLA, including both the lateral and the basal subregions) impair not only the acquisition but also the extinction of fear-associated memories (Maren et al., 1996; Miserendino et al., 1990; Sierra-Mercado et al., 2011; Sotres-Bayon et al., 2007; Zimmerman and Maren, 2010). Accordingly, animals exposed to either fear learning or fear extinction sessions show increased expression of the neuronal activity marker cFos in BLA, suggesting that BLA neurons are recruited during both the

acquisition and the extinction of conditioned fear memories (Ganella et al., 2018; Holahan and White, 2004; Knapska and Maren, 2009). Additional findings using electrophysiological recordings and optogenetic manipulation of projection-defined neurons in BLA have demonstrated that different subpopulations of BLA cells are recruited during the acquisition and extinction of conditioned fear memories. Whereas a specific subpopulation of BLA neurons show increased CS responses after fear conditioning (fear neurons), a distinct subpopulation of BLA neurons exhibit increased CS responses after fear extinction (extinction neurons) (Herry et al., 2008). These fear and extinction neurons in BLA send dense projections to the prelimbic (PL) and infralimbic (IL) subregions of the mPFC, respectively; and pathway-specific optogenetic activation of BLA-IL projections or inhibition of BLA-PL projections facilitate the acquisition of extinction memory (Senn et al., 2014), suggesting that the balance of activity between these two BLA-mPFC pathways is an important factor during the formation of long-term extinction memories.

In line with the abovementioned findings, lesions and electrophysiological studies have demonstrated that PL activity is correlated with/required for fear memory retrieval (Burgos-Robles et al., 2009; Courtin et al., 2014; Dejean et al., 2016; Sierra-Mercado et al., 2011; Sotres-Bayon et al., 2012). In contrast, IL activity is necessary for the formation of fear extinction memory (Bravo-Rivera et al., 2014; Do-Monte et al., 2015a; Laurent and Westbrook, 2009; Santini et al., 2012; Sierra-Mercado et al., 2011). Optogenetic silencing of either BLA projections to PL or the reciprocal connection from PL to BLA attenuates fear memory retrieval (Burgos-Robles et al., 2017; Do-Monte et al., 2015b). In addition, activity in either PL neurons that project to the paraventricular nucleus of the thalamus (PVT) or PVT neurons that project to the central nucleus of the amygdala is critical for the retrieval of well-consolidated fear memories (Do-Monte et al., 2015b; Penzo et al., 2015). On the other hand, fear extinction training increases the excitability of IL-BLA projections (Bloodgood et al., 2018; Cho et al., 2013), and optogenetic or chemogenetic inactivation of IL projections to the amygdala disrupts the formation of fear extinction memory (Adhikari et al., 2015; Bloodgood et al., 2018; Bukalo et al., 2015). While current models have attributed distinct roles for PL and IL in the retrieval and extinction of conditioned fear, a recent study has challenged this anatomical dichotomy view by demonstrating that deep-layer PL glutamatergic neurons that project to IL show increased cFos expression during extinction training, and optogenetically activating or inactivating this specific projection facilitated or impaired fear extinction learning, respectively (Marek et al., 2018). Accounting for the discrepancy between these findings and the previous studies, PL projects to diverse downstream regions and broad manipulation of PL activity could have a range of effects that would cover up the potential role of this region in extinction learning. Future studies using projection-defined and cell-type specific analyses of both PL and IL neurons would help to clarify the precise role of these regions in fear regulation.

Besides its role in fear extinction, BLA neurons have been also implicated in the extinction of reward-associated memories. Increased neuronal activity in a subpopulation of BLA neurons has been correlated with extinction of sucrose-seeking behavior (Tye et al., 2010), and lesions or pharmacological modulation of BLA activity impairs the extinction of appetitive conditioned responses (Balleine et al., 2003; McLaughlin and Floresco, 2007; Portero-Tresserra et al., 2013). BLA neurons send dense projections to the nucleus accumbens (McDonald, 1991; Wright et al., 1996), a critical region in the regulation of reward-seeking responses (for a review see: Baldo and Kelley, 2007; Castro and Bruchas, 2019). In coordination with dopamine inputs to nucleus accumbens, BLA projections to nucleus accumbens drive reward-seeking behaviors in response to conditioned cues that predict reward (Ambroggi et al., 2008; Stuber et al., 2011; Wang et al., 2020b). Studies using optogenetics and electrophysiological recordings in vivo have demonstrated that BLA pyramidal neurons respond to both positive and negative valence stimuli; and activity in BLA downstream neurons

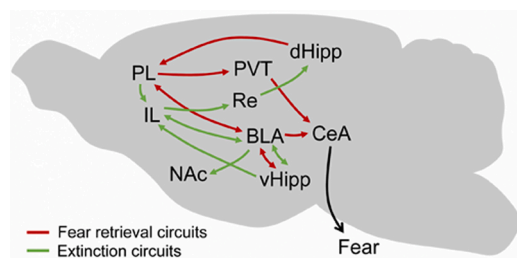


Fig. 3. Schematic of the neural circuits mediating retrieval and extinction of fear memories. Retrieval of fear-associated memories recruits reciprocal activity between PL and BLA neurons, as well as activation of CeA neurons projecting to downstream pathways that mediate fear responses. Retrieval of consolidated fear memories also activate PL neurons that project to PVT, as well as PVT neurons that project to CeA. Extinction of fear-associated memories recruits reciprocal activity between IL and BLA, as well as BLA and vHipp neurons. Both BLA projections to NAc and PL projections to IL are also recruited during extinction. In addition, hippocampal projections to PL, IL, and BLA provide contextual information during both retrieval and extinction of fear memories. Legend: PL, prelimbic cortex; IL, infralimbic cortex; NAc, nucleus accumbens, PVT, paraventricular nucleus of the thalamus, Re, nucleus reuniens, BLA, basolateral nucleus of the amygdala, CeA, central nucleus of the amygdala, dHipp, dorsal hippocampus, vHipp, ventral hippocampus.

in the nucleus accumbens and central nucleus of the amygdala modulates reward and fear responses, respectively (Beyeler et al., 2016; Namburi et al., 2015; Zhang and Li, 2018). Activity in the BLA to nucleus accumbens pathway has been also implicated in the regulation of fear extinction memories, as optogenetic stimulation of this circuit during fear extinction training attenuated the subsequent return of conditioned fear (Correia et al., 2016). Accordingly, a recent study has demonstrated that fear extinction is stored in a genetically distinct subset of BLA neurons (expressing the subunit-1B of the protein phosphatase-1 regulatory inhibitor) which is activated during reward-seeking behaviors, suggesting that fear extinction memory uses the same neuronal ensembles recruited during appetitive memory formation (Zhang et al., 2020).

As previously mentioned, extinction training only reduces the conditioned response to the CS (e.g., fear expression or reward seeking) in the same place where extinction has previously occurred. In other words, extinction is context-dependent and the conditioned response will return (i.e., renewal) when the CS is presented outside the extinction context (e.g., in a novel context or in the original conditioning context) (Goode and Maren, 2014; Podlesnik et al., 2017). The hippocampus has long been involved in the encoding of contextual representations (for a review see: Kubie et al., 2019). Activity in hippocampal neurons is critical to regulate context-evoked fear or reward-seeking responses following extinction. For example, extinction of contextual fear conditioning results in remapping of place cells in the dorsal hippocampus (Wang et al., 2015); and a series of studies have demonstrated that inhibition of the dorsal or ventral hippocampus interferes with the acquisition and retrieval of extinction for both context-dependent fear-associated memories (Bernier et al., 2017; Corcoran et al., 2005; Corcoran and Maren, 2001; Hobin et al., 2006) and reward-associated memories (Bossert and Stern, 2014; Busse and Schwarting, 2016; Hitchcock and Lattal, 2018). A recent study using activity-dependent neural tagging and optogenetic tools in mice has demonstrated that extinction training suppresses the activity of dorsal hippocampal neurons that were responsive during fear acquisition, and recruits a different ensemble of cells that are both necessary and sufficient for fear extinction retrieval (Lacagnina et al., 2019). This study suggests that a balance between fear and extinction representations in the hippocampus governs the suppression or relapse of fear following extinction.

Other studies focusing on the ventral hippocampus have shown that ventral hippocampal neurons that project to the amygdala or mPFC are activated during the renewal of both fear and reward-associated memories (Anderson and Petrovich, 2018; Jin and Maren, 2015), and pathway specific inactivation of these projections attenuates fear renewal (Vasquez et al., 2019; Xu et al., 2016). Exposure to extinction training increases the expression of BDNF in the ventral hippocampus, and infusing BDNF directly into this region exacerbates the firing rate of IL neurons (Rosas-Vidal et al., 2014, 2018). Consistent with a role of the hippocampus-prefrontal pathway in extinction memory regulation, activity in the ventral hippocampus induces feed-forward inhibition of amygdala-projecting neurons in IL by recruiting local parvalbumin interneurons, and chemogenetic inhibition of ventral hippocampus projections to IL attenuates fear renewal (Marek et al., 2019). Together, these findings emphasize the role of the hippocampus and its reciprocal connections with the mPFC and amygdala in the regulation of extinction memories.

Another important brain region in the acquisition and retrieval of context-dependent extinction memories is the nucleus reuniens, a ventral midline thalamic region that is interconnected with the hippocampus and the mPFC (Hoover and Vertes, 2012; Varela et al., 2014). Inactivation of the nucleus reuniens or its inputs from the mPFC increases conditioned fear responses during both the encoding and retrieval of an extinction memory (Ramanathan et al., 2018; Ramanathan and Maren, 2019). These findings are in agreement with previous studies suggesting that activity in the nucleus reuniens regulates the specificity of memory attributes for a particular context by processing information from the mPFC en route to the hippocampus

(Troyner et al., 2018; Xu and Sudhof, 2013). Understanding the mechanisms regulating the context-dependence of fear extinction has special clinical relevance because attenuating the conditioned response beyond the therapeutic setting is a major challenge during extinction-based therapies.

5. Memory forgetting: mechanisms and biological functions

As described above, memory reconsolidation and extinction processes keep our memories updated and useful for predicting the future. However, the vast majority of our daily experiences are forgotten over time. It is believed that forgetting has several important functions, such as emotional regulation (by removing the negative aspects of some experiences), abstraction and generalization (by extracting the rules/gist from related episodes, and forgetting redundant/noisy information), and cognitive economy (by restricting the information that really matters by removing outdated and useless memories) (Hardt et al., 2013; Norby, 2015; Richards and Frankland, 2017). While reconsolidation and extinction mechanisms serve to modify and update our memories, the physiological process of forgetting acts as a filter to remove some memories and prevent unimportant information from being retained. Hence, a system that balances memory maintenance and forgetting is highly adaptive as it retains pertinent information while forgetting unwanted facts. In this section, we explore the neurobiology of forgetting, which is defined here as a failure to retrieve long-term memories that were easily remembered before.

Although the phenomenon of memory forgetting has been studied since the end of the 19th century (for a review see: Medina, 2018; Sachser et al., 2017; Wixted, 2004), until recently no convincing empirical data have demonstrated the mechanisms involved in memory loss over time. Currently, there are three main hypotheses regarding the nature of memory forgetting: interference, retrieval deficit, and memory decay. Below, we discuss each one of these hypotheses.

