Neuroscience and Biobehavioral Reviews 136 (2022) 104598

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review article

The evidence for and against reactivation-induced memory updating in humans and nonhuman animals

Kristen H. Jardine [1], A. Ethan Huff [1], Cassidy E. Wideman [1], Shelby D. McGraw, Boyer D. Winters [*]

Department of Psychology and Collaborative Neuroscience Program, University of Guelph, Guelph, ON, Canada

ARTICLE INFO

Keywords:
Boundary conditions
Destabilization
Human
Labilization
Modification
Rodent
Memory
Reconsolidation
Retrieval
Storage

ABSTRACT

Systematic investigation of reactivation-induced memory updating began in the 1960s, and a wave of research in this area followed the seminal articulation of "reconsolidation" theory in the early 2000s. Myriad studies indicate that memory reactivation can cause previously consolidated memories to become labile and sensitive to weakening, strengthening, or other forms of modification. However, from its nascent period to the present, the field has been beset by inconsistencies in researchers' abilities to replicate seemingly established effects. Here we review these many studies, synthesizing the human and nonhuman animal literature, and suggest that these failures-to-replicate reflect a highly complex and delicately balanced memory modification system, the substrates of which must be finely tuned to enable adaptive memory updating while limiting maladaptive, inaccurate modifications. A systematic approach to the entire body of evidence, integrating positive and null findings, will yield a comprehensive understanding of the complex and dynamic nature of long-term memory storage and the potential for harnessing modification processes to treat mental disorders driven by pervasive maladaptive memories.

1. Introduction

1.1. Long-term memory storage is dynamic

Over a century of memory consolidation research has detailed brain systems that enable memory storage and retrieval over time. Discovery of such storage processes led many to assume that, natural forgetting aside, information remains in long-term memory storage in a relatively unchanged state unless physically affected by lesion, pathology, or other forms of trauma (McGaugh, 1966). However, the conversation surrounding long-term memory storage has drastically changed in recent decades. Evidence now suggests that cellular and synaptic changes induced by exposure to behaviorally relevant stimuli can modify established long-term memory traces under certain circumstances (Misanin et al., 1968; Nadel et al., 2012; Nader, 2003). Thus, the neural connections established during memory consolidation are not permanent and may be rendered modifiable under specific conditions.

The concept that consolidated memories re-enter a labile state following retrieval was first described by Misanin, Miller and Lewis in 1968 when they reported that electroconvulsive shock (ECS) administration after brief exposure to a conditioned stimulus (CS) impaired subsequent expression of a conditioned fear response in rats. Studies following this initial discovery further supported the notion of post-reactivation memory interference, among them a reproduction of Misanin and colleagues' original findings using similar experimental procedures (DeVietti and Holliday, 1972). Building on original demonstrations of post-reactivation interference, one group reported that re-exposure to the training context alone rendered a previously consolidated shock avoidance memory vulnerable to disruption by ECS, puromycin, or other amnesic agents (Davis and Hirtzel, 1970; Davis and Klinger, 1969). Based on a subsequent series of experiments revealing a post-reactivation period of vulnerability (Gordon, 1977a, 1977b; Gordon and Spear, 1973; Judge and Quartermain, 1982; Schneider and Sherman, 1968), Donald Lewis theorized that memories exist in an active state following learning or retrieval, and these active memory traces are vulnerable to disruption by amnesic agents; he suggested that this process likely enables integration of new information into an established memory or the association of multiple established memory

* Correspondence to: Department of Psychology, University of Guelph, Guelph, ON N1G 2W1, Canada.
E-mail address: bwinters@uoguelph.ca (B.D. Winters).
[1] These authors contributed equally to the writing of the manuscript.

https://doi.org/10.1016/j.neubiorev.2022.104598
Received 8 July 2021; Received in revised form 28 February 2022; Accepted 1 March 2022
Available online 3 March 2022

traces together (Lewis, 1979).

Alongside the above findings in support of Lewis' active trace theory, other groups reported failed replication attempts (Dawson and McGaugh, 1969; Squire et al., 1976), dampening confidence in the validity of post-reactivation memory modification. Contradictory findings diminished the momentum of research in this area for a number of decades. Then, in the late 1990s, important advancements were made towards understanding the mechanisms of memory reactivation and re-storage, renewing interest in long-term memory modification. In 1997, Przybyslawski and Sara found that a consolidated spatial memory was impaired if an N-methyl-D-aspartate (NMDA) receptor antagonist was administered systemically shortly after a reminder of the learning context. Soon afterwards, Nader et al. (2000a) provided pivotal evidence of reactivation-based auditory fear memory weakening, which was induced by post-reactivation protein synthesis inhibition within the amygdala. Nader and colleagues outlined a "reconsolidation" theory (Nader, 2003; Nader et al., 2000a, 2000b), which proposed that reactivation can trigger synaptic connection destabilization within a memory representation and, in parallel, can initiate the protein synthesis machinery that is required to re-stabilize (i.e., re-consolidate) the memory trace. Accordingly, protein synthesis inhibitors or ECS would elicit post-retrieval amnesia by interrupting the re-stabilization process and blocking reconsolidation.

The framework of the putative memory reconsolidation process is now better understood (Fig. 1), as the body of research devoted to understanding post-reactivation memory modification has been growing since the foundational reports described above. Parsing of the memory reconsolidation process into distinct subprocesses has further facilitated characterization of the mechanisms that cooperatively support memory modification. Memory reactivation—which is typically achieved through retrieval or a reminder cue of the original learning conditions—initiates the process for returning a stored memory trace to a labile state (Finnie and Nader, 2012; Nader, 2003), after which the memory can be weakened, strengthened, or updated with new material (Lee et al., 2017). A memory reactivation episode must successfully engage mechanisms of memory destabilization for the memory to become labile. Memory destabilization refers to the process of synaptic

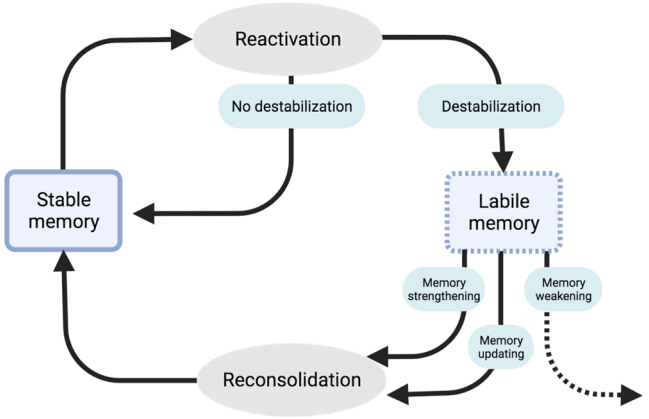

Fig. 1. Framework of the memory reconsolidation process. After consolidation, long-term memories exist in a stable form. Upon reactivation, a memory can become labile, or unstable, contingent on whether the reactivation conditions engage mechanisms of destabilization. It is possible that memory reactivation does not trigger memory destabilization if there are certain boundary conditions in place to prevent modification, in which case the memory will remain in a stable form. When memory destabilization does occur, the memory becomes susceptible to changes. A destabilized memory is labile for a limited period of time before it is reconsolidated and returns to a stable and potentially strengthened or otherwise updated state. Disrupting reconsolidation with pharmacological or behavioural interference will prevent the memory from returning to a stable form (erasure) or lead to restorage of a weakened version of the original memory.

level breakdown which, theoretically, permits changes to the existing core memory trace in the brain. There is growing support that specific synaptic proteins established during consolidation are targeted for degradation during memory destabilization (Lee et al., 2008). Consequently, in order for the core memory trace to persist after destabilization, it must undergo protein synthesis-dependent reconsolidation (Nader, 2003, 2016; Tronson and Taylor, 2007).

Notably, memory reactivation and/or retrieval can occur in the absence of memory destabilization. If mechanisms of memory destabilization are pharmacologically blocked during a reactivation session, memory modification does not occur. The distinction between these two concepts is critical for assessing the relevance of the memory reconsolidation process to memory updating and could potentially explain recent challenges in replicating classic reconsolidation findings.

1.2. *Memory reactivation versus destabilization*

Memory reactivation occurs when a reminder of a past learning experience is presented, which typically elicits memory retrieval. In the reconsolidation literature, the terms 'retrieval' and 'reactivation' are often used interchangeably, but they are distinct cognitive processes. Conscious retrieval is commonly used for memory reactivation in human studies, as this seems to guarantee memory reactivation to some extent (Bridge and Paller, 2012; Nyberg et al., 2000; Sara, 2010; Wheeler et al., 2000). However, memory reactivation can occur during sleep or even when retrieval is blocked pharmacologically (Balderas et al., 2013; Lewis and Bendor, 2019; Sara, 2010), suggesting that reactivation may not require conscious retrieval.

A memory reactivation session in a laboratory setting is typically designed to trigger destabilization mechanisms and render the memory labile. Critically, key features must be present during a memory reactivation session to prompt memory destabilization and/or modification. For example, the duration or quantity of reminder cues during memory reactivation appears to be a critical factor that determines the engagement of the reconsolidation process (Eisenberg et al., 2003; Hu et al., 2018; Pedreira and Maldonado, 2003). Furthermore, memory destabilization seems to be heavily dependent on context re-establishment during reactivation, wherein some contextual factors from the training episode need to be present again during memory reactivation in order for updating to occur (Forcato et al., 2009; Hupbach et al., 2013; Hupbach, Hardt et al., 2008).

Interestingly, however, destabilization does not reliably occur when the reactivation session is an exact repeat of the initial learning session or an extra learning session (Agustina López et al., 2016; Forcato et al., 2011; Tay et al., 2019). Growing evidence suggests that there needs to be some level of surprise (or prediction error) in order for the reactivation session to induce a labile period. Indeed, several studies have indicated that prediction error is key for memory reactivation to trigger destabilization and modification (Exton-McGuinness et al., 2015; Fernández et al., 2016; Li et al., 2019; Rossato et al., 2007; Sevenster et al., 2013; Sinclair and Barense, 2018, 2019). A brief reminder cue of previously learned stimuli may reliably reactivate and destabilize a relatively weak or recent memory (Finnie and Nader, 2012; Hu et al., 2018; Suzuki et al., 2004; Winters et al., 2009), but a higher degree of unexpectedness during a memory reactivation session is required to destabilize a strongly encoded memory that is resistant to modification. Thus, not all reactivated memory traces readily destabilize. Certain 'boundary conditions' to destabilization appear to prevent some memories from entering a labile state (see Boundaries on Memory Destabilization and Updating section). Although the presence of boundary conditions is generally acknowledged, their molecular determinants have not been widely studied, and these critical factors determining memory destabilization likely vary considerably between memory types and brain systems.

Thus, there appears to be a specific, subtle and still poorly understood interplay between the features of a reactivation session and

memory characteristics, which determine the likelihood that memory destabilization will occur (Forcato et al., 2009; Kindt, 2018). Some argue that explicitly novel stimuli *are required* during reactivation to destabilize a memory trace, whereas others have been able to elicit destabilization of recent memories without introducing obvious novel stimuli during reactivation (Eisenberg and Dudai, 2004; Lee et al., 2006b; Milekic and Alberini, 2002; Nader et al., 2000a; Winters et al., 2009). The reasons for specific inconsistencies between studies remain unclear; however, the absence of a perfect replication record for such findings likely reflects the stringent behavioral and biological conditions that must be met in order to destabilize and modify certain types of memories and should not necessarily be taken as evidence against the existence of a reconsolidation-like process.