5.1. The interference hypothesis

Psychologists have posited that the main forgetting mechanism relies on memory interference, a process in which similar memories content "compete" with each other, thereby promoting the incapacity to retrieve memory properly (Wixted, 2004). During interference, a specific memory interferes with items that were learned before memory acquisition (i.e., *proactive interference*) or after it (i.e., *retroactive interference*). For neuroscientists, the process of interference relies on the fact that memories undergo a plastic and labile state after learning or retrieval (e.g., during memory consolidation or reconsolidation, respectively, although these terms have rarely been used by psychologists). In *retroactive interference*, new learning affects previously acquired experiences. Pioneer studies performed in the beginning of the last century (Müller and Pilzecker, 1900) have shown that subjects exposed to a list of syllables immediately after learning a different list of words showed a significant impairment in the retention of the words (Dewar et al., 2007). However, their memories were not affected when the same list of syllables was presented after the time window of consolidation. These findings are consistent with real life situations in which new pieces of information may interfere with memories that are undergoing consolidation/reconsolidation. In contrast, *proactive interference* can be explained by the fact that our memories are formed over a background knowledge framework called schemas. These schemas may either facilitate or impair the acquisition of new memories. For example, memories can be consolidated faster and more efficiently if subjects are pre-exposed to a situation that reminds one of the acquisition phase (Pedraza et al., 2017; Tse et al., 2007). On the other hand, if the prior experience has distinct meaning, the subsequent learning will be impaired. This happens during latent inhibition, a phenomenon in which prior presentation of the CS alone impairs the subsequent association of the CS with the unconditioned stimulus by establishing a

different meaning for the CS (Lingawi et al., 2017).

Another example of memory interference is called retrieval-induced forgetting (Anderson et al., 1994). During retrieval-induced forgetting, a set of information is acquired but only a particular category of information is retrieved. This selective retrieval process reduces the brain's capability to remember the related non-retrieved information. Thus, the non-retrieved memory is inhibited and less remembered in subsequent retrieval trials (for a review see: Murayama et al., 2014; Pica et al., 2018). Pharmacological inactivation of either the mPFC or the hippocampus abolishes retrieval-induced forgetting, suggesting that these regions play an essential role in this process (Bekinschtein et al., 2018; Wu et al., 2014). Although retrieval-induced forgetting may be attributed to the interference caused by the competition between reminders associated with distinct memories, it may be also discussed as an active inhibition processes (see additional discussion in the next section below).

Memory interference has been also explained in the lens of non-monotonic plasticity hypothesis, which predicts that memories can change as a function of experience and their neural representation can move apart (differentiate) or together (integrate) according to the degree of reactivation (Ritvo et al., 2019; Sinclair and Barense, 2019). According to this view, when two overlapping memories are strongly reactivated the connections between them will be strengthened, thereby resulting in memory integration. In contrast, if only one of these overlapped memories is strongly reactivated, their connections will be weakened, thereby resulting in memory differentiation (Ritvo et al., 2019). Previous studies have demonstrated that the mechanisms underlying the balance between memory integration and differentiation are believed to be mediated by inhibitory interneurons (Barnes et al., 1990; Rashid et al., 2016).

5.2. The retrieval deficit hypothesis

An open-ended question in the memory field is whether forgetting reflects a failure of memory retrieval or impairment in memory storage. Methodological challenges have prevented researchers from adequately addressing this question because the absence of retrieval does not necessarily indicate that the memory trace is lost (e.g., storage deficit). Instead, it is possible that the reminders used to retrieve the memory are not sufficiently accurate to access the memory engram.

Consistent with the idea that memory forgetting results from a retrieval deficit rather than a complete engram erosion, recent studies have demonstrated that the memory disruptive effects of protein synthesis inhibitors administered immediately after training (consolidation phase) or post reactivation (reconsolidation phase) can be optogenetically rescued by artificially activating the engram corresponding to the original memory (Roy et al., 2017; Ryan et al., 2015). In these studies, optogenetic activation of the engram cells, but not the presentation of conditioned cues, was sufficient to induce memory retrieval. Furthermore, in a transgenic mice model of Alzheimer's Diseases, optogenetic activation of engram neurons was sufficient to rescue memory deficits (Roy et al., 2016), suggesting that although conditioned cues may be unable to trigger memory retrieval, direct optogenetic activation of the "silent engram" may restore the dormant memory engram. An alternative explanation for these findings is that both the protein synthesis inhibitor and the Alzheimer's Disease mouse model used in these two studies were not enough to eliminate the whole engram. Thus, the residual part of the memory trace that was left over was sufficient to be restored/reconstructed by subsequent optogenetic activation. In agreement with this, a recent study has shown that optogenetic activation of the memory engram is unable to rescue a conditioned fear memory when the memory trace is erased by autophagy-induced protein degradation (Abdou et al., 2018), suggesting that the memory recovery capacity relies on the extent of interference over the original memory trace.

Memories that are not frequently accessed tend to be weakened. In

contrast, memories that are periodically reactivated keep their precision and strength over time (Alvares Lde et al., 2012; Forcato et al., 2013; Inda et al., 2011). It is believed that, except for memories with strong emotional content that are longer maintained, the natural course of our daily life experiences is to be forgotten in a graded form. Accordingly, memories that are not frequently reactivated tend to be more difficult to be rescued (Fukushima et al., 2014; Inda et al., 2011), suggesting that lack of retrieval may activate mechanisms of forgetting. During an initial stage, the forgetting process is a retrieval deficit caused by the partial erosion of the engram. The following stage involves a disconnection of the engram to a point in which it can no longer support the memory content, thereby leading to a storage deficit. A special case of retrieval deficit concerns the state-dependency of memories. As briefly discussed in the reconsolidation section above, learning occurs under certain mental states that are required for subsequent memory retrieval. Prior studies have shown that memories that cannot be appropriately retrieved under certain conditions can be fully retrieved if the subject achieves the same mental state that was present during the memory acquisition phase. This state-dependency phenomenon has been extensively described with psychostimulants, opioids, benzodiazepines and other drugs and experimental conditions such as high arousal levels and hypothermia (for a review see: Radulovic et al., 2017). These studies suggest that the mental state acts as an important reminder that is "incorporated" into the memory trace during memory acquisition and/or reconsolidation, hence becoming a critical component of the retrieval process.

5.3. The active decay hypothesis

Although forgetting has been viewed as a passive mechanism, a number of studies have proposed that forgetting is an active process that involves the removal of previously consolidated memories (Davis and Zhong, 2017; Hardt et al., 2013). A pioneer study in the early 2000's provided the first evidence, finding that chronic administration of CPP, an antagonist of the NMDA glutamate receptor, prevents the natural decay of LTP in the hippocampus of rodents (Villarréal et al., 2002). This finding was corroborated by further studies demonstrating that spatial memory is maintained as long as NMDA receptors are blocked (Sachser et al., 2016; Shinohara and Hata, 2014), particularly NMDA receptors containing the GluN2B subunit (Migues et al., 2019; Sachser et al., 2016). It has been proposed that calcium entrance through NMDA receptors induces forgetting by activating calcineurin and synaptogamin-3, which ultimately removes GluA2-AMPA receptors from the synapse (Awasthi et al., 2019; Sachser et al., 2016). Consistent with the idea that glutamatergic transmission underlies memory forgetting, inhibiting the endocytosis of GluA2-AMPA receptors from synapses extends the duration of memories with neutral, appetitive, or aversive valence (Migues et al., 2016), and blocks LTP depotentiation (Dong et al., 2015; Migues et al., 2016).

Another potential candidate to modulate the mechanisms of memory forgetting is the enzyme Rac1, which has been implicated in the shrinkage of dendritic spines by regulating actin dynamics. Pharmacological inhibition of Rac1 extends memory life-time, whereas pharmacological activation or its overexpression speeds up memory forgetting in both rodent hippocampus and flies (Liu et al., 2016, 2018; Shuai et al., 2010; Zhang et al., 2018b). Forgetting has been also associated with the formation of functional mature neurons from neural stem cells, as neurogenesis in the dentate gyrus accelerates forgetting of hippocampal dependent memories, mediates infantile amnesia in juveniles, and enables behavioral flexibility in adult mice (Akers et al., 2014; Epp et al., 2016). In addition, the engulfment of large particles in the synapse or cell surface observed during phagocytosis seems to play a critical role in the regulation of forgetting. Either depletion of microglia or the inhibition of phagocytosis by microglia cells prevents memory forgetting, with active synapses being less prone to phagocytosis (Wang et al., 2020a). Thus, synapse elimination by microglia may contribute to the

degradation of memory engrams observed during forgetting.

Taken together, these studies suggest that the molecular bases of memory forgetting rely on both functional and structural reorganization of synapses that have been potentiated during learning. We propose that calcium entrance through the activation of NMDA receptors triggers the endocytosis of AMPA receptors and the initiation of Rac1 intracellular cascades, which will lead to synaptic depotentiation and dendritic spine shrinkage, two critical processes for memory forgetting. Further studies are needed to investigate this possibility.

6. General considerations on memory destiny

Here we explored the distinct processes that a previously acquired memory can follow after retrieval: reconsolidation, extinction, and forgetting. We have observed that, depending on the similarities between the information represented by the original memory and what is experienced during retrieval, memories can be conducted to distinct fates. If a high degree of similarity exists between the original memory and the retrieval phase, no changes are observed in the natural course of the memory and the information is maintained in its current form. In contrast, if a mismatching occurs between the retrieval and the original memory, the new piece of information presented during the retrieval phase is incorporated into the original memory, thereby strengthening, weakening, or modifying the existing memory trace. When this mismatching goes beyond certain levels, extinction mechanisms take place and new cells are recruited to create a new memory that will inhibit the existing memory trace without eliminating it. Finally, if the information stored by the original memory is no longer important or is rarely assessed during retrieval, the memory trace is removed by an active process of forgetting. From an evolutionary perspective, this dynamic nature of memory has important adaptive functions including updating our mental representation of past experiences, optimizing our predictions about the future, and properly adjusting our behaviors to make the most appropriate choices.

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Declaration of Competing Interest

The authors declare no conflict of interest.

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References

- Abdou, K., Shehata, M., Choko, K., Nishizono, H., Matsuo, M., Muramatsu, S.I., Inokuchi, K., 2018. Synapse-specific representation of the identity of overlapping memory engrams. *Science* 360, 1227–1231.
- Adhikari, A., Lerner, T.N., Finkelstein, J., Pak, S., Jennings, J.H., Davidson, T.J., Ferenczi, E., Gunaydin, L.A., Mirzabekov, J.J., Ye, L., Kim, S.Y., Lei, A., Deisseroth, K., 2015. Basomedial amygdala mediates top-down control of anxiety and fear. *Nature* 527, 179–185.
- Akers, K.G., Martinez-Canabal, A., Restivo, L., Yiu, A.P., De Cristofaro, A., Hsiang, H.L., Wheeler, A.L., Guskjolen, A., Niibori, Y., Shoji, H., Ohira, K., Richards, B.A., Miyakawa, T., Josselyn, S.A., Frankland, P.W., 2014. Hippocampal neurogenesis regulates forgetting during adulthood and infancy. *Science* 344, 598–602.
- Alberini, C.M., Ledoux, J.E., 2013. Memory reconsolidation. *Curr. Biol.* 23, R746–750.
- Alvares Lde, O., Einarsson, E.O., Santana, F., Crestani, A.P., Haubrich, J., Cassini, L.F., Nader, K., Quilfeldt, J.A., 2012. Periodically reactivated context memory retains its precision and dependence on the hippocampus. *Hippocampus* 22, 1092–1095.
- Ambroggi, F., Ishikawa, A., Fields, H.L., Nicola, S.M., 2008. Basolateral amygdala neurons facilitate reward-seeking behavior by exciting nucleus accumbens neurons. *Neuron* 59, 648–661.
- Anderson, L.C., Petrovich, G.D., 2018. Distinct recruitment of the hippocampal, thalamic, and amygdalar neurons projecting to the prefrontal cortex in male and female rats during context-mediated renewal of responding to food cues. *Neurobiol. Learn. Mem.* 150, 25–35.
- Anderson, M.C., Bjork, R.A., Bjork, E.L., 1994. Remembering can cause forgetting: retrieval dynamics in long-term memory. *J. Exp. Psychol. Learn. Mem. Cogn.* 20, 1063–1087.
- Arellano Perez, A.D., Popik, B., de Oliveira Alvares, L., 2020. Rewarding information presented during reactivation attenuates fear memory: methylphenidate and fear memory updating. *Neuropharmacology* 171, 108107.
- Asok, A., Leroy, F., Rayman, J.B., Kandel, E.R., 2019. Molecular mechanisms of the memory trace. *Trends Neurosci.* 42, 14–22.
- Awasthi, A., Ramachandran, B., Ahmed, S., Benito, E., Shinoda, Y., Nitzan, N., Heukamp, A., Rannio, S., Martens, H., Barth, J., Burk, K., Wang, Y.T., Fischer, A., Dean, C., 2019. Synaptotagmin-3 drives AMPA receptor endocytosis, depression of synapse strength, and forgetting. *Science* 363.
- Baldi, E., Bucherelli, C., 2015. Brain sites involved in fear memory reconsolidation and extinction of rodents. *Neurosci. Biobehav. Rev.* 53, 160–190.
- Baldo, B.A., Kelley, A.E., 2007. Discrete neurochemical coding of distinguishable motivational processes: insights from nucleus accumbens control of feeding. *Psychopharmacology (Berl.)* 191, 439–459.
- Balleine, B.W., Killcross, A.S., Dickinson, A., 2003. The effect of lesions of the basolateral amygdala on instrumental conditioning. *J. Neurosci.* 23, 666–675.
- Barnes, C.A., McNaughton, B.L., Mizumori, S.J., Leonard, B.W., Lin, L.H., 1990. Comparison of spatial and temporal characteristics of neuronal activity in sequential stages of hippocampal processing. *Prog. Brain Res.* 83, 287–300.
- Barreiro, K.A., Suarez, L.D., Lynch, V.M., Molina, V.A., Delorenzi, A., 2013. Memory expression is independent of memory labilization/reconsolidation. *Neurobiol. Learn. Mem.* 106, 283–291.
- Barry, D.N., Maguire, E.A., 2019. Remote memory and the Hippocampus: a constructive critique. *Trends Cogn. Sci.* 23, 128–142.
- Beckers, T., Kindt, M., 2017a. Memory reconsolidation interference as an emerging treatment for emotional disorders: strengths, limitations, challenges, and opportunities. *Annu. Rev. Clin. Psychol.* 13, 99–121.
- Beckers, T., Kindt, M., 2017b. Memory reconsolidation interference as an emerging treatment for emotional disorders: strengths, limitations, challenges, and opportunities. *Annu. Rev. Clin. Psychol.* 13, 99–121.
- Bekinschtein, P., Weisstaub, N.V., Gallo, F., Renner, M., Anderson, M.C., 2018. A retrieval-specific mechanism of adaptive forgetting in the mammalian brain. *Nat. Commun.* 9, 4660.
- Ben Mamou, C., Gamache, K., Nader, K., 2006. NMDA receptors are critical for unleashing consolidated auditory fear memories. *Nat. Neurosci.* 9, 1237–1239.
- Berger, S.M., Bartsch, D., 2014. The role of L-type voltage-gated calcium channels Cav1.2 and Cav1.3 in normal and pathological brain function. *Cell Tissue Res.* 357, 463–476.
- Berlau, D.J., McGaugh, J.L., 2006. Enhancement of extinction memory consolidation: the role of the noradrenergic and GABAergic systems within the basolateral amygdala. *Neurobiol. Learn. Mem.* 86, 123–132.
- Bernardi, R.E., Lattal, K.M., 2010. A role for alpha-adrenergic receptors in extinction of conditioned fear and cocaine conditioned place preference. *Behav. Neurosci.* 124, 204–210.
- Bernier, B.E., Lacagnina, A.F., Ayoub, A., Shue, F., Zemelman, B.V., Krasne, F.B., Drew, M.R., 2017. Dentate gyrus contributes to retrieval as well as encoding: evidence from context fear conditioning, recall, and extinction. *J. Neurosci.* 37, 6359–6371.
- Besnard, A., Caboche, J., Laroche, S., 2012. Reconsolidation of memory: a decade of debate. *Prog. Neurobiol.* 99, 61–80.
- Beyeler, A., Namburi, P., Glover, G.F., Simonnet, C., Calhoun, G.G., Conyers, G.F., Luck, R., Wildes, C.P., Tye, K.M., 2016. Divergent routing of positive and negative information from the amygdala during memory retrieval. *Neuron* 90, 348–361.
- Bisby, M.A., Richardson, R., Baker, K.D., 2020. Developmental differences in the effects of CB1/2R agonist WIN55212-2 on extinction of learned fear. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 99, 109834.
- Bitencourt, R.M., Pamplona, F.A., Takahashi, R.N., 2008. Facilitation of contextual fear memory extinction and anti-anxiogenic effects of AM404 and cannabidiol in conditioned rats. *Eur. Neuropsychopharmacol.* 18, 849–859.
- Bloodgood, D.W., Sugam, J.A., Holmes, A., Kash, T.L., 2018. Fear extinction requires infralimbic cortex projections to the basolateral amygdala. *Transl. Psychiatry* 8, 60.
- Bossert, J.M., Stern, A.L., 2014. Role of ventral subiculum in context-induced reinstatement of heroin seeking in rats. *Addict. Biol.* 19, 338–342.
- Bouton, M.E., 1993. Context, time, and memory retrieval in the interference paradigms of Pavlovian learning. *Psychol. Bull.* 114, 80–99.
- Bouton, M.E., 2004. Context and behavioral processes in extinction. *Learn. Mem.* 11, 485–494.
- Bouton, M.E., Bolles, R.C., 1979. Role of conditioned contextual stimuli in reinstatement of extinguished fear. *J. Exp. Psychol. Anim. Behav. Process.* 5, 368–378.
- Bouton, M.E., Westbrook, R.F., Corcoran, K.A., Maren, S., 2006. Contextual and temporal modulation of extinction: behavioral and biological mechanisms. *Biol. Psychiatry* 60, 352–360.