2. Forms of post-reactivation memory modification

Since evidence for post-retrieval retrograde amnesia was first reported in the 1960s, it has been suggested that additional labile periods provide an opportunity for memory modification. Many believe that the reconsolidation process 'opens a window' of opportunity to update consolidated memories with new information. Accordingly, numerous studies have indicated that reactivated memory traces can be weakened, strengthened, or otherwise 'updated' during the post-reactivation window. These concepts are summarized here, and evidence for and against their existence is discussed in later sections.

2.1. Memory weakening

Reactivation-based amnesia paradigms follow a typical format in animals and humans: a consolidated memory trace is reactivated with a reminder cue associated with the original learning event, and then an amnesic drug or informational interference is introduced within a few hours post-reactivation with the intention to interrupt the neural processes required for the memory to re-stabilize. Subsequent memory impairment for the original information is assumed to be the result of blocking restorage of the labile memory. Historically, studies of reactivation-induced memory 'erasure' dominate the literature. This approach is effective for revealing the presence of a post-reactivation labile window, but reactivation-based memory weakening—while potentially an important contributor to natural forgetting processes (Bekinschtein et al., 2018)—is likely not the primary role of reconsolidation. Indeed, researchers recognizing the potential for other forms of memory modification have also used reconsolidation procedures to study memory strengthening and integrative updating.

2.2. Memory strengthening

Strengthening a memory with additional training during the post-reactivation labile period has become a cornerstone for showing the potentially adaptive properties of reconsolidation-like processes. Sara (2000) was the first to discuss the potential of such a process for memory strengthening. Models of reactivation-based memory strengthening are largely drawn from human declarative memory and rodent fear memory paradigms. In rodents, these paradigms typically involve post-reactivation additional training sessions or post-reactivation administration of cognitive enhancing drugs, resulting in stronger behavioural responses during subsequent testing (Lee, 2008; Tay et al., 2019; Tronson et al., 2006). Multiple labilization sessions (Forcato et al., 2013, 2011; MacLeod et al., 2018; Tay et al., 2019) or repeated reminder presentations within a labile period (Forcato et al., 2013, 2011) also suffice for strengthening declarative memories in humans.

Reactivation-induced memory strengthening paradigms indicate that this process can be engaged to improve subsequent retrieval of memories. However, similarly to reactivation-induced amnesia models, these results do not directly demonstrate how a post-reactivation labile window might also provide an opportunity for incorporating new information into existing memories, rather than merely influencing the magnitude of expression of those memories. Reactivation-induced memory strengthening is often described as memory updating, but it does not represent clear evidence for the putative memory remodelling that might occur within the reconsolidation window.

2.3. Integrative memory updating

Incorporating new information into existing memory networks is another type of memory updating that likely occurs regularly in the real world. It has been challenging, however, to produce such qualitative memory updating in the laboratory setting, especially in animal models, potentially because there has been a lack of viable tasks for this kind of constructive memory modification in non-human animal models. Human studies have more successfully addressed this gap in the literature (Agren, 2014; Elsey et al., 2018).

The retrieval-extinction phenomenon is the most extensively studied form of memory updating outside of memory weakening or strengthening models. Retrieval-extinction paradigms demonstrate that targeting and remodelling an established memory during the post-reactivation window could more effectively update memory performance compared to typical extinction procedures, which are thought to result in a stronger competing novel memory (Flavell et al., 2013). However, while retrieval-extinction provides an excellent example of memory updating, it does not directly illustrate how a memory could be updated with new, constructive information. Declarative memory reconsolidation tasks more clearly demonstrate evidence for reactivation-dependent information integration, especially in the human literature. These tasks typically show how content introduced in the post-reactivation window 'intrudes' on the reactivated memory, as long as the reminder of the original memory trace is sufficient to induce destabilization (Forcato et al., 2010; Hupbach et al., 2007; Sinclair and Barense, 2018, 2019; St. Jacques et al., 2013; Wichert et al., 2013). These studies bridge the gap between reactivation-based memory weakening/strengthening to potentially more naturalistic forms of memory updating (Garry et al., 1996; Loftus and Pickrell, 1995; Schacter and Loftus, 2013). Recently, more evidence of reactivation-based information updating in rodents using declarative-like memory paradigms has been reported, enabling investigation of the mechanisms that regulate updating of object, spatial, and context memories (Choi et al., 2010; Jardine et al., 2020; Jones et al., 2012; Kwapis et al., 2019; Lukowiak et al., 2007; Morris et al., 2006; Rodriguez-Ortiz et al., 2008; Rossato et al., 2007; Winters et al., 2009, 2011). There are also a few examples of new information (e.g. a new context) updating a reactivated aversive memory (Jarome et al., 2015; Lee, 2010; Tronel et al., 2005) or appetitive memory (Escosteguy-Neto et al., 2016).

While each of these studies contributes to our growing understanding of reactivation-induced information integration, each uses unique behavioral parameters; caution should therefore be exercised when generalizing these findings, but we are clearly at an important juncture in the study of reactivation-related mechanisms of complex memory updating. The following sections will describe in more detail the typical methods used to study the various forms of memory modification in animals, a consideration of the literature from humans describing evidence for and against this type of memory updating, followed by a review of how these procedures have been utilized so far to uncover the neurobiological mechanisms triggered by certain memory reactivation conditions to initiate destabilization.

3. Evidence for reactivation-induced memory modification in rodents

In non-human animal research, the basic reactivation-dependent memory updating protocol involves three phases, most commonly separated by 24 h (Fig. 2). The first phase or day is the training phase, in which an animal learns something new. This is followed by the

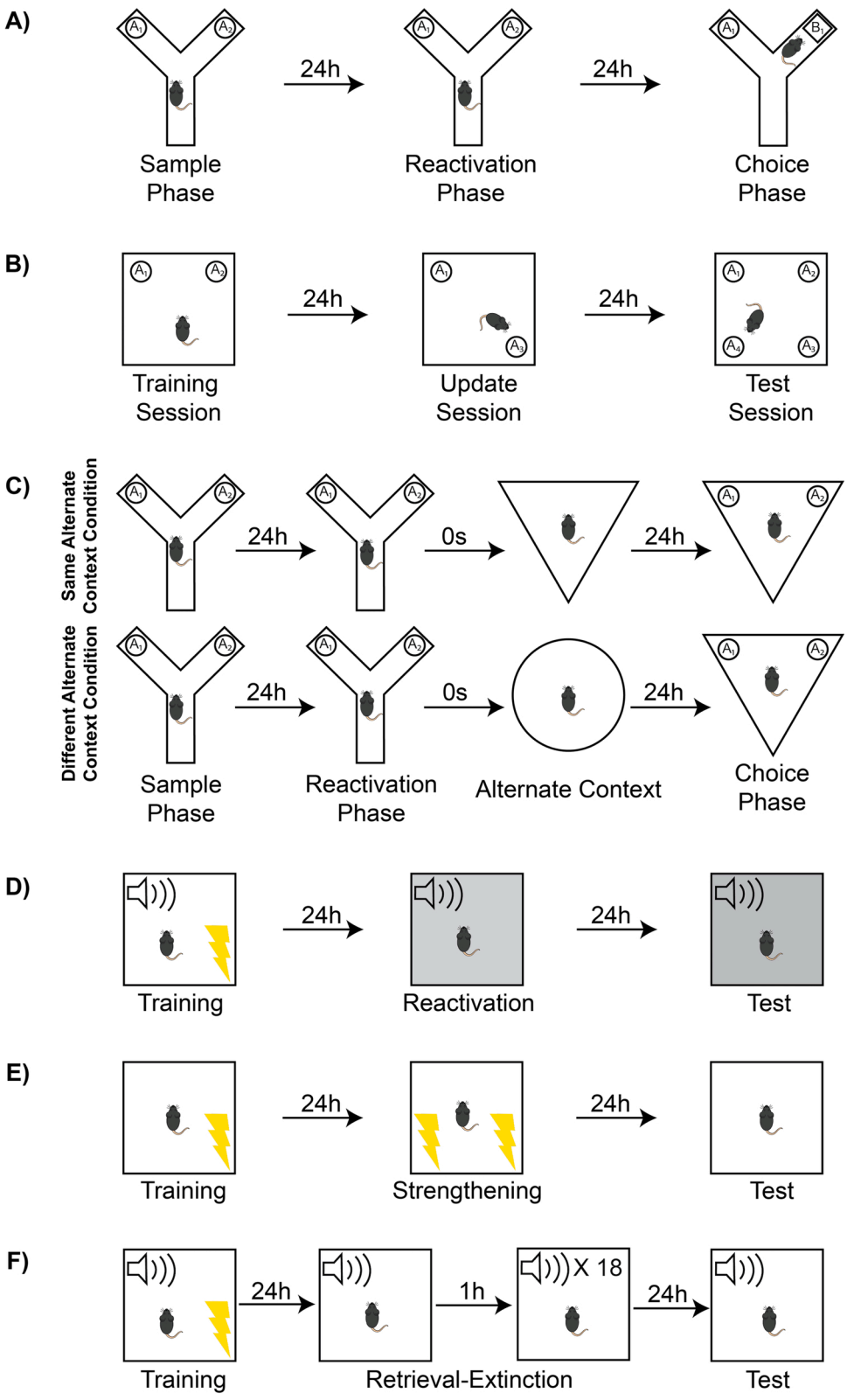

Fig. 2. Common paradigms used to study memory updating in rodents. A) Typical memory reconsolidation experiment using the spontaneous object recognition (SOR) task. During the sample phase, rodents explore two identical objects. To reactivate the object memory, the rodents are re-exposed to the same two objects 24 h later in the reactivation phase (note, one of these objects can be substituted for a novel object to provide a built-in test of retrieval in the reactivations session). In the choice phase 24 h later, memory is tested by exposing the rodent to one copy of the familiar object and one novel object. Rodents prefer novelty, so preferential exploration of the novel object indicates intact memory for the sampled object. B) The objects-in-updated-locations (OUL) task. During the sample phase, rodents are exposed to two identical objects in two specific locations (A_1 and A_2). The object location memory is updated 24 h later by exposing rodents to one object in a sampled location (A_1), and one object in a different location (A_3). Memory is then tested 24 h later by exposing rodents to four copies of the same object: three in familiar locations (A_1, A_2 and A_3) and one in a novel location (A_4). Rodents that have intact memory for both the original object locations (A_1 and A_2), as well as the updated object location (A_3), should show preferential exploration of the novel object location (A_4). C) The post-reactivation object memory modification (PROMM) task. Following reactivation of the object memory, rodents are immediately placed in an alternate context. In the test session, rodents are placed in either the same alternate context they were exposed to post-reactivation, or a different alternate context. Rodents display lower exploration in the same alternate context condition, suggesting that the object-context configuration is familiar, indicating that the contextual information presented post-reactivation was integrated into the existing object identity memory. D) Standard memory reconsolidation experiment using Pavlovian fear conditioning. Rodents are trained to associate a tone (i.e. conditioned stimulus [CS]) with a footshock (i.e. unconditioned stimulus [US]). The fear memory is reactivated 24 h later by exposing the animal to the tone, typically in a different context (shaded in the figure). The memory for the CS-US association is tested 24 h later by exposing rodents again to the tone. Rodents with intact memory for the CS-US association will demonstrate the typical rodent fear response of freezing. Contextual fear conditioning is conducted in a similar fashion, except rodents are trained with unsignalled (i.e., no tone) footshocks, and reactivation and testing are conducted in the same context as training. E) Strengthening fear memories by additional training. Instead of exposure to only the CS during memory reactivation, rodents undergo a second training session (CS and US exposure) 24 h following the initial training session, which typically produces higher freezing during subsequent exposure to the CS. F) The retrieval-extinction paradigm. In a variation of the standard Pavlovian fear conditioning protocol, rodents undergo fear extinction 1 h following memory reactivation. This

typically produces a persistent reduction in the fear response observed during the memory test. Retrieval-extinction has been shown to produce persistent attenuation of fear and does not show spontaneous recovery, renewal, or reinstatement.

reactivation or reminder phase, in which the animal is exposed to reminder cues associated with the initial learning event. Lastly, the memory is tested during the third phase. Numerous approaches have been developed to assess the effects of weakening, strengthening, or the integration of new information to modify memories by using pharmacological or behavioural manipulations around the time of memory reactivation.