- Bravo-Rivera, C., Roman-Ortiz, C., Brignoni-Perez, E., Sotres-Bayon, F., Quirk, G.J., 2014. Neural structures mediating expression and extinction of platform-mediated avoidance. *J. Neurosci.* 34, 9736–9742.
- Bukalo, O., Pinard, C.R., Silverstein, S., Brehm, C., Hartley, N.D., Whittle, N., Colacicco, G., Busch, E., Patel, S., Singewald, N., Holmes, A., 2015. Prefrontal inputs to the amygdala instruct fear extinction memory formation. *Sci. Adv.* 1.
- Burgos-Robles, A., Vidal-Gonzalez, I., Quirk, G.J., 2009. Sustained conditioned responses in prelimbic prefrontal neurons are correlated with fear expression and extinction failure. *J. Neurosci.* 29, 8474–8482.
- Burgos-Robles, A., Kimchi, E.Y., Izadmehr, E.M., Porzenheim, M.J., Ramos-Guasp, W.A., Nieh, E.H., Felix-Ortiz, A.C., Namburi, P., Leppla, C.A., Presbrey, K.N., Anandalingam, K.K., Pagan-Rivera, P.A., Anahar, M., Beyeler, A., Tye, K.M., 2017. Amygdala inputs to prefrontal cortex guide behavior amid conflicting cues of reward and punishment. *Nat. Neurosci.*
- Busse, S., Schwarting, R.K., 2016. Decoupling actions from consequences: dorsal hippocampal lesions facilitate instrumental performance, but impair behavioral flexibility in rats. *Front. Behav. Neurosci.* 10, 118.
- Bustos, S.G., Maldonado, H., Molina, V.A., 2009. Disruptive effect of midazolam on fear memory reconsolidation: decisive influence of reactivation time span and memory age. *Neuropsychopharmacology* 34, 446–457.
- Bustos, S.G., Giachero, M., Maldonado, H., Molina, V.A., 2010. Previous stress attenuates the susceptibility to Midazolam's disruptive effect on fear memory reconsolidation: influence of pre-reactivation D-cycloserine administration. *Neuropsychopharmacology* 35, 1097–1108.
- Cahill, E.N., Wood, M.A., Everitt, B.J., Milton, A.L., 2019. The role of prediction error and memory destabilization in extinction of cued-fear within the reconsolidation window. *Neuropsychopharmacology* 44, 1762–1768.
- Cain, C.K., Blouin, A.M., Barad, M., 2004. Adrenergic transmission facilitates extinction of conditional fear in mice. *Learn. Mem.* 11, 179–187.
- Carpenter, J.K., Pinaire, M., Hofmann, S.G., 2019. From extinction learning to anxiety treatment: mind the gap. *Brain Sci.* 9.
- Cassini, L.F., Flavell, C.R., Amaral, O.B., Lee, J.L.C., 2017. On the transition from reconsolidation to extinction of contextual fear memories. *Learn. Mem.* 24, 392–399.
- Castro, D.C., Bruchas, M.R., 2019. A motivational and neuropeptidergic hub: anatomical and functional diversity within the nucleus accumbens shell. *Neuron* 102, 529–552.
- Chalkia, A., Schroyens, N., Leng, L., Vanhasbroeck, N., Zenses, A.K., Van Oudenhove, L., Beckers, T., 2020a. No persistent attenuation of fear memories in humans: a registered replication of the reactivation-extinction effect. *Cortex* 129, 496–509.
- Chalkia, A., Van Oudenhove, L., Beckers, T., 2020b. Preventing the return of fear in humans using reconsolidation update mechanisms: a verification report of Schiller et al. (2010). *Cortex* 129, 510–525.
- Chan, W.Y., Leung, H.T., Westbrook, R.F., McNally, G.P., 2010. Effects of recent exposure to a conditioned stimulus on extinction of Pavlovian fear conditioning. *Learn. Mem.* 17, 512–521.
- Cho, J.H., Deisseroth, K., Bolshakov, V.Y., 2013. Synaptic encoding of fear extinction in mPFC-amygdala circuits. *Neuron* 80, 1491–1507.
- Clem, R.L., Huganir, R.L., 2010. Calcium-permeable AMPA receptor dynamics mediate fear memory erasure. *Science* 330, 1108–1112.
- Colombo, G., Vacca, G., Serra, S., Carai, M.A., Gessa, G.L., 2004. Suppressing effect of the cannabinoid CB1 receptor antagonist, SR 141716, on alcohol's motivational properties in alcohol-preferring rats. *Eur. J. Pharmacol.* 498, 119–123.
- Corcoran, K.A., Maren, S., 2001. Hippocampal inactivation disrupts contextual retrieval of fear memory after extinction. *J. Neurosci.* 21, 1720–1726.
- Corcoran, K.A., Desmond, T.J., Frey, K.A., Maren, S., 2005. Hippocampal inactivation disrupts the acquisition and contextual encoding of fear extinction. *J. Neurosci.* 25, 8978–8987.
- Correia, S.S., McGrath, A.G., Lee, A., Graybiel, A.M., Goossens, K.A., 2016. Amygdala-ventral striatum circuit activation decreases long-term fear. *Elife* 5.
- Costanzi, M., Cannas, S., Sarauli, D., Rossi-Arnaud, C., Cestari, V., 2011. Extinction after retrieval: effects on the associative and nonassociative components of remote contextual fear memory. *Learn. Mem.* 18, 508–518.
- Courtin, J., Chaudun, F., Rozeske, R.R., Karalis, N., Gonzalez-Campo, C., Wurtz, H., Abdi, A., Baufreton, J., Bienvenu, T.C., Herry, C., 2014. Prefrontal parvalbumin interneurons shape neuronal activity to drive fear expression. *Nature* 505, 92–96.
- Dandolo, L.C., Schwabe, L., 2019. Time-dependent motor memory representations in prefrontal cortex. *Neuroimage* 197, 143–155.
- Davis, R.L., Zhong, Y., 2017. The biology of Forgetting-A perspective. *Neuron* 95, 490–503.
- de la Fuente, V., Freudenthal, R., Romano, A., 2011. Reconsolidation or extinction: transcription factor switch in the determination of memory course after retrieval. *J. Neurosci.* 31, 5562–5573.
- de Oliveira Alvares, L., Pasqualini Genro, B., Diehl, F., Molina, V.A., Quillfeldt, J.A., 2008. Opposite action of hippocampal CB1 receptors in memory reconsolidation and extinction. *Neuroscience* 154, 1648–1655.
- De Oliveira Alvares, L., Crestani, A.P., Cassini, L.F., Haubrich, J., Santana, F., Quillfeldt, J.A., 2013. Reactivation enables memory updating, precision-keeping and strengthening: exploring the possible biological roles of reconsolidation. *Neuroscience* 244, 42–48.
- Dejean, C., Courtin, J., Karalis, N., Chaudun, F., Wurtz, H., Bienvenu, T.C., Herry, C., 2016. Prefrontal neuronal assemblies temporally control fear behaviour. *Nature* 535, 420–424.
- DeNardo, L.A., Liu, C.D., Allen, W.E., Adams, E.L., Friedmann, D., Fu, L., Guenther, C.J., Tessier-Lavigne, M., Luo, L., 2019. Temporal evolution of cortical ensembles promoting remote memory retrieval. *Nat. Neurosci.*
- Dewar, M.T., Cowan, N., Sala, S.D., 2007. Forgetting due to retroactive interference: a fusion of Muller and Pilzecker's (1900) early insights into everyday forgetting and recent research on anterograde amnesia. *Cortex* 43, 616–634.
- Dickinson, A., 1981. Conditioning and associative learning. *Br. Med. Bull.* 37, 165–168.
- Dickinson, A., 2012. Associative learning and animal cognition. *Philos. Trans. R. Soc. Lond., B, Biol. Sci.* 367, 2733–2742.
- Do Monte, F.H., Souza, R.R., Bitencourt, R.M., Kroon, J.A., Takahashi, R.N., 2013. Infusion of cannabidiol into infralimbic cortex facilitates fear extinction via CB1 receptors. *Behav. Brain Res.* 250, 23–27.
- Do Monte, F.H., Quirk, G.J., Li, B., Penzo, M.A., 2016. Retrieving fear memories, as time goes by. *Mol. Psychiatry* 21, 1027–1036.
- Do-Monte, F.H., Allensworth, M., Carobrez, A.P., 2010a. Impairment of contextual conditioned fear extinction after microinjection of alpha-1-adrenergic blocker prazosin into the medial prefrontal cortex. *Behav. Brain Res.* 211, 89–95.
- Do-Monte, F.H., Kincheski, G.C., Pavesi, E., Sordi, R., Assreuy, J., Carobrez, A.P., 2010b. Role of beta-adrenergic receptors in the ventromedial prefrontal cortex during contextual fear extinction in rats. *Neurobiol. Learn. Mem.* 94, 318–328.
- Do-Monte, F.H., Manzano-Nieves, G., Quinones-Laracuente, K., Ramos-Medina, L., Quirk, G.J., 2015a. Revisiting the role of infralimbic cortex in fear extinction with optogenetics. *J. Neurosci.* 35, 3607–3615.
- Do-Monte, F.H., Quinones-Laracuente, K., Quirk, G.J., 2015b. A temporal shift in the circuits mediating retrieval of fear memory. *Nature* 519, 460–463.
- Dong, L.D., Gao, F., Wang, X.H., Miao, Y., Wang, S.Y., Wu, Y., Li, F., Wu, J., Cheng, X.L., Sun, X.H., Yang, X.L., Wang, Z., 2015. GluA2 trafficking is involved in apoptosis of retinal ganglion cells induced by activation of EphB/EphrinB reverse signaling in a rat chronic ocular hypertension model. *J. Neurosci.* 35, 5409–5421.
- Dudai, Y., 2012. The restless engram: consolidations never end. *Annu. Rev. Neurosci.* 35, 227–247.
- Dunsmoor, J.E., Niv, Y., Daw, N., Phelps, E.A., 2015. Rethinking extinction. *Neuron* 88, 47–63.
- Else, J.W.B., Kindt, M., 2017. Breaking boundaries: optimizing reconsolidation-based interventions for strong and old memories. *Learn. Mem.* 24, 472–479.
- Else, J.W.B., Van Ast, V.A., Kindt, M., 2018. Human memory reconsolidation: a guiding framework and critical review of the evidence. *Psychol. Bull.* 144, 797–848.
- Epp, J.R., Silva Mera, R., Kohler, S., Josselyn, S.A., Frankland, P.W., 2016. Neurogenesis-mediated forgetting minimizes proactive interference. *Nat. Commun.* 7, 10838.
- Exton-McGuinness, M.T., Lee, J.L., Reichelt, A.C., 2015. Updating memories—the role of prediction errors in memory reconsolidation. *Behav. Brain Res.* 278, 375–384.
- Fernandez, R.S., Boccia, M.M., Pedreira, M.E., 2016. The fate of memory: reconsolidation and the case of Prediction Error. *Neurosci. Biobehav. Rev.* 68, 423–441.
- Fitzgerald, P.J., Giustino, T.F., Seemann, J.R., Maren, S., 2015. Noradrenergic blockade stabilizes prefrontal activity and enables fear extinction under stress. *Proc. Natl. Acad. Sci. U. S. A.* 112, E3729–3737.
- Foa, E.B., McLean, C.P., 2016. The efficacy of exposure therapy for anxiety-related disorders and its underlying mechanisms: the case of OCD and PTSD. *Annu. Rev. Clin. Psychol.* 12, 1–28.
- Fonseca, R., 2012. Activity-dependent actin dynamics are required for the maintenance of long-term plasticity and for synaptic capture. *Eur. J. Neurosci.* 35, 195–206.
- Forcato, C., Fernandez, R.S., Pedreira, M.E., 2013. The role and dynamic of strengthening in the reconsolidation process in a human declarative memory: what decides the fate of recent and older memories? *PLoS One* 8, e61688.
- Forcato, C., Fernandez, R.S., Pedreira, M.E., 2014. Strengthening a consolidated memory: the key role of the reconsolidation process. *J. Physiol. Paris* 108, 323–333.
- Frankland, P.W., Bontempi, B., 2005. The organization of recent and remote memories. *Nat. Rev. Neurosci.* 6, 119–130.
- Fukushima, H., Zhang, Y., Archbold, G., Ishikawa, R., Nader, K., Kida, S., 2014. Enhancement of fear memory by retrieval through reconsolidation. *Elife* 3, e02736.
- Furlong, T.M., Richardson, R., McNally, G.P., 2016. Habituation and extinction of fear recruit overlapping forebrain structures. *Neurobiol. Learn. Mem.* 128, 7–16.
- Ganella, D.E., Nguyen, L.D., Lee-Kardashyan, L., Kim, L.E., Paolini, A.G., Kim, J.H., 2018. Neurocircuitry of fear extinction in adult and juvenile rats. *Behav. Brain Res.* 351, 161–167.
- Gessa, G.L., Serra, S., Vacca, G., Carai, M.A., Colombo, G., 2005. Suppressing effect of the cannabinoid CB1 receptor antagonist, SR147778, on alcohol intake and motivational properties of alcohol in alcohol-preferring sP rats. *Alcohol Alcohol.* 40, 46–53.
- Gisquet-Verrier, P., Riccio, D.C., 2018. Memory integration as a challenge to the Consolidation/Reconsolidation hypothesis: similarities, differences and perspectives. *Front. Syst. Neurosci.* 12, 71.
- Gisquet-Verrier, P., Lynch 3rd, J.F., Cutolo, P., Toledano, D., Ulmen, A., Jasnow, A.M., Riccio, D.C., 2015. Integration of new information with active memory accounts for retrograde Amnesia: a challenge to the Consolidation/Reconsolidation hypothesis? *J. Neurosci.* 35, 11623–11633.
- Gold, M.G., 2012. A frontier in the understanding of synaptic plasticity: solving the structure of the postsynaptic density. *Bioessays* 34, 599–608.
- Gomez-Ospina, N., Tsuruta, F., Barreto-Chang, O., Hu, L., Dolmetsch, R., 2006. The C terminus of the L-type voltage-gated calcium channel Ca(V)1.2 encodes a transcription factor. *Cell* 127, 591–606.
- Goode, T.D., Maren, S., 2014. Animal models of fear relapse. *ILAR J.* 55, 246–258.
- Goode, T.D., Holloway-Erickson, C.M., Maren, S., 2017. Extinction after fear memory reactivation fails to eliminate renewal in rats. *Neurobiol. Learn. Mem.* 142, 41–47.
- Graff, J., Joseph, N.F., Horn, M.E., Samiei, A., Meng, J., Seo, J., Rei, D., Bero, A.W., Phan, T.X., Wagner, F., Holson, E., Xu, J., Sun, J., Neve, R.L., Mach, R.H., Haggarty, S.J., Tsai, L.H., 2014. Epigenetic priming of memory updating during reconsolidation to attenuate remote fear memories. *Cell* 156, 261–276.
- Gunduz-Cinar, O., MacPherson, K.P., Cinar, R., Gamble-George, J., Sugden, K., Williams, B., Godlewski, G., Ramikie, T.S., Gorka, A.X., Alapafuja, S.O., Nikas, S.P.,

- Makriyannis, A., Poulton, R., Patel, S., Hariri, A.R., Caspi, A., Moffitt, T.E., Kunos, G., Holmes, A., 2013. Convergent translational evidence of a role for anandamide in amygdala-mediated fear extinction, threat processing and stress-reactivity. *Mol. Psychiatry* 18, 813–823.
- Hardt, O., Nader, K., Nadel, L., 2013. Decay happens: the role of active forgetting in memory. *Trends Cogn. Sci. (Regul. Ed.)* 17, 111–120.
- Hart, G., Harris, J.A., Westbrook, R.F., 2009. Systemic or intra-amygdala injection of a benzodiazepine (midazolam) impairs extinction but spares re-extinction of conditioned fear responses. *Learn. Mem.* 16, 53–61.
- Haubrich, J., Nader, K., 2018. Memory reconsolidation. *Curr. Top. Behav. Neurosci.* 37, 151–176.
- Haubrich, J., Crestani, A.P., Cassini, L.F., Santana, F., Sierra, R.O., Alvares Lde, O., Quilfeldt, J.A., 2015. Reconsolidation allows fear memory to be updated to a less aversive level through the incorporation of appetitive information. *Neuropsychopharmacology* 40, 315–326.
- Haubrich, J., Bernabo, M., Nader, K., 2020. Noradrenergic projections from the locus coeruleus to the amygdala constrain fear memory reconsolidation. *Elife* 9.
- Havekes, R., Nijholt, I.M., Visser, A.K., Eisel, U.L., Van der Zee, E.A., 2008. Transgenic inhibition of neuronal calcineurin activity in the forebrain facilitates fear conditioning, but inhibits the extinction of contextual fear memories. *Neurobiol. Learn. Mem.* 89, 595–598.
- Hawkins, R.D., Byrne, J.H., 2015. Associative learning in invertebrates. *Cold Spring Harb. Perspect. Biol.* 7.
- Herry, C., Trifilieff, P., Micheau, J., Luthi, A., Mons, N., 2006. Extinction of auditory fear conditioning requires MAPK/ERK activation in the basolateral amygdala. *Eur. J. Neurosci.* 24, 261–269.
- Herry, C., Ciocchi, S., Senn, V., Demmou, L., Muller, C., Luthi, A., 2008. Switching on and off fear by distinct neuronal circuits. *Nature* 454, 600–606.
- Hitchcock, L.N., Lattal, K.M., 2018. Involvement of the dorsal hippocampus in expression and extinction of cocaine-induced conditioned place preference. *Hippocampus* 28, 226–238.
- Hobin, J.A., Ji, J., Maren, S., 2006. Ventral hippocampal muscimol disrupts context-specific fear memory retrieval after extinction in rats. *Hippocampus* 16, 174–182.
- Holahan, M.R., White, N.M., 2004. Amygdala c-Fos induction corresponds to unconditioned and conditioned aversive stimuli but not to freezing. *Behav. Brain Res.* 152, 109–120.
- Hollandt, M., Wroblewski, A., Yang, Y., Ridderbusch, I.C., Kircher, T., Hamm, A.O., Straube, B., Richter, J., 2020. Facilitating translational science in anxiety disorders by adjusting extinction training in the laboratory to exposure-based therapy procedures. *Transl. Psychiatry* 10, 110.
- Hong, I., Song, B., Lee, S., Kim, J., Choi, S., 2009. Extinction of cued fear memory involves a distinct form of depotentiation at cortical input synapses onto the lateral amygdala. *Eur. J. Neurosci.* 30, 2089–2099.
- Hong, I., Kim, J., Lee, S., Ko, H.G., Nader, K., Kaang, B.K., Tsien, R.W., Choi, S., 2013. AMPA receptor exchange underlies transient memory destabilization on retrieval. *Proc. Natl. Acad. Sci. U. S. A.* 110, 8218–8223.
- Hoover, W.B., Vertes, R.P., 2012. Collateral projections from nucleus reuniens of thalamus to hippocampus and medial prefrontal cortex in the rat: a single and double retrograde fluorescent labeling study. *Brain Struct. Funct.* 217, 191–209.
- Hu, S.S., Liu, Y.W., Yu, L., 2015. Medial prefrontal cannabinoid CB1 receptors modulate consolidation and extinction of cocaine-associated memory in mice. *Psychopharmacology (Berl)* 232, 1803–1815.
- Hupbach, A., Hardt, O., Gomez, R., Nadel, L., 2008. The dynamics of memory: context-dependent updating. *Learn. Mem.* 15, 574–579.
- Inda, M.C., Muravieva, E.V., Alberini, C.M., 2011. Memory retrieval and the passage of time: from reconsolidation and strengthening to extinction. *J. Neurosci.* 31, 1635–1643.
- Ishii, D., Matsuzawa, D., Matsuda, S., Tomizawa, H., Sutoh, C., Shimizu, E., 2012. No erasure effect of retrieval-extinction trial on fear memory in the hippocampus-independent and dependent paradigms. *Neurosci. Lett.* 523, 76–81.
- Jarome, T.J., Werner, C.T., Kwapis, J.L., Helmstetter, F.J., 2011. Activity dependent protein degradation is critical for the formation and stability of fear memory in the amygdala. *PLoS One* 6, e24349.
- Jarome, T.J., Ferrara, N.C., Kwapis, J.L., Helmstetter, F.J., 2016. CaMKII regulates proteasome phosphorylation and activity and promotes memory destabilization following retrieval. *Neurobiol. Learn. Mem.* 128, 103–109.
- Jin, J., Maren, S., 2015. Fear renewal preferentially activates ventral hippocampal neurons projecting to both amygdala and prefrontal cortex in rats. *Sci. Rep.* 5, 8388.
- Josselyn, S.A., Kohler, S., Frankland, P.W., 2015. Finding the engram. *Nat. Rev. Neurosci.* 16, 521–534.
- Khaleghzadeh-Ahangar, H., Haghighparast, A., 2015. Intra-accumbal CB1 receptor blockade reduced extinction and reinstatement of morphine. *Physiol. Behav.* 149, 212–219.
- Kida, S., 2019. Reconsolidation/destabilization, extinction and forgetting of fear memory as therapeutic targets for PTSD. *Psychopharmacology (Berl)* 236, 49–57.
- Kiefer, F., Dinter, C., 2013. New approaches to addiction treatment based on learning and memory. *Curr. Top. Behav. Neurosci.* 13, 671–684.
- Kim, W.B., Cho, J.H., 2017. Encoding of discriminative fear memory by input-specific LTP in the amygdala. *Neuron* 95, 1129–1146 e1125.
- Kim, J., Lee, S., Park, K., Hong, I., Song, B., Son, G., Park, H., Kim, W.R., Park, E., Choe, H.K., Kim, H., Lee, C., Sun, W., Kim, K., Shin, K.S., Choi, S., 2007. Amygdala depotentiation and fear extinction. *Proc. Natl. Acad. Sci. U. S. A.* 104, 20955–20960.
- Knapka, E., Maren, S., 2009. Reciprocal patterns of c-Fos expression in the medial prefrontal cortex and amygdala after extinction and renewal of conditioned fear. *Learn. Mem.* 16, 486–493.
- Kritman, M., Maroun, M., 2013. Inhibition of the PI3 kinase cascade in corticolimbic circuit: temporal and differential effects on contextual fear and extinction. *Int. J. Neuropsychopharmacol.* 16, 825–833.
- Kubie, J.L., Levy, E.R.J., Fenton, A.A., 2019. Is hippocampal remapping the physiological basis for context? *Hippocampus*.
- Kwapis, J.L., Jarome, T.J., Lee, J.L., Gilmartin, M.R., Helmstetter, F.J., 2014. Extinguishing trace fear engages the retrosplenial cortex rather than the amygdala. *Neurobiol. Learn. Mem.* 113, 41–54.
- Lacagnina, A.F., Brockway, E.T., Crovetti, C.R., Shue, F., McCarty, M.J., Sattler, K.P., Lim, S.C., Santos, S.L., Denny, C.A., Drew, M.R., 2019. Distinct hippocampal engrams control extinction and relapse of fear memory. *Nat. Neurosci.* 22, 753–761.
- Lai, C.S., Franke, T.F., Gan, W.B., 2012. Opposite effects of fear conditioning and extinction on dendritic spine remodelling. *Nature* 483, 87–91.
- Laurent, V., Westbrook, R.F., 2009. Inactivation of the infralimbic but not the prelimbic cortex impairs consolidation and retrieval of fear extinction. *Learn. Mem.* 16, 520–529.
- Lee, J.L., 2008. Memory reconsolidation mediates the strengthening of memories by additional learning. *Nat. Neurosci.* 11, 1264–1266.
- Lee, J.L., 2009. Reconsolidation: maintaining memory relevance. *Trends Neurosci.* 32, 413–420.
- Lee, J.L., 2010. Memory reconsolidation mediates the updating of hippocampal memory content. *Front. Behav. Neurosci.* 4, 168.
- Lee, J.L., Milton, A.L., Everitt, B.J., 2006. Reconsolidation and extinction of conditioned fear: inhibition and potentiation. *J. Neurosci.* 26, 10051–10056.
- Lee, S.H., Choi, J.H., Lee, N., Lee, H.R., Kim, J.I., Yu, N.K., Choi, S.L., Kim, H., Kaang, B. K., 2008. Synaptic protein degradation underlies destabilization of retrieved fear memory. *Science* 319, 1253–1256.
- Lee, J.L.C., Nader, K., Schiller, D., 2017. An update on memory reconsolidation updating. *Trends Cogn. Sci.* 21, 531–545.
- Lewis, D.J., 1979. Psychobiology of active and inactive memory. *Psychol. Bull.* 86, 1054–1083.
- Lewis, D.J., Misanin, J.R., Miller, R.R., 1968. Recovery of memory following amnesia. *Nature* 220, 704–705.
- Lieberman, D.N., Mody, I., 1994. Regulation of NMDA channel function by endogenous Ca(2+)-dependent phosphatase. *Nature* 369, 235–239.
- Lingawi, N.W., Westbrook, R.F., Laurent, V., 2017. Extinction and latent inhibition involve a similar form of inhibitory learning that is stored in and retrieved from the infralimbic cortex. *Cereb. Cortex* 27, 5547–5556.
- Lisboa, S.F., Vila-Verde, C., Rosa, J., Uliana, D.L., Stern, C.A.J., Bertoglio, L.J., Resstel, L. B., Guimarães, F.S., 2019. Tempering aversive/traumatic memories with cannabinoids: a review of evidence from animal and human studies. *Psychopharmacology (Berl)* 236, 201–226.
- Liu, Y., Du, S., Lv, L., Lei, B., Shi, W., Tang, Y., Wang, L., Zhong, Y., 2016. Hippocampal activation of Rac1 regulates the forgetting of object recognition memory. *Curr. Biol.* 26, 2351–2357.
- Liu, Y., Lv, L., Wang, L., Zhong, Y., 2018. Social isolation induces Rac1-Dependent forgetting of social memory. *Cell Rep.* 25, 288–295 e283.
- Loftus, E.F., Davis, D., 2006. Recovered memories. *Annu. Rev. Clin. Psychol.* 2, 469–498.
- Lu, K.T., Walker, D.L., Davis, M., 2001. Mitogen-activated protein kinase cascade in the basolateral nucleus of amygdala is involved in extinction of fear-potentiated startle. *J. Neurosci.* 21, RC162.
- Luchkina, N.V., Bolshakov, V.Y., 2019. Mechanisms of fear learning and extinction: synaptic plasticity-fear memory connection. *Psychopharmacology (Berl.)* 236, 163–182.
- Lunardi, P., Sachser, R.M., Sierra, R.O., Pedraza, L.K., Medina, C., de la Fuente, V., Romano, A., Quilfeldt, J.A., de Oliveira Alvares, L., 2018. Effects of hippocampal LIMK inhibition on memory acquisition, consolidation, retrieval, reconsolidation, and extinction. *Mol. Neurobiol.* 55, 958–967.
- Lunardi, P., de Souza, L.W., Dos Santos, B., Popik, B., de Oliveira Alvares, L., 2020. Effect of the endocannabinoid system in memory updating and forgetting. *Neuroscience* 444, 33–42.
- Lutz, B., 2007. The endocannabinoid system and extinction learning. *Mol. Neurobiol.* 36, 92–101.
- Marek, R., Xu, L., Sullivan, R.K.P., Sah, P., 2018. Excitatory connections between the prelimbic and infralimbic medial prefrontal cortex show a role for the prelimbic cortex in fear extinction. *Nat. Neurosci.* 21, 654–658.
- Marek, R., Sun, Y., Sah, P., 2019. Neural circuits for a top-down control of fear and extinction. *Psychopharmacology (Berl.)* 236, 313–320.
- Maren, S., Quirk, G.J., 2004. Neuronal signalling of fear memory. *Nat. Rev. Neurosci.* 5, 844–852.
- Maren, S., Aharonov, G., Stote, D.L., Fanselow, M.S., 1996. N-methyl-D-aspartate receptors in the basolateral amygdala are required for both acquisition and expression of conditional fear in rats. *Behav. Neurosci.* 110, 1365–1374.
- Marsicano, G., Wotjak, C.T., Azad, S.C., Bisogno, T., Rammes, G., Cascio, M.G., Hermann, H., Tang, J., Hofmann, C., Ziegler, W., Di Marzo, V., Lutz, B., 2002. The endogenous cannabinoid system controls extinction of aversive memories. *Nature* 418, 530–534.
- McDonald, A.J., 1991. Organization of amygdaloid projections to the prefrontal cortex and associated striatum in the rat. *Neuroscience* 44, 1–14.
- McGaugh, J.L., 2000. Memory—a century of consolidation. *Science* 287, 248–251.
- McLaughlin, R.J., Floresco, S.B., 2007. The role of different subregions of the basolateral amygdala in cue-induced reinstatement and extinction of food-seeking behavior. *Neuroscience* 146, 1484–1494.
- Medina, J.H., 2018. Neural, cellular and molecular mechanisms of active forgetting. *Front. Syst. Neurosci.* 12, 3.