3.1. Declarative memory

3.1.1. Object-based declarative-like memory tasks

In contrast to Pavlovian fear conditioning, object-based memory tasks provide an opportunity to study the updating of relatively emotionally neutral memories. Potentially because it is less commonly utilized in the memory updating literature, or possibly because non-significant findings are less likely to be reported (Schroyens et al., 2021), there have been little to no reported failures to replicate reactivation-based weakening of object-based memories. The spontaneous object recognition (SOR) task (Fig. 2A) and variants such as object location and object-in-place tasks, which assess spatial memory for objects, operate under the assumption that rodents prefer to explore novelty, and therefore, a rat that remembers a studied object (or location) will preferentially explore a novel object/location when later tested (Ennaceur and Delacour, 1988). These tasks are thought to be a model of declarative-like memory, as they assess memory for previously encountered objects, or places where objects have been encountered before, which are thought to be important aspects of human declarative memory (Winters et al., 2008, 2010). These object-based tasks can be considered "declarative-like" tests of memory, as successful performance may only utilize a subset of the cognitive processes involved in declarative memory.

By using an object recognition paradigm, Bozon et al. (2003) showed that blockade of zinc finger 268 (zif268)-mediated transcriptional regulation weakened a reactivated object memory. That is, zif268 mutant mice were able to form a new long-term object memory, but after the object memory was reactivated the mice were impaired in subsequent testing, which suggests that the reactivated memory was weakened (Bozon et al., 2003). Winters et al. (2009) demonstrated that object memories could also be weakened by administration of the NMDA receptor antagonist MK-801 prior to memory reactivation, specifically by showing that rats did not display a novel object preference during the choice phase of the SOR task. Follow-up work showed that administration of anisomycin into perirhinal cortex (PRh), a brain region important for the storage of object memories, post-reactivation similarly weakened object memories (Winters et al., 2011). Others have implicated the hippocampus (HPC) in aspects of reactivation-induced object memory modification. For example, Kelly et al. (2003) showed that post-reactivation intracerebroventricular administration of a mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) inhibitor impaired subsequent object recognition. In addition, Rossato et al. (2007) found that administration of anisomycin into the dorsal HPC (dHPC) post-reactivation weakened object memory. Interestingly, this only occurred when the object memory was reactivated with one familiar object and one novel object, instead of two copies of the familiar object. This result is similar to the report by Winters et al. (2011) that object memory impairments following intra-HPC post-reactivation anisomycin occurred only when contextual novelty was presented during memory reactivation, consistent with the idea that salient novel cues during memory reactivation facilitate the destabilization/updating process.

Variations of the object location task, another HPC-dependent test (Assini et al., 2009; Barker and Warburton, 2011; Mumby et al., 2002; Murai et al., 2007), have been primarily used to study integrative memory updating (see below) rather than memory weakening. However, it has recently been shown that, like object identity memories, reactivation of object location memories renders them vulnerable to the impairing effects of intra-HPC anisomycin (Huff et al., 2021). In the choice phase, rats that received anisomycin post-reactivation were unable to discriminate between the novel object location and a familiar object location, suggesting that reactivation-dependent memory weakening occurred.

The above findings indicate that object memories appear to be subject to post-reactivation memory modification. These object-based tasks have since been exploited to study integrative memory updating more directly in rodents and begin to isolate the neurobiological mechanisms involved in this form of memory updating. Two recently developed object-based tasks have been used for this purpose, the Objects in Updated Locations (OUL) task (Kwapis et al., 2019; Wright et al., 2020) and the Post-Reactivation Object Memory Modification (PROMM) task (Jardine et al., 2020). Kwapis et al. (2019) developed the OUL task (Fig. 2B), which enables assessment of both the original object-location memory and the modified object-location memory within the same test phase. In their initial study, Kwapis et al. (2019) showed that only mice that underwent memory updating during the reactivation phase showed a preference to explore the object in the novel location compared to exploration of the object in the updated location or the objects in the original locations. They then showed that reconsolidation of the updated memory depends on protein synthesis in the dHPC, as mice that received anisomycin into dHPC failed to discriminate between the different object locations. These findings demonstrate that mice can update existing object location memories and that both the original memory and the updated memory can be expressed. Findings similar to this were also reported by Choi et al. (2010).

In contrast to the OUL task, in which updating information is presented during the memory reactivation session, Jardine et al. (2020) developed the PROMM task (Fig. 2C) to assess whether new information given post-reactivation could be incorporated into an existing memory. In the PROMM task, rats are exposed to two identical objects in a sample phase. Twenty-four hours later, they are exposed to a distinct alternate context immediately following reactivation of the object memory to promote the integration of this contextual information into the existing object memory. Rats are tested 24 h later by being exposed to the sampled objects in either the same alternate context they were exposed to following reactivation, or a different alternate context. When tested in the same alternate context, rats explore the objects less than when they are tested in the different alternate context. This suggests that in the same alternate context condition, rats treat the object-context configuration as familiar, even though they have never previously been exposed to the objects in that specific context. This implies that the contextual information is incorporated into the existing object memory. Critically, Jardine et al. (2020) also demonstrated that this apparent object memory updating effect is time- and reactivation-dependent; that is, it does not occur if the original object memory is not reactivated prior to alternate context exposure, nor is it seen when the alternate context exposure is delayed until after the reconsolidation window has closed. Thus, there is a growing body of literature illustrating that object memories can be modified to incorporate new information when that information is presented within the post-reactivation labile window.

One of the main weaknesses of object-based tasks is that they tend to produce a less robust form of learning than other forms of learning, such as Pavlovian fear conditioning. In rodents, fear memories can be observed for days to weeks following learning, however object memories do not typically persist for longer than 48–72 h. Furthermore, the neural circuits underlying object memory have not been as widely

studied as those involved in fear memory. However, a major strength of using object-based tasks such as the OUL and PROMM tasks to study memory modification is that they may more accurately reflect the forms of declarative memory updating that most commonly occur in humans (Hupbach et al., 2007).

3.1.2. Maze-based declarative memory tasks

Distinct from object-based declarative-like memory tasks, maze tasks, such as the Morris Water Maze (MWM) and the radial arm maze, have been used sparingly to study updating of declarative-like memory in rodents. Typically, these tasks are HPC-dependent and are used to test spatial reference memory, which is an important component of declarative memory (Buzsáki and Moser, 2013; Eichenbaum et al., 1999; Morris and Frey, 1997; Vorhees and Williams, 2014). Due to the ability to alter features of the maze, such as with the hidden platform in the MWM, these tests provide an opportunity to study information integration. Przybyslawski and Sara (1997) demonstrated that following training in a radial arm maze, spatial memory could be weakened by post-reactivation administration of the NMDA receptor antagonist MK-801. Beyond follow-up reports from the same research group, in which they similarly implicate β-adrenergic receptors for weakening spatial memories (Przybyslawski et al., 1999), the vast majority of reports concerning spatial memory updating using maze tasks are limited to the MWM.

Post-reactivation weakening of MWM memories has been demonstrated using multiple amnesic agents, including protein synthesis inhibitors and NMDA receptor antagonists (R. Kim et al., 2011; Suzuki et al., 2004). Typically, in this task rats are repeatedly trained to find a hidden platform located within a pool of opaque water and can do so by making use of spatial cues within the room. The spatial memory is then reactivated by conducting a probe trial in which the platform is removed; memory is then tested by conducting a second probe trial. One interesting example of this procedure was conducted by Morris et al. (2006), who showed that only rats trained in a delayed-matching-to-sample version of the MWM that required novel memory encoding during training every day were vulnerable to memory disruption by post-reactivation anisomycin. In contrast, rats that were trained on a version of the MWM that did not require novel memory encoding during reactivation were not vulnerable to anisomycin-induced memory weakening. Importantly, there was no difference between the two versions of the task on the reactivation day. However, rats trained in the delayed-matching-to-sample version of the task were trained to expect a mismatch between where the platform was on the previous day compared to where it was on the current day. This opportunity for memory updating could explain why the memory was vulnerable to anisomycin-induced weakening.

Reports concerning the strengthening of MWM memories are less common. However, using a suboptimal training protocol, Villain et al. (2016) showed that intra-HPC administration of the class 1 specific histone deacetylase (HDAC) inhibitor sodium butyrate (NaB) following memory reactivation resulted in increased time spent within the target quadrant relative to vehicle administered mice 24 h after training, suggesting the memory had been enhanced, potentially through increased levels of acetylated histone H3 and H4. Importantly, intact memory was displayed 1 h following reactivation in both groups, and the facilitative effect on long-term spatial memory was reactivation-dependent.

As mentioned previously, the ability to alter the platform location in the MWM provides an opportunity to study more integrative forms of spatial memory updating in rodents. Rossato et al. (2006) trained rats for 5 days, and then 24 h later gave them 8 consecutive trials in which the platform had shifted to a different location (reversal training). While all rats acquired the reversal, only those that were administered anisomycin into the CA1 region of the HPC following reversal training showed impaired memory for both the original platform location and the new platform location when they were tested 24 h later. This suggests that memory reconsolidation was impaired, as the authors note that if the consolidation of the reversal learning was only impaired, the rats should have shown a preference for the original platform location. This study therefore appears to demonstrate how the post-reactivation window can be used to incorporate new information for adaptive updating of spatial memories.

In an effort to develop an animal model of memory integration that does not involve aversive learning, researchers created a task that mimicked a task widely used in humans (Hupbach et al., 2007), that could then be used to test spatial memory updating in rats. This task utilized rodents ability to learn a list of operant feeders that were only active in a specific context (Jones et al., 2012). In this task, rats were trained to obtain food at 3 operant feeders (of 8 total feeders) in context A (list 1). The next day, rats were trained either in context A or B to obtain food at 3 different feeders (list 2). On the third day, rats were tested for their memory of list 1 in context A. The researchers found that when rats learned list 2 in the same context as list 1, on day 3 they made more errors about which feeders were part of list 1. Similar to what is observed in humans (Hupbach et al., 2007), rats integrated information about the second learning experience into the existing memory of the first when a contextual reminder of the first learning experience was presented prior to the second.

Spatial memory tasks such as the MWM provide the opportunity to study information integration in rodents given that different elements of the maze, such as the spatial landmarks and the location of the hidden platform, can be altered. In addition, reversal training can be conducted, and MWM training can be extinguished. The MWM also has numerous control measures, such as swim speed, that help to rule out alternative interpretations. One of the main weaknesses of the MWM is that it is stress-inducing. There are also several procedural elements that can impact performance, such as consistency of the start position, number of spatial cues and maze size. However, given the nature of changing environments, as well as the common finding that age- and dementia-related cognitive impairment often involves severe navigational deficits (Allison et al., 2016; Coughlan et al., 2018; Lester et al., 2017; Muffato et al., 2019), studies in this field should endeavor to include spatial memory tasks more often to help uncover the neuronal mechanisms underlying this adaptive form of memory updating.

3.2. Aversive memories

In rodents, aversive memories are typically studied using variations of Pavlovian fear conditioning. These are fear based, emotional tasks that generally associate stimuli with foot shocks (i.e. an unconditioned stimulus [US]) to promote the formation of an aversive memory. Pavlovian fear conditioning (Fig. 2D)–either with auditory or contextual conditioned stimuli–is one of the most common forms of learning used to explore reactivation-dependent memory updating. In their seminal study, Nader et al. (2000a) demonstrated that fear memories could be modified such that freezing was persistently reduced if a protein synthesis inhibitor was administered following memory reactivation. Twenty-four hours after auditory fear conditioning, they reactivated the memory by exposing rats to the CS to destabilize the memory for the CS-US association, and then administered the protein synthesis inhibitor anisomycin directly into the basolateral amygdala (BLA). When rats were tested 24 h later, those that were administered anisomycin showed reduced freezing. This suggested that upon re-exposure to the CS, the memory for the CS-US association was destabilized and susceptible to reconsolidation blockade by protein synthesis inhibition. Importantly, the amnesic effect of anisomycin was both time- and reactivation-dependent. That is, when memory reactivation was omitted, or when anisomycin was administered 6 h post-reactivation, there was no effect of anisomycin on freezing in response to the CS during the memory test. This reactivation-dependent memory weakening process is also distinct from extinction. Initial challenges to reconsolidation theory posited that the memory was being weakened by

extinction, as a result of the presentation of the CS in the absence of the US during reactivation, and not by anisomycin. However, Duvarci and Nader (2004) demonstrated that anisomycin given after extinction blocked consolidation of the learning that occurred during extinction training, resulting in successful retrieval of the CS-US memory during the test. This contrasts with what occurs following post-reactivation anisomycin, where the reconsolidation of the CS-US memory appears to be blocked, resulting in reduced freezing during the test, a finding that has been reported extensively in the literature (Debiec et al., 2002; Díaz-Mataix et al., 2013; Frankland et al., 2006; Hong et al., 2013; Jarome et al., 2015, 2011, 2016; Kida et al., 2002; Lee, 2008; Lee et al., 2008; Mamiya et al., 2009; Mamou et al., 2006; Milton et al., 2013; Nader et al., 2000a; Wang et al., 2009).

It has been argued that the memory deficits induced by administration of drugs like anisomycin are not due to a storage deficit (i.e., 'erasure' or weakening), but rather impaired retrieval related to inconsistent internal states between the memory reactivation and testing phases (Gisquet-Verrier et al., 2015). These researchers suggest that because the change in internal state caused by post-reactivation administration of protein synthesis inhibitors is not present during memory testing, the memory is not accessible. In other words, memory 'erasure' observed in the test phase may actually reflect state-dependent memory performance. Indeed, in some studies, pre-test administration of the protein synthesis inhibitor cycloheximide resulted in an apparent reversal of amnesia in an inhibitory avoidance memory paradigm (Gisquet-Verrier et al., 2015). Others have also failed to replicate reconsolidation impairment using fear conditioning in rats (Luyten et al., 2021; Schroyens et al., 2019). These two reports are particularly important as they failed to replicate previous findings that demonstrated reactivation-based weakening of auditory fear memories (Luyten et al., 2021) and contextual fear memories (Schroyens et al., 2019) using a variety of different systemically administered amnestic drugs (e.g., midazolam, propranolol, cycloheximide, anisomycin) and a variety of different behavioural protocols. The authors do acknowledge that local drug administration into specific brain areas such as the amygdala or HPC could have resulted in amnesia; however, they note that local drug administration is less clinically relevant and amnestic effects have also been observed with systemic drug administration (Luyten et al., 2021). They also note that it was possible the memory had not destabilized, which could explain why the memory did not seem to be vulnerable to post-reactivation manipulations. This group has also conducted a systematic review of the literature suggesting that evidence for failures to reproduce reactivation-based memory weakening is perhaps underreported and the reconsolidation-mediated amnesic effect may be less robust than the extant literature indicates (Schroyens et al., 2021). These contradictory findings are important to recognize, and it is essential that such failures to replicate continue to be published, as they indicate that post-reactivation memory modification does not always occur. The fact that a growing body of evidence contradicts much of the existing literature should be an impetus to researchers to design increasingly systematic studies to investigate the specific conditions under which memory will and will not destabilize following presentation of reminder cues.

Consistent with the earlier fear conditioning studies, several reports also suggest that fear associations can be weakened by the presence of appetitive stimuli during or after memory reactivation. Haubrich et al. (2015) showed that when a fear memory was reactivated in the presence of palatable food, rodents froze less than controls during the memory test, suggesting that the availability of palatable food during reactivation caused the memory to be updated as less fearful. Importantly, reinstatement of fear by exposure to a single shock, and spontaneous recovery (retested 21 days after the initial test) did not occur, suggesting that this was a persistent modification of the original memory. In a similar report, the post-reactivation availability of 30% sucrose solution, but not water or exploration in an open field arena, reduced fear responding (Ferrer Monti et al., 2016), suggesting that in order to for a stimulus to update the memory to become less fearful, the stimulus must be appetitive. Additionally, Pérez et al. (2020) showed that when methylphenidate, a psychostimulant that possesses hedonic value, was administered prior to reactivation of a contextual fear memory, rats froze less during the test and this reduction in fear responding was persistent. Thus, it appears that stimuli that possess hedonic value given around the time of memory reactivation can impact fear memory. Whether these findings can be construed as a reactivation-dependent weakening of the memory, or as integrating the appetitive information into the memory to make it less fearful, is unclear. It also remains possible that state-dependent factors could explain some of these effects. However, the fact that reactivation-dependent changes to some aspect of the original memory occurred does not seem to be in question.

In contrast to reducing fear responding by weakening fear memories with post-reactivation reconsolidation inhibitors, it has been shown that giving additional training trials during memory reactivation can result in apparent strengthening of fear memory. Lee (2008) used the standard 3-day reconsolidation protocol, but instead of reactivating the contextual fear memory with presentation of only the CS, rats underwent a second training trial following reactivation (Fig. 2E). This resulted in enhanced freezing during the memory test 24 h later, relative to freezing during the second conditioning trial. This suggests that the addition of a second training trial while the memory trace was labile strengthened the fear association. Ferrara et al. (2019) also showed strengthening of contextual fear memories by giving additional training trials following memory reactivation. Rats that underwent additional CS-US training during reactivation froze more during the memory test than those that received CS-only reactivation. Therefore, it appears that Pavlovian fear memories can be strengthened by the presentation of additional training trials following memory reactivation, and it appears that this strengthening is not the result of the co-occurring reconsolidation of the first training trial with consolidation of the second. These findings also do not support the state-dependent explanation of reconsolidation that is discussed above.

While it is perhaps not surprising that additional training following memory reactivation can strengthen the memory, it has also been shown that repeated, unreinforced, brief retrieval of an inhibitory avoidance memory appears to strengthen the memory in a reconsolidation-dependent manner (Inda et al., 2011). This repeated destabilization-stabilization process resulted in the memory becoming resistant to disruption by administration of cycloheximide following a fourth reactivation session. Therefore, not only did repeated retrieval strengthen the behavioural response, it made the memory less vulnerable to modification. Extending the length of the retrieval sessions resulted in extinction. Interestingly, repeated artificial activation of lateral amygdala neurons that encoded an auditory fear memory had a similar effect at enhancing the freezing response to fear associated cues (Kim et al., 2013).

It has also been demonstrated that the freezing response associated with fear memories can be strengthened by pharmacological activation of protein kinase A (PKA) within the BLA immediately following memory reactivation (Tronson et al., 2006), by pre-reactivation systemic or intra-BLA activation of NMDA receptors using D-cycloserine (Lee et al., 2006b) and by pre- or post-reactivation administration of HDAC inhibitors (Bredy and Barad, 2008; Maddox and Schafe, 2011). These pharmacological treatments caused an increase of the freezing response during the test 24 h later, which the authors interpreted was the result of enhanced memory reconsolidation. In summary, it appears that Pavlovian conditioned fear memories can be strengthened by reinforced, or unreinforced, exposure to the CS during memory reactivation and by pharmacological interventions administered around the time of memory reactivation.

Another manner in which Pavlovian fear memories can be updated to reduce fear responding is with the retrieval-extinction protocol, in which extinction training follows targeted memory reactivation (Fig. 2F). Monfils et al. (2009) noted that the efficacy of reconsolidation

or extinction-based treatments in the clinical setting has been limited. They combined these two techniques, however, and showed that when rats were presented with a single, isolated retrieval trial, followed by extinction training, they displayed a reduction in fear (i.e., less freezing during memory test), and this effect was not subject to spontaneous recovery, reinstatement, or renewal. Recovery, reinstatement, and renewal typically occur after extinction training (Bouton, 2002), as a result of extinction training generating a new memory that competes for behavioural expression rather than overwriting the original memory.

The retrieval-extinction theory suggests that by reactivating the original memory prior to extinction training, the original memory is updated to incorporate the extinction learning (Cahill and Milton, 2019). However, a direct replication of the retrieval-extinction effect demonstrated by Monfils et al. (2009) failed to prevent the return of fear, as rats displayed spontaneous recovery, reinstatement, and renewal following retrieval-extinction training (Luyten and Beckers, 2017). Within both the human (Elsey et al., 2018) and animal (Cahill and Milton, 2019) literature there has been mixed evidence to support this phenomenon (Chalkia et al., 2020; Luyten and Beckers, 2017) prompting doubt as to whether retrieval-extinction protocols actually produce effects that are more robust or distinct from basic extinction. It is also possible, however, given the often very specific conditions that must be met to destabilize strongly encoded memories, that a genuine reconsolidation process merely was not engaged in the studies failing to report retrieval-extinction effects. Additional parametric alterations may be necessary to ensure engagement of the reconsolidation process in the retrieval-extinction paradigm (Huang et al., 2020; Pineyro et al., 2013). This is clearly an essential area for future research.