- Meir Drexler, S., Wolf, O.T., 2017. The role of glucocorticoids in emotional memory reconsolidation. *Neurobiol. Learn. Mem.* 142, 126–134.
- Merlo, E., Milton, A.L., Goozee, Z.Y., Theobald, D.E., Everitt, B.J., 2014. Reconsolidation and extinction are distinct but mutually exclusive processes: behavioral and molecular evidence. *J. Neurosci.* 34, 2422–2431.
- Merlo, E., Ratano, P., Ilioi, E.C., Robbins, M.A., Everitt, B.J., Milton, A.L., 2015. Amygdala dopamine receptors are required for the destabilization of a reconsolidating appetitive memory. *eNeuro* 2.
- Merlo, E., Milton, A.L., Everitt, B.J., 2018. A novel retrieval-dependent memory process revealed by the arrest of ERK1/2 activation in the basolateral amygdala. *J. Neurosci.* 38, 3199–3207.
- Migues, P.V., Liu, L., Archbold, G.E., Einarsson, E.O., Wong, J., Bonasia, K., Ko, S.H., Wang, Y.T., Hardt, O., 2016. Blocking synaptic removal of GluN2B- and GluN2A-containing AMPA receptors prevents the natural forgetting of long-term memories. *J. Neurosci.* 36, 3481–3494.
- Migues, P.V., Wong, J., Lyu, J., Hardt, O., 2019. NMDA receptor activity bidirectionally controls active decay of long-term spatial memory in the dorsal hippocampus. *Hippocampus* 29, 883–888.
- Milekic, M.H., Alberini, C.M., 2002. Temporally graded requirement for protein synthesis following memory reactivation. *Neuron* 36, 521–525.
- Milton, A.L., Merlo, E., Ratano, P., Gregory, B.L., Dumbreck, J.K., Everitt, B.J., 2013. Double dissociation of the requirement for GluN2B- and GluN2A-containing NMDA receptors in the destabilization and restabilization of a reconsolidating memory. *J. Neurosci.* 33, 1109–1115.
- Miserendino, M.J., Sananes, C.B., Melia, K.R., Davis, M., 1990. Blocking of acquisition but not expression of conditioned fear-potentiated startle by NMDA antagonists in the amygdala. *Nature* 345, 716–718.
- Monfils, M.H., Holmes, E.A., 2018. Memory boundaries: opening a window inspired by reconsolidation to treat anxiety, trauma-related, and addiction disorders. *Lancet Psychiatry* 5, 1032–1042.
- Monfils, M.H., Cowansage, K.K., Klann, E., LeDoux, J.E., 2009. Extinction-reconsolidation boundaries: key to persistent attenuation of fear memories. *Science* 324, 951–955.
- Morena, M., Berardi, A., Colucci, P., Palmery, M., Trezza, V., Hill, M.N., Campolongo, P., 2018. Enhancing endocannabinoid neurotransmission augments the efficacy of extinction training and ameliorates traumatic stress-induced behavioral alterations in rats. *Neuropsychopharmacology* 43, 1284–1296.
- Morris, R.G., Inglis, J., Ainge, J.A., Olverman, H.J., Tulloch, J., Dudai, Y., Kelly, P.A., 2006. Memory reconsolidation: sensitivity of spatial memory to inhibition of protein synthesis in dorsal hippocampus during encoding and retrieval. *Neuron* 50, 479–489.
- Moscovitch, M., Cabeza, R., Winocur, G., Nadel, L., 2016. Episodic memory and beyond: the Hippocampus and neocortex in transformation. *Annu. Rev. Psychol.* 67, 105–134.
- Mueller, D., Porter, J.T., Quirk, G.J., 2008. Noradrenergic signaling in infralimbic cortex increases cell excitability and strengthens memory for fear extinction. *J. Neurosci.* 28, 369–375.
- Müller, G., Pilzecker, A., 1900. Experimentelle Beiträge zur Lehre vom Gedächtnis. *Ergänzungsband Z. Psychol.* 1, 1–300.
- Murayama, K., Miyatsu, T., Buchli, D., Storm, B.C., 2014. Forgetting as a consequence of retrieval: a meta-analytic review of retrieval-induced forgetting. *Psychol. Bull.* 140, 1383–1409.
- Nader, K., 2015. Reconsolidation and the dynamic nature of memory. *Cold Spring Harb. Perspect. Biol.* 7, a021782.
- Nader, K., Schafe, G.E., LeDoux, J.E., 2000a. Fear memories require protein synthesis in the amygdala for reconsolidation after retrieval. *Nature* 406, 722–726.
- Nader, K., Schafe, G.E., LeDoux, J.E., 2000b. The labile nature of consolidation theory. *Nat. Rev. Neurosci.* 1, 216–219.
- Namburi, P., Beyeler, A., Yorozu, S., Calhoon, G.G., Halbert, S.A., Wichmann, R., Holden, S.S., Mertens, K.L., Anahtar, M., Felix-Ortiz, A.C., Wickersham, I.R., Gray, J. M., Tye, K.M., 2015. A circuit mechanism for differentiating positive and negative associations. *Nature* 520, 675–678.
- Norby, S., 2015. Why forget? On the adaptive value of memory loss. *Perspect. Psychol. Sci.* 10, 551–578.
- Okuda, S., Roozendaal, B., McGaugh, J.L., 2004. Glucocorticoid effects on object recognition memory require training-associated emotional arousal. *Proc. Natl. Acad. Sci. U. S. A.* 101, 853–858.
- Otis, J.M., Werner, C.T., Mueller, D., 2015. Noradrenergic regulation of fear and drug-associated memory reconsolidation. *Neuropsychopharmacology* 40, 793–803.
- Pagani, M.R., Merlo, E., 2019. Kinase and phosphatase engagement is dissociated between memory formation and extinction. *Front. Mol. Neurosci.* 12, 38.
- Park, J., Choi, J.S., 2010. Long-term synaptic changes in two input pathways into the lateral nucleus of the amygdala underlie fear extinction. *Learn. Mem.* 17, 23–34.
- Park, H., Kaang, B.K., 2019. Balanced actions of protein synthesis and degradation in memory formation. *Learn. Mem.* 26, 299–306.
- Pavlov, I., 1927. *Conditioned Reflexes*. Oxford University Press.
- Pearce, J.M., Bouton, M.E., 2001. Theories of associative learning in animals. *Annu. Rev. Psychol.* 52, 111–139.
- Pedraza, L.K., Sierra, R.O., Crestani, A.P., Quillfeldt, J.A., de Oliveira Alvares, L., 2017. Sequential learning during contextual fear conditioning guides the rate of systems consolidation: implications for consolidation of multiple memory traces. *Hippocampus* 27, 518–528.
- Pedraza, L.K., Sierra, R.O., Lotz, F.N., de Oliveira Alvares, L., 2018. Periodical reactivation under the effect of caffeine attenuates fear memory expression in rats. *Sci. Rep.* 8, 7260.
- Pedreira, M.E., Maldonado, H., 2003. Protein synthesis subserves reconsolidation or extinction depending on reminder duration. *Neuron* 38, 863–869.
- Pedreira, M.E., Perez-Cuesta, L.M., Maldonado, H., 2004. Mismatch between what is expected and what actually occurs triggers memory reconsolidation or extinction. *Learn. Mem.* 11, 579–585.
- Penzo, M.A., Robert, V., Tucciarone, J., De Bundel, D., Wang, M., Van Aelst, L., Darvas, M., Parada, L.F., Palmiter, R.D., He, M., Huang, Z.J., Li, B., 2015. The paraventricular thalamus controls a central amygdala fear circuit. *Nature* 519, 455–459.
- Phelps, E.A., Hofmann, S.G., 2019. Memory editing from science fiction to clinical practice. *Nature* 572, 43–50.
- Pica, G., Chernikova, M., Pierro, A., Giannini, A.M., Kruglanski, A.W., 2018. Retrieval-induced forgetting as motivated cognition. *Front. Psychol.* 9, 2030.
- Pineyro, M.E., Ferrer Monti, R.I., Alfei, J.M., Bueno, A.M., Urcelay, G.P., 2013. Memory destabilization is critical for the success of the reactivation-extinction procedure. *Learn. Mem.* 21, 46–54.
- Podlesnik, C.A., Kelley, M.E., Jimenez-Gomez, C., Bouton, M.E., 2017. Renewed behavior produced by context change and its implications for treatment maintenance: a review. *J. Appl. Behav. Anal.* 50, 675–697.
- Popik, B., Amorim, F.E., Amaral, O.B., De Oliveira Alvares, L., 2020. Shifting from fear to safety through deconditioning-update. *Elife* 9.
- Portero-Tresserra, M., Marti-Nicolovius, M., Guillaizo-Blanch, G., Boadas-Vaello, P., Vale-Martinez, A., 2013. D-cycloserine in the basolateral amygdala prevents extinction and enhances reconsolidation of odor-reward associative learning in rats. *Neurobiol. Learn. Mem.* 100, 1–11.
- Przybylski, J., Sara, S.J., 1997. Reconsolidation of memory after its reactivation. *Behav. Brain Res.* 84, 241–246.
- Quirk, G.J., Mueller, D., 2008. Neural mechanisms of extinction learning and retrieval. *Neuropsychopharmacology* 33, 56–72.
- Radulovic, J., Jovasevic, V., Meyer, M.A., 2017. Neurobiological mechanisms of state-dependent learning. *Curr. Opin. Neurobiol.* 45, 92–98.
- Ramachandran, B., Frey, J.U., 2009. Interfering with the actin network and its effect on long-term potentiation and synaptic tagging in hippocampal CA1 neurons in slices in vitro. *J. Neurosci.* 29, 12167–12173.
- Ramanathan, K.R., Maren, S., 2019. Nucleus reuniens mediates the extinction of contextual fear conditioning. *Behav. Brain Res.* 374, 112114.
- Ramanathan, K.R., Jin, J., Giustino, T.F., Payne, M.R., Maren, S., 2018. Prefrontal projections to the thalamic nucleus reuniens mediate fear extinction. *Nat. Commun.* 9, 4527.
- Ramirez, S., Liu, X., Lin, P.A., Suh, J., Pignatelli, M., Redondo, R.L., Ryan, T.J., Tonegawa, S., 2013. Creating a false memory in the hippocampus. *Science* 341, 387–391.
- Rao-Ruiz, P., Rotaru, D.C., van der Loo, R.J., Mansvelder, H.D., Stiedl, O., Smit, A.B., Spijker, S., 2011a. Retrieval-specific endocytosis of GluA2-AMPA receptors underlies adaptive reconsolidation of contextual fear. *Nat. Neurosci.* 14, 1302–1308.
- Rao-Ruiz, P., Rotaru, D.C., van der Loo, R.J., Mansvelder, H.D., Stiedl, O., Smit, A.B., Spijker, S., 2011b. Retrieval-specific endocytosis of GluA2-AMPA receptors underlies adaptive reconsolidation of contextual fear. *Nat. Neurosci.* 14, 1302–1308.
- Rashid, A.J., Yan, C., Mercaldo, V., Hsiang, H.L., Park, S., Cole, C.J., De Cristofaro, A., Yu, J., Ramakrishnan, C., Lee, S.Y., Deisseroth, K., Frankland, P.W., Josselyn, S.A., 2016. Competition between engrams influences fear memory formation and recall. *Science* 353, 383–387.
- Redondo, R.L., Kim, J., Arons, A.L., Ramirez, S., Liu, X., Tonegawa, S., 2014. Bidirectional switch of the valence associated with a hippocampal contextual memory engram. *Nature* 513, 426–430.
- Rescorla, R.A., 1988. Behavioral studies of Pavlovian conditioning. *Annu. Rev. Neurosci.* 11, 329–352.
- Rescorla, R.A., 2004. Spontaneous recovery. *Learn. Mem.* 11, 501–509.
- Richards, B.A., Frankland, P.W., 2017. The persistence and transience of memory. *Neuron* 94, 1071–1084.
- Ritvo, V.J.H., Turk-Browne, N.B., Norman, K.A., 2019. Nonmonotonic plasticity: how memory retrieval drives learning. *Trends Cogn. Sci.* 23, 726–742.
- Roozendaal, B., McGaugh, J.L., 2011. Memory modulation. *Behav. Neurosci.* 125, 797–824.
- Rosa, J., Myskiw, J.C., Furini, C.R., Sapiras, G.G., Izquierdo, I., 2014. Fear extinction can be made state-dependent on peripheral epinephrine: role of norepinephrine in the nucleus tractus solitarius. *Neurobiol. Learn. Mem.* 113, 55–61.
- Rosas-Vidal, L.E., Do-Monte, F.H., Sotres-Bayon, F., Quirk, G.J., 2014. Hippocampal-prefrontal BDNF and memory for fear extinction. *Neuropsychopharmacology* 39, 2161–2169.
- Rosas-Vidal, L.E., Lozada-Miranda, V., Cantres-Rosario, Y., Vega-Medina, A., Melendez, L., Quirk, G.J., 2018. Alteration of BDNF in the medial prefrontal cortex and the ventral hippocampus impairs extinction of avoidance. *Neuropsychopharmacology* 43, 2636–2644.
- Roy, D.S., Arons, A., Mitchell, T.I., Pignatelli, M., Ryan, T.J., Tonegawa, S., 2016. Memory retrieval by activating engram cells in mouse models of early Alzheimer's disease. *Nature* 531, 508–512.
- Roy, D.S., Muralidhar, S., Smith, L.M., Tonegawa, S., 2017. Silent memory engrams as the basis for retrograde amnesia. *Proc. Natl. Acad. Sci. U. S. A.* 114, E9972–E9979.
- Ryan, T.J., Roy, D.S., Pignatelli, M., Arons, A., Tonegawa, S., 2015. Memory. Engram cells retain memory under retrograde amnesia. *Science* 348, 1007–1013.
- Sacco, T., Sacchetti, B., 2010. Role of secondary sensory cortices in emotional memory storage and retrieval in rats. *Science* 329, 649–656.
- Sachser, R.M., Crestani, A.P., Quillfeldt, J.A., Mello, E.S.T., de Oliveira Alvares, L., 2015. The cannabinoid system in the retrosplenial cortex modulates fear memory consolidation, reconsolidation, and extinction. *Learn. Mem.* 22, 584–588.