Evidence for this interpretation was demonstrated in one report by Gräff et al. (2014), who showed that, unlike recent fear memories, remote fear memories were not persistently attenuated by the retrieval-extinction effect. These contextual fear memories were subject to spontaneous recovery and reinstatement. However, when HDAC2 was inhibited prior to conducting retrieval-extinction, the aversive memory was permanently weakened such that it was not vulnerable to spontaneous recovery or reinstatement. They then provided evidence to suggest that the same cell ensemble is activated during training and retrieval-extinction, and that manipulating this cellular ensemble can potentiate or weaken the effects of retrieval-extinction (Khalaf and Gräff, 2019; Khalaf et al., 2018). This lends support to the idea that retrieval-extinction updates the existing CS-US memory rather than generating a new CS-no US memory that inhibits the original memory, which is what is thought to occur during standard extinction training (Bouton, 2002; Khalaf et al., 2018; Myers and Davis, 2007). However, they, and others (Clem and Schiller, 2016), suggest that both processes may be occurring at the same time. These findings indicate that even long-lasting aversive memories can be permanently weakened, which is a challenge that needs to be overcome to increase the efficacy of reconsolidation-based clinical interventions.

There have been very few published examples of fear memory updating that are not strengthening or weakening. In one demonstration, however, Kwapis et al. (2017) trained rats on trace fear conditioning and then exposed the rats to a delay fear conditioning trial during reactivation. While destabilization did not occur when rats were given a trace fear conditioning trial during both training and reactivation, the memory was vulnerable to memory weakening with anisomycin when there was a mismatch between the type of fear conditioning received during training and reactivation. The authors had previously reported a double dissociation between the roles of the amygdala and retrosplenial cortex (RSC) in the extinction of delay and trace fear memories (Kwapis et al., 2014); however, Kwapis et al. (2017) reported that the mismatch updating procedure resulted in a trace-delay fear memory requiring the amygdala for extinction. In addition, although the RSC is important for retrieval of trace fear memories, it was no longer required for retrieval of the updated trace-delay memory. The authors suggest that these findings support the idea that this updating procedure changed the neural circuitry underlying the memory (Kwapis et al., 2017). Thus, while future research should attempt to expand on this area, it does appear that fear memories can be updated to incorporate new information.

Pavlovian fear conditioning produces robust and long lasting fear-memories (Suzuki et al., 2004). For this reason, studies using this paradigm have important implications for the understanding and treatment of human disorders that are associated with persistent, maladaptive emotional memories, such as posttraumatic stress disorder (PTSD) and phobias. Fear conditioning is also subject to extinction training, which makes it possible to use extinction training and reconsolidation together to weaken fear associations using the retrieval-extinction paradigm. Moreover, the phenomena of spontaneous recovery, renewal, and reinstatement provide additional behavioral indices with which to probe the precise nature of observed amnesic effects, to ensure that modification of the original memory occurred. However, a potential weakness of Pavlovian fear conditioning is that it is a relatively simple associative form of learning that may not reflect the detail that is generally associated with human episodic memories. As such, the generalizability of modification using the retrieval-extinction paradigm in other forms of memory is uncertain, especially with regard to modification of human declarative memory. This is also a stress-inducing emotional form of learning which may impact the manner in which specific neurotransmitter systems are recruited. Thus, it is essential that other forms of learning and memory be studied when assessing the neural mechanisms and therapeutic potential of reactivation-induced memory modification.

3.3. *Appetitive memory tasks*

Recent research on memory updating has also focused on appetitive memories that are typically studied in rodents with drug-cue associative tasks such as drug self-administration and conditioned place preference (CPP), due to their clinical implications for the treatment of addiction. Like fear memories, drug-CS memories can be weakened by manipulations given following reactivation, but the clinical relevance of such procedures has been questioned (Exton-Mcguinness and Milton, 2018; Taylor et al., 2009). Lee et al. (2005) provided one of the first demonstrations of weakening a drug-CS memory by training rats for 9 days on IV self-administered cocaine that was paired with the presentation of a light CS. They then reactivated the drug associative memory by exposing the rats to the light CS with infusions of saline instead of cocaine. Because the drug-paired CS becomes a conditioned reinforcer due to its motivational association with the drug, it can support the development of a new instrumental drug-seeking response in the form of lever pressing (Di Ciano and Everitt, 2004). Therefore, to test whether post-reactivation anisomycin impaired the memory of the drug-CS association, the authors assessed whether the CS could support the acquisition of a lever-pressing response following memory reactivation. Rats administered anisomycin post-reactivation made fewer lever presses across the acquisition sessions, suggesting that they were not motivated by the light CS to learn the new instrumental response, likely because the reconsolidation of the drug-CS association had been impaired. They replicated this memory weakening effect with intra-BLA Zif268 antisense oligodeoxynucleotides (ASO), having previously shown that the transcription factor Zif268 is critical for reconsolidation of contextual fear memories (Lee et al., 2004). Similar reactivation-induced weakening of self-administration models has been shown for sucrose (Exton-McGuinness et al., 2015; Lee and Everitt, 2008; Milton et al., 2008).

As discussed previously, extinction training does not lead to permanent suppression of original learning, because it is thought that extinction generates a new memory that competes for behavioural expression with the previously existing memory (Bouton, 2002). Thus, spontaneous recovery, renewal, and reinstatement of drug associative memories are typically observed in rodents that have undergone

extinction training. In contrast, the literature generally supports the idea that fear memories that have been weakened in a reactivation-dependent manner do not show recovery, reinstatement, or renewal (Duvarci and Nader, 2004); however, the evidence concerning reactivation-dependent weakening of drug-CS memories is mixed. While Lee et al. (2006a) reported no evidence for spontaneous recovery or reinstatement of a CS-cocaine association following Zif268 ASO-induced memory weakening, Exton-McGuinness et al. (2019) found evidence for reinstatement of drug-seeking behaviours after MK-801-induced memory weakening following cue- and cocaine-induced priming; this was seen despite the absence of apparent spontaneous recovery or stress-induced reinstatement. Exton-McGuinness et al. (2019) suggested that memories for the lever-cocaine (instrumental) and light CS-cocaine (Pavlovian) associations can be selectively destabilized depending on the information presented during reactivation, and that Lee et al. (2006a) reactivated the Pavlovian memory by changing the cue-reward contingency, while Exton-McGuiness et al. (2019) reactivated the instrumental memory by changing the response-reward contingency. When Lee et al. (2006a) reactivated the drug memory, they did so by exposing the rats to 30 non-contingent presentations of the light CS, with no levers or cocaine infusions available. When Exton-McGuinness et al. (2019) reactivated the drug memory, they did so by using a variable-ratio reactivation session in which cocaine infusions were accompanied by the same light CS as in training and were obtained following a random number of lever presses (range: 1–9). Therefore, while the self-administration training (fixed-ratio-1 schedule of reinforcement) was almost identical in the two studies, these different reactivation sessions produced different effects on the persistence of the responding for cocaine during testing, such that both resulted in a weakened memory, but one was more vulnerable than the other to relapse. More research should be conducted to assess under what circumstances drug associative memories can show recovery from weakening, and under what circumstances the instrumental and Pavlovian memories that contribute to the behaviours can be destabilized and weakened.

Another paradigm used to study post-reactivation modification of drug associative memories in rodents is the CPP task. CPP training typically takes place in a two chambered compartment, where the chambers are distinct and divided from one another, and CPP is established by pairing a drug (e.g., morphine, cocaine) with one context and saline with the other. Following repeated pairings, preference for the drug-paired chamber versus the saline-paired chamber is tested. Generally, the reactivation session in this paradigm is the same as a test session, where rats are placed in the chamber with the divider removed in a drug-free state.

Reports concerning post-reactivation weakening of CPP memories have been mixed, with some observing that these memories can be weakened by inhibiting reconsolidation pharmacologically (Bernardi et al., 2006, 2009; Miller and Marshall, 2005; Robinson and Franklin, 2007; Wang et al., 2008) and some reporting that memories can only be modified when the reactivation session is conducted under the influence of the paired drug (i.e., morphine administered during memory reactivation, followed by the amnestic drug post-reactivation and a drug-free test 24 h later; Brown et al., 2008; Milekic et al., 2006; Valjent et al., 2006). This last observation is notable because testing/reactivation for CPP is typically done in a drug free state. These findings have been observed with multiple types of amnestic drugs and have been observed in CPP induced by different drugs, such as morphine, methamphetamine, and cocaine. In general, it does appear that these associative memories can be weakened by amnestic drugs administered following reactivation; however, it is curious that in some cases the paired drug needs to be on board during reactivation to induce destabilization, but not in others. This speaks to the idea that the reactivation conditions must occur in a specific manner for destabilization to be initiated, which appears to be consistent across different types of memories. It is possible that the strength of the CPP memory plays a role in whether the memory destabilizes without the presence of the paired drug. Different observations using this paradigm may also result from the variation in the protocols used between groups.

Drug associative memories in rodents have also been studied regarding their ability to be modified using retrieval-extinction procedures. Xue et al. (2012) reported that both CPP and self-administration are subject to weakening following retrieval-extinction. They first showed that brief reactivation of cocaine or morphine CPP memories (10 min exposure to chamber with divider removed) followed 10 min or 1 h, but not 6 h, later by extinction (45 min exposure to chamber with divider removed; repeated for 8 days) prevented drug-priming-induced reinstatement of CPP. They also did not observe spontaneous recovery of CPP 14 days following extinction. Next, they showed that, following self-administration training of cocaine or heroin and subsequent retrieval-extinction training, self-administration memories were not subject to drug-priming-induced reinstatement, spontaneous recovery, or renewal. In a follow-up paper, Luo et al. (2015) replicated the effect of CS retrieval-induced extinction (described above) on cocaine self-administration memories, and extended this by showing that when the retrieval cue was the US (priming injection of cocaine), instead of the CS, the retrieval-extinction effect was more robust. In addition, Cofresí et al. (2017) showed that the retrieval-extinction paradigm can also persistently attenuate alcohol cue reactivity in rats. Rats that underwent retrieval-extinction displayed reduced spontaneous recovery and reinstatement compared to rats that underwent typical extinction procedures, which further suggests a potential advantage of the retrieval-extinction paradigm for preventing relapse of substance use.

One of the major strengths of drug-based appetitive memory tasks are that they have implications for the understanding and treatment of substance abuse disorders. While much of the focus on the implications of reactivation-induced memory modification research is on PTSD, drug-based tasks can be used to mimic different aspects of drug addiction. One of the drawbacks of drug-based tasks is that they typically take long periods of time to conduct, as extended training is necessary for CS-US associations to develop and for rodents to reach robust levels of responding. However, this may actually be a strength, not a weakness, of drug-based appetitive memory tasks, as this can model the development of substance abuse disorders. One possible consideration is that if memory reactivation is not conducted in a drug free state, there could be interactions between the drug of abuse and method by which memory updating is modulated.

While the reactivation-induced memory modification literature is dominated by human and rodent research, memory updating has been demonstrated in several other species, including *Aplysia* (Cai et al., 2012; Lee et al., 2012), the crab *Chasmagnathus* (Pedreira and Maldonado, 2003; Pedreira et al., 2002), chicks (Anokhin et al., 2002), monkeys (Philippens et al., 2021), and fish (Eisenberg and Dudai, 2004). These studies have been critical in showing that evidence for reactivation-induced memory change can be observed across a variety of species and for various memory types. This extensive literature demonstrates that memory updating is reactivation-, protein synthesis-, and time-dependent. While there is debate as to the replicability of some findings, there is now a large body of evidence supporting the idea that modifications to memories can be made during or following memory reactivation. Ongoing work in this area is essential to continue to uncover the specific behavioural and biological factors regulating reactivation-induced memory updating. This should lead to important advancements in our understanding of the basic mechanisms of long-term memory, as well as the potential for therapeutic applications of this process in human mental disorders. To this end, the next section will consider more direct evidence for and against the existence of reactivation-induced memory modification in humans.