- Sachser, R.M., Santana, F., Crestani, A.P., Lunardi, P., Pedraza, L.K., Quillfeldt, J.A., Hardt, O., Alvares Lde, O., 2016. Forgetting of long-term memory requires activation of NMDA receptors, L-type voltage-dependent Ca²⁺ channels, and calcineurin. *Sci. Rep.* 6, 22771.
- Sachser, R.M., Haubrich, J., Lunardi, P.S., de Oliveira Alvares, L., 2017. Forgetting of what was once learned: exploring the role of postsynaptic ionotropic glutamate receptors on memory formation, maintenance, and decay. *Neuropharmacology* 112, 94–103.
- Salinas-Hernandez, X.I., Vogel, P., Betz, S., Kalisch, R., Sigurdsson, T., Duvanci, S., 2018. Dopamine neurons drive fear extinction learning by signaling the omission of expected aversive outcomes. *Elife* 7.
- Sananbenesi, F., Fischer, A., Wang, X., Schrick, C., Neve, R., Radulovic, J., Tsai, L.H., 2007. A hippocampal Cdk5 pathway regulates extinction of contextual fear. *Nat. Neurosci.* 10, 1012–1019.
- Sangha, S., Scheibenstock, A., Lukowiak, K., 2003. Reconsolidation of a long-term memory in *Lymanaea* requires new protein and RNA synthesis and the soma of right pedal dorsal 1. *J. Neurosci.* 23, 8034–8040.
- Santini, E., Sepulveda-Orengo, M., Porter, J.T., 2012. Muscarinic receptors modulate the intrinsic excitability of infralimbic neurons and consolidation of fear extinction. *Neuropsychopharmacology* 37, 2047–2056.
- Schacter, D.L., Guerin, S.A., St Jacques, P.L., 2011. Memory distortion: an adaptive perspective. *Trends Cogn. Sci. (Regul. Ed.)* 15, 467–474.
- Segev, A., Korem, N., Mizrahi Zer-Aviv, T., Abush, H., Lange, R., Sauber, G., Hillard, C. J., Akirav, I., 2018. Role of endocannabinoids in the hippocampus and amygdala in emotional memory and plasticity. *Neuropsychopharmacology* 43, 2017–2027.
- Senn, V., Wolff, S.B., Herry, C., Grenier, F., Ehrlich, I., Grundemann, J., Fadok, J.P., Muller, C., Letzkus, J.J., Luthi, A., 2014. Long-range connectivity defines behavioral specificity of amygdala neurons. *Neuron* 81, 428–437.
- Sevenster, D., Beckers, T., Kindt, M., 2012. Retrieval per se is not sufficient to trigger reconsolidation of human fear memory. *Neurobiol. Learn. Mem.* 97, 338–345.
- Sevenster, D., Beckers, T., Kindt, M., 2013. Prediction error governs pharmacologically induced amnesia for learned fear. *Science* 339, 830–833.
- Sevenster, D., Beckers, T., Kindt, M., 2014. Prediction error demarcates the transition from retrieval, to reconsolidation, to new learning. *Learn. Mem.* 21, 580–584.
- Shehata, M., Abdou, K., Choko, K., Matsuo, M., Nishizono, H., Inokuchi, K., 2018. Autophagy enhances memory erasure through synaptic destabilization. *J. Neurosci.* 38, 3809–3822.
- Shinohara, K., Hata, T., 2014. [Post-training N-methyl-D-aspartate receptor blockade facilitates retention of acquired spatial memory in rats]. *Shinrigaku Kenkyu* 84, 618–624.
- Shuai, Y., Lu, B., Hu, Y., Wang, L., Sun, K., Zhong, Y., 2010. Forgetting is regulated through Rac activity in *Drosophila*. *Cell* 140, 579–589.
- Sierra, R.O., Cassini, L.F., Santana, F., Crestani, A.P., Duran, J.M., Haubrich, J., de Oliveira Alvares, L., Quillfeldt, J.A., 2013. Reconsolidation may incorporate state-dependency into previously consolidated memories. *Learn. Mem.* 20, 379–387.
- Sierra-Mercado, D., Padilla-Coreano, N., Quirk, G.J., 2011. Dissociable roles of prelimbic and infralimbic cortices, ventral hippocampus, and basolateral amygdala in the expression and extinction of conditioned fear. *Neuropsychopharmacology* 36, 529–538.
- Simonyi, A., Serfozo, P., Shelat, P.B., Dopheide, M.M., Coulibaly, A.P., Schachtman, T.R., 2007. Differential roles of hippocampal metabotropic glutamate receptors 1 and 5 in inhibitory avoidance learning. *Neurobiol. Learn. Mem.* 88, 305–311.
- Sinclair, A.H., Barense, M.D., 2018. Surprise and destabilize: prediction error influences episodic memory reconsolidation. *Learn. Mem.* 25, 369–381.
- Sinclair, A.H., Barense, M.D., 2019. Prediction error and memory reactivation: how incomplete reminders drive reconsolidation. *Trends Neurosci.* 42, 727–739.
- Singewald, N., Schmuckermair, C., Whittle, N., Holmes, A., Ressler, K.J., 2015. Pharmacology of cognitive enhancers for exposure-based therapy of fear, anxiety and trauma-related disorders. *Pharmacol. Ther.* 149, 150–190.
- Soeter, M., Kindt, M., 2012. Stimulation of the noradrenergic system during memory formation impairs extinction learning but not the disruption of reconsolidation. *Neuropsychopharmacology* 37, 1204–1215.
- Sotres-Bayon, F., Bush, D.E., LeDoux, J.E., 2007. Acquisition of fear extinction requires activation of NR2B-containing NMDA receptors in the lateral amygdala. *Neuropsychopharmacology* 32, 1929–1940.
- Sotres-Bayon, F., Sierra-Mercado, D., Pardilla-Delgado, E., Quirk, G.J., 2012. Gating of fear in prelimbic cortex by hippocampal and amygdala inputs. *Neuron* 76, 804–812.
- Squire, L.R., Genzel, L., Wixted, J.T., Morris, R.G., 2015. Memory consolidation. *Cold Spring Harb. Perspect. Biol.* 7, a021766.
- Stiver, M.L., Jacklin, D.L., Mitchnick, K.A., Vicic, N., Carlin, J., O'Hara, M., Winters, B.D., 2015. Cholinergic manipulations bidirectionally regulate object memory destabilization. *Learn. Mem.* 22, 203–214.
- Stuber, G.D., Sparta, D.R., Stamatakis, A.M., van Leeuwen, W.A., Hardjoprajitno, J.E., Cho, S., Tye, K.M., Kempadoo, K.A., Zhang, F., Deisseroth, K., Bonci, A., 2011. Excitatory transmission from the amygdala to nucleus accumbens facilitates reward seeking. *Nature* 475, 377–380.
- Suzuki, A., Josselyn, S.A., Frankland, P.W., Masushige, S., Silva, A.J., Kida, S., 2004. Memory reconsolidation and extinction have distinct temporal and biochemical signatures. *J. Neurosci.* 24, 4787–4795.
- Suzuki, A., Mukawa, T., Tsukagoshi, A., Frankland, P.W., Kida, S., 2008. Activation of LVCs and CB1 receptors required for destabilization of reactivated contextual fear memories. *Learn. Mem.* 15, 426–433.
- Szabo, E.C., Manguinhas, R., Fonseca, R., 2016. The interplay between neuronal activity and actin dynamics mimic the setting of an LTD synaptic tag. *Sci. Rep.* 6, 33685.
- Szapiro, G., Vianna, M.R., McGaugh, J.L., Medina, J.H., Izquierdo, I., 2003. The role of NMDA glutamate receptors, PKA, MAPK, and CAMKII in the hippocampus in extinction of conditioned fear. *Hippocampus* 13, 53–58.
- Taujanskaitė, U., Cahill, E.N., Milton, A.L., 2020. Targeting drug memory reconsolidation: a neural analysis. *Curr. Opin. Pharmacol.* 56, 7–12.
- Thompson, R.F., Spencer, W.A., 1966. Habituation: a model phenomenon for the study of neuronal substrates of behavior. *Psychol. Rev.* 73, 16–43.
- Todd, T.P., Jiang, M.Y., DeAngeli, N.E., Bucci, D.J., 2018. A functional circuit for the retrieval of remote cued fear memory. *Behav. Neurosci.* 132, 403–408.
- Toledano, D., Gisquet-Verrier, P., 2014. Only susceptible rats exposed to a model of PTSD exhibit reactivity to trauma-related cues and other symptoms: an effect abolished by a single amphetamine injection. *Behav. Brain Res.* 272, 165–174.
- Tonegawa, S., Morrissey, M.D., Kitamura, T., 2018. The role of engram cells in the systems consolidation of memory. *Nat. Rev. Neurosci.* 19, 485–498.
- Torquatto, K.I., Menegolla, A.P., Popik, B., Casagrande, M.A., de Oliveira Alvares, L., 2019. Role of calcium-permeable AMPA receptors in memory consolidation, retrieval and updating. *Neuropharmacology* 144, 312–318.
- Troyner, F., Bicca, M.A., Bertoglio, L.J., 2018. Nucleus reuniens of the thalamus controls fear memory intensity, specificity and long-term maintenance during consolidation. *Hippocampus* 28, 602–616.
- Tse, D., Langston, R.F., Kakeyama, M., Bethus, I., Spooner, P.A., Wood, E.R., Witter, M. P., Morris, R.G., 2007. Schemas and memory consolidation. *Science* 316, 76–82.
- Tye, K.M., Cone, J.J., Schairer, W.W., Janak, P.H., 2010. Amygdala neural encoding of the absence of reward during extinction. *J. Neurosci.* 30, 116–125.
- Uematsu, A., Tan, B.Z., Ycu, E.A., Cuevas, J.S., Koivumaa, J., Junyent, F., Kremer, E.J., Witten, I.B., Deisseroth, K., Johansen, J.P., 2017. Modular organization of the brainstem noradrenergic system coordinates opposing learning states. *Nat. Neurosci.* 20, 1602–1611.
- Vahdat, S., Fogel, S., Benali, H., Doyon, J., 2017. Network-wide reorganization of procedural memory during NREM sleep revealed by fMRI. *Elife* 6.
- Van den Oever, M.C., Rotaru, D.C., Heinsbroek, J.A., Gouwenberg, Y., Deisseroth, K., Stuber, G.D., Mansvelder, H.D., Smit, A.B., 2013. Ventromedial prefrontal cortex pyramidal cells have a temporal dynamic role in recall and extinction of cocaine-associated memory. *J. Neurosci.* 33, 18225–18233.
- Varela, C., Kumar, S., Yang, J.Y., Wilson, M.A., 2014. Anatomical substrates for direct interactions between hippocampus, medial prefrontal cortex, and the thalamic nucleus reuniens. *Brain Struct. Funct.* 219, 911–929.
- Varvel, S.A., Anum, E.A., Lichtman, A.H., 2005. Disruption of CB(1) receptor signaling impairs extinction of spatial memory in mice. *Psychopharmacology (Berl.)* 179, 863–872.
- Vasquez, J.H., Leong, K.C., Gagliardi, C.M., Harland, B., Apicella, A.J., Muzzio, I.A., 2019. Pathway specific activation of ventral hippocampal cells projecting to the prelimbic cortex diminishes fear renewal. *Neurobiol. Learn. Mem.* 161, 63–71.
- Vervliet, B., Craske, M.G., Hermans, D., 2013. Fear extinction and relapse: state of the art. *Annu. Rev. Clin. Psychol.* 9, 215–248.
- Vetere, G., Tran, L.M., Moberg, S., Steadman, P.E., Restivo, L., Morrison, F.G., Ressler, K. J., Josselyn, S.A., Frankland, P.W., 2019. Memory formation in the absence of experience. *Nat. Neurosci.* 22, 933–940.
- Villareal, D.M., Do, V., Haddad, E., Derrick, B.E., 2002. NMDA receptor antagonists sustain LTP and spatial memory: active processes mediate LTP decay. *Nat. Neurosci.* 5, 48–52.
- Wang, S.H., de Oliveira Alvares, L., Nader, K., 2009. Cellular and systems mechanisms of memory strength as a constraint on auditory fear reconsolidation. *Nat. Neurosci.* 12, 905–912.
- Wang, M.E., Yuan, R.K., Keinath, A.T., Ramos Alvarez, M.M., Muzzio, I.A., 2015. Extinction of learned fear induces hippocampal place cell remapping. *J. Neurosci.* 35, 9122–9136.
- Wang, C., Yue, H., Hu, Z., Shen, Y., Ma, J., Li, J., Wang, X.D., Wang, L., Sun, B., Shi, P., Gu, Y., 2020a. Microglia mediate forgetting via complement-dependent synaptic elimination. *Science* 367, 688–694.
- Wang, Y., Liu, Z., Cai, L., Guo, R., Dong, Y., Huang, Y.H., 2020b. A critical role of basolateral amygdala-to-Nucleus accumbens projection in sleep regulation of reward seeking. *Biol. Psychiatry* 87, 954–966.
- Wideman, C.E., Jardine, K.H., Winters, B.D., 2018. Involvement of classical neurotransmitter systems in memory reconsolidation: focus on destabilization. *Neurobiol. Learn. Mem.* 156, 68–79.
- Winters, B.D., Tucci, M.C., DaCosta-Furtado, M., 2009. Older and stronger object memories are selectively destabilized by reactivation in the presence of new information. *Learn. Mem.* 16, 545–553.
- Wixted, J.T., 2004. The psychology and neuroscience of forgetting. *Annu. Rev. Psychol.* 55, 235–269.
- Wright, C.I., Beijer, A.V., Groenewegen, H.J., 1996. Basal amygdaloid complex afferents to the rat nucleus accumbens are compartmentally organized. *J. Neurosci.* 16, 1877–1893.
- Wu, J.Q., Peters, G.J., Rittner, P., Cleland, T.A., Smith, D.M., 2014. The hippocampus, medial prefrontal cortex, and selective memory retrieval: evidence from a rodent model of the retrieval-induced forgetting effect. *Hippocampus* 24, 1070–1080.
- Xu, W., Sudhof, T.C., 2013. A neural circuit for memory specificity and generalization. *Science* 339, 1290–1295.
- Xu, C., Krabbe, S., Grundemann, J., Botta, P., Fadok, J.P., Osakada, F., Saur, D., Grewe, B.F., Schnitzer, M.J., Callaway, E.M., Luthi, A., 2016. Distinct hippocampal pathways mediate dissociable roles of context in memory retrieval. *Cell* 167 (961–972), e916.
- Yamada, D., Zushida, K., Wada, K., Sekiguchi, M., 2009. Pharmacological discrimination of extinction and reconsolidation of contextual fear memory by a potentiator of AMPA receptors. *Neuropsychopharmacology* 34, 2574–2584.