4. Evidence for post-reactivation memory modification in humans

The foundational work by Przybyslawski and Sara (1997) and Nader, Schafe and LeDoux (2000a) sparked renewed interest in the phenomenon of a temporary period of memory malleability following reactivation. The putative flexibility of memories following reactivation gained great interest as it not only modified our perspective of long-term memory storage and maintenance over time (Lee, 2009), but also had significant clinical implications for treating conditions associated with maladaptive memories such as anxiety disorders, PTSD, phobias, and substance abuse disorders in humans (Schwabe et al., 2014).

The existence of post-reactivation memory modification in humans has been debated since early studies attempting to utilize post-reactivation memory malleability to treat psychiatric disorders. Historically, ECS had been used for therapeutic treatment of psychiatric disorders, but the study by Misanin et al. (1968) was the first to demonstrate that administration of ECS following fear memory reactivation resulted in amnesia for a CS-US association in rodents. This study suggested that brief exposure to a reminder can render fear memory vulnerable to sustained and persistent disruption by ECS (Misanin et al., 1968). Rubin (1976) attempted to determine whether human memories could similarly be modified by ECS paired with memory reactivation and if this could be used to treat psychiatric conditions associated with maladaptive memories. Patients with delusions, obsession, hallucinations, or compulsive behaviours were exposed to reminders to reactivate pathological conditions or behaviours before administration of ECS (Rubin, 1976). It was reported that all patients' symptoms were improved in the months following treatment, and this was sustained for up to 10 years (Rubin, 1976). These results were challenged when a follow-up study demonstrated that reactivation of previously learned information could not be disrupted with ECS following reactivation in patients with clinical depression (Squire et al., 1976). The differences between the results reported in these two studies began the ongoing debate as to whether memories in humans can be rendered modifiable following reactivation. In the following sections, we summarize evidence both for and against the occurrence of post-reactivation memory modification in humans.

4.1. Procedural memory

Recent research in this area has focused on less invasive post-reactivation manipulations that could be used to modify memories. Given that the presentation of competing information shortly after a learning event can disrupt consolidation of the original information, a study using a finger tapping task sought to determine if presentation of competing information shortly after memory reactivation could similarly disrupt reconsolidation. When participants were asked to perform a previously learned finger tapping sequence, this rendered the memory susceptible to disruption by the learning of a new sequence immediately, but not 6 h, following its reactivation (Walker et al., 2003). This study provided an important demonstration that memories could be disrupted following reactivation without the use of invasive pharmacological interventions.

A replication study conducted by Hardwicke et al. (2016), however, failed to find support for the results of Walker et al. (2003). Walker and Stickgold (2016) attributed the lack of replication to differences in the experimental design including participant age, time of day of testing, and differences in instructions given to participants (Walker and Stickgold, 2016). However, in their replication study, Hardwicke et al. (2016) accounted for the difference in participant age and time of testing in their analysis, and these were ruled out as potential confounding variables. Findings from recent studies suggest that the discrepancies between these findings may be related to procedural differences at the time of reactivation. It has been demonstrated that the length of the memory reactivation session poses a significant boundary on motor memory destabilization (De Beukelaar et al., 2014). A reactivation session less then 60 s was found to successfully destabilize memory for a finger tapping sequence. However, as reactivation session lengths increased, susceptibility to interfering information decreased (De Beukelaar et al., 2014). Furthermore, timing of the presentation of an interfering sequence following reactivation can also influence whether or not memory will destabilize (De Beukelaar et al., 2016). These findings therefore suggest that subtle differences in reactivation methodology can limit or prevent induction of memory destabilization.

It could also be noted that speed and accuracy of performance of the original sequence were used as the primary measures in Walker et al. (2003) and Hardwicke et al. (2016), with poor performance speed and accuracy following post-reactivation intervention being used to infer that memory reconsolidation was disrupted. More recent studies might suggest that memory was likely reconsolidated and that reduced speed and accuracy occurred as a result of the interfering sequence becoming integrated into the memory trace for the original sequence. The inclusion of a measure assessing information integration may have provided an indication of memory destabilization, especially with work in other memory systems demonstrating that reactivation-induced memory updating can occur without disruption of the original memory trace (Hupbach et al., 2007, 2008; Kindt et al., 2009; Soeter and Kindt, 2011).

Indeed, there is evidence to suggest that new information can become incorporated into a motor memory without disrupting the original memory. In this study, researchers had participants learn a novel motor sequence with their right hand (Herszage and Censor, 2017). A day later, if participants were asked to learn the motor sequence with the left hand and then repeat the task with their right hand, they had decreased performance of the motor sequence task with the right hand. The authors hypothesized that poor performance was the result of proactive interference from learning the task with the left hand prior to testing memory with the right hand. However, if on the second day participants were asked to perform the motor sequence task with the right hand prior to learning the sequence with their left hand, participants had high performance in both hands the following day. This effect was only observed if the new information was learned shortly following reactivation and could be observed up to a month later. The authors suggested that reactivation of the motor memory with the original hand prior to learning the task with the left hand prevented interference as a result of the memories becoming integrated (Herszage and Censor, 2017). They further demonstrate that brief and accurate reactivations of a motor sequence memory can enhance performance to a similar degree as full extensive practice sessions (Herszage et al., 2021). Given previous perceptions that motor skill learning requires extensive practice, these results have significant implications for our understanding of motor skill learning and post-reactivation modification of motor memory as a form of motor rehabilitation (Herszage et al., 2021).

4.2. Declarative memory

Studies investigating this phenomenon in human declarative memory have also demonstrated that post-reactivation modification does not always disrupt the original memory. In a study by Hupbach et al. (2007), participants were asked to remember a group of objects as the experimenter drew them from a bag and placed them in a distinct blue basket. The following day, participants were separated into a reminder or a no-reminder group and asked to learn a new list of objects. Those in the reminder group were shown the basket from the previous day and encouraged to recount the events from the previous day before learning list 2. On the third day, all participants were able to recall objects from list 1, suggesting that memory for these items was intact. However, there was a higher number of intrusions from list 2 in the reminder group. That is, participants in the reminder group incorrectly recalled items from list 2 as being part of list 1. These results suggested that reactivation successfully destabilized the memory for list 1 and that the items from list 2 became incorporated into the trace for list 1 (Hupbach

et al., 2007).

These results were replicated in a series of follow-up studies, which also identified important experimental conditions required for post-reactivation declarative memory modification. First, reactivation needed to occur in the same context as initial learning (Hupbach et al., 2008). Returning participants to the same context as original learning was found to be both necessary and sufficient to destabilize memory for the object list and allow incorporation of new information. Support for these findings has been reported in studies demonstrating that returning participants to the original learning context renders paired-associate memory active and vulnerable to integration of new word pairs (Forcato et al., 2007, 2010).

Second, the degree of familiarity of the context in which participants learn the original list of objects plays an important role in determining whether post-reactivation memory modification will occur. When the original learning and reactivation context are relatively unfamiliar, information integration occurs (Hupbach et al., 2011). If the context is highly familiar, such as the participants' home, information integration does not occur (Hupbach et al., 2011). However, despite context familiarity constraining memory destabilization and subsequent updating, introduction of novel information, such as changing the experimenter, at the time of reactivation in a highly familiar context was sufficient to initiate destabilization and subsequent updating (Hupbach et al., 2011).

Third, for a declarative memory reminder cue to promote destabilization, it must be brief. In each of the previously mentioned studies, at the time of reactivation participants were asked to recall the events of the original learning episode but were stopped if they began recalling the object list (Hupbach et al., 2007, 2008, 2011). Indeed, when participants were asked to recall the objects from list 1 before learning list 2, information integration did not occur (Hupbach, 2015). Studies of procedural motor memory have similarly shown that practice or rehearsal is not an effective reminder for promoting destabilization; instead it appears to protect the memory from interference with new information (Hardwicke et al., 2016; Potts and Shanks, 2012), which is consistent with the hypothesis that testing can improve memory (Karpicke and Roediger, 2008).

These studies provide critical information regarding the nature of declarative memory reactivation and demonstrate the importance of reactivation conditions for destabilizing memories. Given the complexity of declarative memory, it is not surprising that other groups have found contradictory findings regarding appropriate reactivation conditions required for successful destabilization. Initially, Klingmüller et al. (2017) were unable to replicate the high intrusion rate observed by Hupbach et al. (2007) when using the same methodology. However, when they changed the reactivation context to be highly salient and unique from the original learning context they were able to replicate the intrusion effect, but at a smaller magnitude (Klingmüller et al., 2017). While this contradicts the findings from Hupbach and colleagues (2007, 2008) that reactivation in the original learning context is necessary for returning the memory to an active state, there are several studies in the rodent literature demonstrating that destabilization is less likely to occur if the events during reactivation are predictable (Choi et al., 2010; Jarome et al., 2015; Morris et al., 2006; Pedreira et al., 2004; Rossato et al., 2007; Winters et al., 2009).

To better understand the nature of post-reactivation modification of declarative memory, researchers have also used more naturalistic paradigms. One study utilized participants' personal autobiographical memories rather than a memory formed in the lab. They found that participants' subsequent memory for neutral autobiographical events was impaired if that information was recalled before learning a new story in the lab, suggesting that the original memory was rendered labile upon recall and new episodic learning disrupted its reconsolidation (Schwabe and Wolf, 2009). A study by St. Jacques and Schacter (2013) had participants tour a museum wearing a camera that took photographs of the stops made on the tour. Two days later participants were shown photographs from their camera to reactivate memory for the tour. Following this reactivation, they were shown a series of photographs that included false photographs from a different museum tour and asked to make a judgment as to whether the photos depicted stops on the tour they had taken. On the final test day (48 h following reactivation), participants were shown images from their camera and false images. Participants had increased false recognition of photographs depicting stops that they did not make on the tour. While the authors suggest that the false images had become incorporated into the reactivated episodic memory trace, the study did not include a no reactivation control group to demonstrate that the false recognition was reactivation-dependent.

Other types of naturalistic paradigms involve the use of video clips to form highly detailed episodic memories (Chan and LaPaglia, 2013; Gotthard and Gura, 2018; James et al., 2015; Sinclair and Barense, 2018). Chan and LaPaglia (2013) presented participants with a 40-min video and the following day reactivated memory by asking participants a series of questions regarding the events of the video. Following reactivation, participants listened to audio summarizing the video. Participants who heard audio containing incorrect information had a higher incidence of reporting incorrect information when later asked to recall the events of the video, suggesting that the incorrect information became incorporated into the labile memory trace and produced a "false memory" for the video events (Chan and LaPaglia, 2013). However, it should be noted that participants' memory for the events in the video was tested only 25 min after reactivation, making it difficult to conclude whether the incorrect information was integrated into the existing memory trace, which likely had not reconsolidated before testing. A more recent study, however, provided a convincing demonstration using the canonical 3-day reconsolidation paradigm. Specifically, memory for the events in a series of video clips was more likely to destabilize following the occurrence of a prediction error (Sinclair and Barense, 2018). Memory was reactivated with either complete reminders (full video clip was replayed) or incomplete reminders (video was stopped before the ending) before participants viewed a new series of video clips. When asked to recall the events of the original video clips, participants whose memory was reactivated with incomplete reminders reported more incorrect details compared to those reactivated with complete reminders, suggesting that episodic memory is more likely to be destabilized and updated when a prediction error occurs (Sinclair and Barense, 2018).

Other research has focused on modifying the strength of declarative memories following reactivation by manipulating the stress response. Administration of a mildly stressful cold pressor test (CPT) following reactivation of paired-associate memory was shown to enhance memory recall the following day compared to non-stressed controls (Coccoz et al., 2011). Similarly, exposure to a social evaluative CPT following reactivation of memory for lists of neutral, positive, and negative words was found to enhance recall the following day compared to stress/no reactivation and no stress/reactivation control groups (Bos et al., 2014). Another study found that undergoing a Trier social stress test following reactivation of memory for a video containing both neutral and emotional information enhanced recall of emotional information both immediately following the stressor as well as the following day (Marin et al., 2010). Correspondingly, some studies have shown that suppression of the stress hormone cortisol during or after reactivation can subsequently weaken emotional memories in humans (Antypa et al., 2019; Rimmele et al., 2015). Together these studies demonstrate that stress can modulate reconsolidation to enhance declarative memory. These effects are consistent with those observing that stress can enhance consolidation of declarative memory (R. Brown and Kulik, 1977; McGaugh, 1989). However, too much arousal can also interfere with consolidation and lead to memory impairment (Baldi and Bucherelli, 2005; McGaugh, 1989). Similarly, studies have found that exposure to stress following reactivation can impair or prevent facilitation of autobiographical (Schwabe and Wolf, 2010) and object (Hupbach and Dorskind, 2014) memory recall.

Post-reactivation, but not pre-reactivation, stressors can also prevent information integration and subsequent updating of episodic memories (Dongaonkar et al., 2013). Another study found that stress induction prior to reactivation of memory for movie clips prevented the incorporation of misinformation presented in the form of misleading questionnaires, suggesting that pre-reactivation stress might also prevent memory destabilization and subsequent formation of false memory (Schmidt et al., 2014). There is evidence to suggest that the modulating effects of stress on reactivated declarative memory is likely mediated by noradrenergic activity. Administration of propranolol prior to declarative memory reactivation prevented the enhancing effect of stress and emotional arousal on subsequent memory recall (Kroes et al., 2010; Schwabe et al., 2013, 2012). Another study found no effect of pre-reactivation administration of propranolol on subsequent emotional declarative memory recall (Tollenaar et al., 2009). They did however find support for studies demonstrating that post-reactivation stress can impair memory recall, as pre-reactivation administration of cortisol impaired memory recall. Despite discrepancies regarding the effects of stress on enhancing or inhibiting declarative memory reconsolidation, together these studies provide convincing evidence that stress and arousal can modify declarative memory when experienced around the time of memory reactivation.

In summary, research investigating declarative memory modification following reactivation has provided new insights into the nature of declarative memory storage and maintenance over time. There is compelling evidence to suggest that, following reactivation, declarative memories can be updated, and this is dependent upon the reactivation context, the type of reminder and the timing of its presentation, and the duration between memory reactivation and test. A meta-analysis evaluating evidence from 34 studies of reactivation-induced updating of human episodic memory suggested that evidence favors the existence of reactivation-induced updating (Scully et al., 2017). The analysis included memory age, reactivation method, type of memory studied, interference manipulation, and the type of final memory test as moderator variables. However, this analysis did not demonstrate how the reactivation conditions moderated results. While the specificity of reactivation conditions makes it difficult to replicate results across memory paradigms and research labs, the importance of these conditions should not be overlooked as they provide important insight regarding the nature of long-term declarative memory storage and updating. In order for post-reactivation memory modification to remain adaptive, memory destabilization is likely limited to situations that clearly signal the opportunity for relevant updating. Thus, it is important that research continues not only determining the optimal reactivation conditions for declarative memory updating, but also why these conditions are conducive to updating.

4.3. Aversive memory

Given the therapeutic potential for modifying aversive memories following memory reactivation, research investigating post-reactivation malleability of aversive memories in humans is abundant. However, similar to what has been found with human procedural and declarative memory, there is mixed evidence regarding the viability of post-reactivation manipulations for modifying aversive memories in humans.

The earliest research demonstrating reduced fear responding following memory reactivation was conducted using animal models and pharmacological agents that are not safe to administer to humans, such as anisomycin and MK-801 (Eisenberg and Dudai, 2004; Nader and Hardt, 2009; Nader et al., 2000a; Przybyslawski and Sara, 1997). The challenge was then not only to verify that fear memory could be rendered labile in humans following reactivation, but also to determine ways in which fear memories could safely be disrupted. Debiec and LeDoux (2004) demonstrated that administration of propranolol, a β-adrenergic receptor antagonist that can prevent the enhancing effect of emotional arousal on consolidation in animals and humans (McGaugh, 2000), at the time of fear memory reactivation impaired reconsolidation in rodents, prompting a wave of research investigating propranolol as a means to disrupting fear memory reconsolidation in humans.

Propranolol had been used with moderate success in humans to reduce symptoms associated with PTSD if given shortly following the occurrence of a traumatic event (Pitman et al., 2002; Taylor and Cahill, 2002; Vaiva et al., 2003). With these promising results, Kindt et al. (2009) assessed the translatability of Debiec and LeDoux (2004) findings by utilizing a differential fear conditioning procedure for humans. Fear memory was acquired on the first day by pairing the presentation of fear relevant stimuli (e.g., pictures of spiders) with the administration of a finger shock. On the second day, participants were given either 40 mg of propranolol or placebo 90 min prior to viewing the spider image, in the absence of a shock, in a memory reactivation session. There was also a no reactivation control group that received propranolol to rule out any effects of propranolol administration on memory retention. On the third day, the effects of propranolol on startle response were tested by presenting the images in the absence of the shock over 10 extinction trials, followed by a reinstatement test. They found that fear learning was successfully acquired on day 1 and startle response did not differ between the propranolol and placebo group at training or during reactivation. On the day of test, participants that received propranolol prior to memory reactivation had decreased startle response across all 10 extinction trials compared to those in the placebo group and the propranolol + no reactivation group. Furthermore, the reinstatement test (administration of an un-signaled shock) failed to recover fear responding only in the propranolol group. This suggests that propranolol paired with memory reactivation altered fear responding and reduced susceptibility to spontaneous recovery, positioning this as a potentially more effective treatment than extinction training.

Interestingly, while propranolol reduced fear responding to the CS, participants' declarative memory for the events of acquisition were intact (Kindt et al., 2009; Soeter and Kindt, 2010). Thus, propranolol administration followed by memory reactivation not only robustly reduced fear responding but also appeared to selectively disrupt the emotional aspect of the memory without interfering with the content of the memory (Kindt et al., 2009). Indeed, a follow-up study found that participants that received propranolol prior to fear memory reactivation had intact memory for the previously learned fear association but a significantly diminished startle response and low subjective feelings of anxiety while recalling the association of the CS+ with the shock (Soeter and Kindt, 2012a). These results have significant moral implications for the use of reactivation-induced memory updating protocols as a means of modifying human memory in a clinical setting for adaptive updating without erasing the memory altogether.

Subsequent studies have replicated the effectiveness of propranolol administration at the time of memory reactivation for reducing fear responding (Soeter and Kindt, 2010, 2011, 2012a) and have extended the findings to demonstrate that the neutralizing effects of propranolol are specific to the reactivated memory (Deng et al., 2020; Soeter and Kindt, 2011), only when administered prior to (Brunet et al., 2018; Kindt and Soeter, 2018; Thomas et al., 2017), or closely following reactivation (Kindt and Soeter, 2018), and that attenuated fear responding is long lasting (Soeter and Kindt, 2010). Strongly encoded fear memories could also be reactivated and modified by propranolol (Soeter and Kindt, 2012b). Boundary conditions, such as memory strength, pose a significant challenge to the plausibility of utilizing reactivation-induced memory updating as a means of modifying maladaptive memories in a clinical setting given that the memories being targeted for treatment are likely strongly encoded. By activating the noradrenergic system, which plays a role in enhancing consolidation of fear memories, with yohimbine prior to fear memory acquisition, Soeter and Kindt (2012b) were able to establish strongly encoded fear memories in participants. Despite the strength of the memory, they were able to reduce participants' startle response with propranolol administered prior to memory

reactivation, suggesting that the memory trace could still be destabilized at reactivation and neutralized with propranolol. Perhaps in this study, the strong association developed between the fear stimuli and the shock led to the occurrence of a prediction error at the time of memory reactivation when the image was presented in the absence of the shock. This may have been sufficient to overcome boundary conditions to destabilize the memory. Indeed, there is evidence that fear memory in humans is more likely to destabilize and become susceptible to modification by propranolol if the events at the time of memory reactivation violate expectations (Sevenster et al., 2013, 2014).

Several studies have also utilized naturalistic fear memory paradigms to better assess the translatability of the effects of propranolol on reducing fear responding for treatment of phobias and anxiety disorders. One study recruited participants with a fear of spiders and reactivated this fear by briefly presenting a live tarantula (Soeter and Kindt, 2015). Administration of propranolol following the reactivation session greatly reduced avoidance behaviour such that participants were able to touch and hold spiders for 1 year following treatment (Soeter and Kindt, 2015). Preliminary findings also suggest that propranolol may be effective at reducing fear of public speaking when administered following reactivation (Elsey et al., 2020). In a study reviewing four case studies of patients with PTSD that received a reconsolidation intervention, in which patients underwent a brief memory reactivation session followed by administration of propranolol, found that three of the four patients demonstrated a substantial reduction in fear symptoms after only one or two intervention sessions (Kindt and van Emmerik, 2016).

While these studies provide evidence for the use of propranolol paired with reactivation for neutralizing fear memories, several studies have failed to replicate the effectiveness of propranolol for attenuating fear responding. In an attempt to further delineate reactivation conditions to reliably destabilize fear memory, Bos et al. (2014) were unable to demonstrate reduced startle response in participants administered propranolol prior to memory reactivation in a manner consistent with their previous work. Furthermore, when attempting to determine if reactivation in a novel context poses boundaries on fear memory destabilization, they were unable to destabilize and disrupt fear memories with propranolol in the novel context or the original context, the latter of which was contradictory to their original findings (Schroyens et al., 2017). Research from other groups has also reported no effects of propranolol on reducing or neutralizing fear responding when given at the time of memory reactivation (Spring et al., 2015; Wood et al., 2015). There are also contradictory findings regarding the longevity of reduced fear responding following propranolol treatment at the time of memory reactivation, with some studies suggesting that propranolol reduces fear responding for months to years (Soeter and Kindt, 2010, 2015) and others finding only acute effects (Chalkia et al., 2019).