- Zalcman, G., Federman, N., de la Fuente, V., Romano, A., 2015. Nuclear factor kappa B-dependent Zif268 expression in hippocampus is required for recognition memory in mice. *Neurobiol. Learn. Mem.* 119, 10–17.
- Zentall, T.R., 2013. Animals represent the past and the future. *Evol. Psychol.* 11, 573–590.
- Zhang, X., Li, B., 2018. Population coding of valence in the basolateral amygdala. *Nat. Commun.* 9, 5195.
- Zhang, X.M., Luo, J.H., 2013. GluN2A versus GluN2B: twins, but quite different. *Neurosci. Bull.* 29, 761–772.
- Zhang, J.J., Haubrich, J., Bernabo, M., Finnie, P.S.B., Nader, K., 2018a. Limits on lability: boundaries of reconsolidation and the relationship to metaplasticity. *Neurobiol. Learn. Mem.* 154, 78–86.
- Zhang, X., Li, Q., Wang, L., Liu, Z.J., Zhong, Y., 2018b. Active protection: learning-activated Raf/MAPK activity protects labile memory from Rac1-Independent forgetting. *Neuron* 98 (142–155), e144.
- Zhang, X., Kim, J., Tonegawa, S., 2020. Amygdala reward neurons form and store fear extinction memory. *Neuron* 105, 1077–1093 e1077.
- Zimmerman, J.M., Maren, S., 2010. NMDA receptor antagonism in the basolateral but not central amygdala blocks the extinction of Pavlovian fear conditioning in rats. *Eur. J. Neurosci.* 31, 1664–1670.
- Zinn, R., Leake, J., Krasne, F.B., Corbit, L.H., Fanselow, M.S., Vissel, B., 2020. Maladaptive properties of context-impooverished memories. *Curr. Biol.* 30, 2300–2311 e2306.