Thus, the current literature suggests that propranolol paired with memory reactivation holds promise as a means for neutralizing fear memory in humans without disrupting memory for the event itself (Lonergan et al., 2013). However, with a number of studies unable to find a reactivation-dependent effect of propranolol, future research must continue to elucidate the reactivation conditions that are more likely to destabilize fear memories as well as develop naturalistic paradigms to begin to assess the translatability to clinical settings as memories associated with conditions such as PTSD are likely strongly encoded and may be resistant to destabilization. Given the importance of noradrenaline (NA) for attention and arousal during events that signal a prediction error (Berridge and Waterhouse, 2003; Schultz and Dickinson, 2000), such as those occurring at the time of memory reactivation, one possible consideration for future studies is that administration of propranolol prior to memory reactivation with the intention of modulating reconsolidation may have the unintended effect of preventing the memory trace from destabilizing by impairing prediction error signaling and thereby failing to indicate any change to the underlying fear memory. While the role of NA in memory destabilization is not fully understood, studies in rodent models have demonstrated that administration of propranolol prior to fear memory reactivation prevented destabilization (Lim et al., 2018).

Other pharmacological agents have been studied for their ability to modify maladaptive memories when administered following memory reactivation but have shown limited potential. Rapamycin, an inhibitor of the mammalian target of rapamycin (mTOR) pathway which is involved in synaptic stabilization process required for reconsolidation, was found to have minimal efficacy at minimizing PTSD symptoms among veterans compared to placebo treatment (Suris et al., 2013). However, rapamycin was found to reduce self- and clinician-rated PTSD symptoms among veterans with more recent traumas compared to veterans with older traumatic memories at a one-month follow up, but not a three-month follow up (Suris et al., 2013). This study suggests that more recent traumatic memories may be more likely to destabilize.

Other researchers have turned to non-pharmacological interventions to attempt to modify maladaptive fear memories in humans. Accordingly, it has been proposed that extinction training could persist if the original fear memory was reactivated prior to extinction training (Monfils et al., 2009). That is, memory reactivation could allow the original fear memory to be updated with the CS-no US association learned during extinction if training occurred directly following reactivation of the original fear memory. Indeed, extinction training shortly following fear memory reactivation can lead to long-lasting attenuation of fear memory with low levels of reinstatement or spontaneous recovery in rats (Monfils et al., 2009), and researchers have moved to adapt this protocol to assess its efficacy for human memory updating. In a study conducted by Schiller et al. (2010), participants were conditioned to associate fear irrelevant stimuli with administration of an electric shock. They found that reactivating fear memory prior to extinction training, where the CS was presented in the absence of the shock, attenuated skin conductance and reduced levels of spontaneous recovery relative to participants that underwent extinction training in the absence of memory reactivation (Schiller et al., 2010). Attenuated fear responding was selective to the reactivated memory and only occurred if extinction training occurred 10 min, not 6 h, following memory reactivation. Furthermore, post-reactivation extinction training was effective at minimizing reinstatement 1 year later (Schiller et al., 2010).

Studies have since replicated and built on the results of Schiller et al. (2010) that post-retrieval extinction can effectively and persistently update fear memories to minimize fear responding in humans using traditional extinction paradigms (Björkstrand et al., 2016, 2017; Chen et al., 2021; Johnson and Casey, 2015; Kitamura et al., 2020; Li et al., 2019; Liu et al., 2014; Oyarzún et al., 2012; Steinfurth et al., 2014; Thompson and Lipp, 2017) and unconventional extinction paradigms (Agren et al., 2017; Golkar et al., 2017; Grégoire and Greening, 2019; Yang et al., 2019) in both clinical and laboratory settings. Research has also begun to examine how post-retrieval extinction modifies fear memories within the brain. There are several studies demonstrating long-term changes in functional connectivity between the amygdala and brain regions such as the insula, HPC, midline anterior cingulate, and the ventromedial prefrontal cortex following post-retrieval extinction of fear memories (Agren et al., 2012; Feng et al., 2016). Furthermore, post-retrieval extinction has been found to modify activity within brain regions associated with fear memory, such as the amygdala (Björkstrand et al., 2015) and prefrontal cortex (Phelps et al., 2004; Schiller et al., 2013).

Several studies, however, have also failed to find that post-retrieval extinction persistently reduces fear responding to fear-relevant stimuli (Fricchione et al., 2016; Golkar et al., 2012; Kindt and Soeter, 2013; Meir Drexler et al., 2014) or fear-irrelevant stimuli (Chalkia et al., 2020; Golkar et al., 2012; Soeter and Kindt, 2011) in humans. Indeed, a meta-analysis examining the magnitude of post-retrieval extinction effects in both humans and animal models found a moderate-to-large effect when fear-irrelevant stimuli are used; however when fear-relevant stimuli are used the effect is near zero (Kredlow et al., 2016). This suggests that the efficacy of post-retrieval extinction in a clinical setting

for modifying memories associated with anxiety disorders and phobias, which involve fear-relevant stimuli, may be limited. Only a handful of studies have assessed the therapeutic potential of post-retrieval extinction in a clinically relevant setting, and they find little evidence that presentation of a reminder prior to exposure therapy enhances attenuation of fear responding over standard exposure therapy (Maples-Keller et al., 2017; Shiban et al., 2015; Telch et al., 2017; Vermes et al., 2020). However, one study suggested that post-retrieval extinction may help to accelerate exposure therapy, as reactivation of spider phobia prior to extinction was found to reduce fear responding faster even when the duration of exposure therapy was reduced (Lancaster et al., 2020).

The limited success of post-retrieval extinction at attenuating fear responding long-term in a clinical setting is likely due to the complex nature of fear memories associated with conditions characterized by maladaptive memories, such as PTSD and anxiety disorders. Studies investigating the efficacy of post-retrieval extinction for treating maladaptive memories often use a single CS paired with an US, which a dramatically simplified form of fear memory compared to those associated with PTSD. Indeed, the validity of reminder cues has been found to significantly limit whether a fear memory can be destabilized and modified with extinction training (Li et al., 2017). It is also important to consider that conflicting results regarding the efficacy of post-reactivation manipulations to persistently modify fear memories likely results from complex individual differences between participants. There is evidence that genetic variations may influence whether an individual's fear memory can be rendered modifiable following reactivation. For example, brain derived neurotrophic factors (Asthana et al., 2016), serotonin-transporter (Agren et al., 2012), and catechol-O-methyltransferase (Agren et al., 2012) gene variations have been found to modulate reconsolidation of fear memories and influence the effectiveness of post-retrieval extinction at preventing the return of fear long-term. Thus, reactivation conditions and stimuli, as well as individual genetic differences, pose a challenge for translating laboratory research utilizing post-retrieval extinction to attenuate fear memories to clinical populations. It is therefore likely that parameters developed in laboratory settings will require modification for successful clinical application.

4.4. Appetitive memory

While the effects of post-retrieval extinction on attenuation of aversive memories are mixed and have not yet been reliably translated to a clinical setting for treatment of phobias and anxiety disorders, research looking at the use of post-retrieval extinction for attenuating appetitive memory has been promising. When abstinent heroin addicts were shown a 5 min heroin related video prior to extinction training, heroin craving was attenuated at 1, 30, and 180 days post-treatment compared to those who received no reminder prior to extinction or underwent extinction training 6 h following the reminder (Xue et al., 2012). Similarly, post-retrieval extinction has been found to be more effective than standard extinction at attenuating cue-induced craving in cigarette smokers (Germeroth et al., 2017; Zandonai et al., 2021). Another study used post-reactivation counterconditioning, during which alcohol cues were paired with disgusting outcomes, to determine if drinking memories could be modified to reduce alcohol consumption in hazardous drinkers. They reported a significant reduction in attentional bias and liking to alcohol compared to no-reactivation controls, however reduction in drinking behaviour declined similarly in both groups (Das et al., 2015). Reductions in alcohol consumption were found to be longer lasting in participants that underwent counterconditioning following memory reactivation, suggesting that leveraging the post-reactivation window for behavioural intervention may enhance reductions in problematic drinking behaviour (Gale et al., 2020).

Given that addicted individuals have a high propensity for relapse when exposed to drug associated cues during sustained periods of drug abstinence, the results of these clinical trials are promising for retrieval-extinction as a more effective treatment compared to standard extinction training. While this area has received less attention in humans, a meta-analysis demonstrated that appetitive memories were more susceptible to modification with retrieval-extinction training in rodents than aversive memories (Kredlow et al., 2016). The increased susceptibility of appetitive memories to modification by retrieval-extinction likely lies within differences in the neural circuitry underlying aversive and appetitive memories. The effectiveness of retrieval-extinction for attenuating drug craving provides strong evidence for retrieval-extinction as a means to modifying memory in humans and suggests that further research regarding the nature of aversive memory reactivation and reconsolidation is likely required before retrieval-extinction is found to consistently attenuate aversive memories.

Pharmacological interventions post-reactivation may also provide a promising means of updating maladaptive appetitive memories. Post-reactivation mTOR inhibition has been found to have limited success for persistently modifying chocolate binge eating behaviour (Walsh et al., 2021). While subjects that received rapamycin following reactivation showed a mild reduction in binge eating episodes and improved food choices, they did not show greater reductions in motivational saliency of chocolate cues, motivation to consume chocolate, or liking of chocolate compared to control groups (Walsh et al., 2021). Additionally, the NMDA receptor antagonist memantine given following reactivation of associative-smoking memories did not have an effect at minimizing cigarette smoking (Das, Hindocha et al., 2015). Furthermore, inhalation of nitrous oxide following reactivation, that involved a prediction error, was found to have potential at reducing alcohol consumption in hazardous drinkers (Das et al., 2018a, 2018b). Propranolol has also been studied regarding its efficacy at modifying smoking-related memories to reduce nicotine cravings. One study found that a single dose of propranolol prior to memory reactivation, where participants were shown smoking-related images, was able to significantly reduce nicotine craving the following day (Lin et al., 2021). In accordance with previous studies demonstrating that disruption of reconsolidation of fear memories alters activation brain regions involved in emotional memory (Agren et al., 2012; Björkstrand et al., 2016, 2015; Schiller et al., 2013; Schwabe et al., 2012), they found that decreased nicotine craving was associated with decreased postcentral gyrus activity in response to smoking-related cues and enhanced connectivity between the HPC and striatum (Lin et al., 2021). It should be noted, however, that nicotine craving was assessed 24 h following reactivation and long-term attenuation of nicotine craving was not assessed. Indeed, another study found that a single dose of propranolol following reactivation of smoking-related memories had no effect on nicotine craving one week later (Pachas et al., 2015). Similar mixed results have also been found in studies investigating the efficacy of pharmacological manipulations post-reactivation for attenuating alcohol consumption in problem drinking (for a more comprehensive review see Barak and Goltseker, 2021).

It should be noted that the studies reviewed here represent only a portion of evidence from the rapidly growing literature and substantial body of evidence both for and against reactivation-induced updating in humans across a number of memory systems. Research in this field has created two opposing views regarding memory reconsolidation in humans, with some interpreting the inconsistencies between research groups as evidence that memory reconsolidation does not exist and others suggesting that reconsolidation has provided an important framework for research investigating memory updating. While it cannot be concluded that reconsolidation specifically is the neurobiological mechanism responsible for the post-reactivation memory updating effects observed in humans, it is currently the only mechanism proposed to explain these results (Elsey et al., 2018). Long-term memory, especially in humans, is complex and this is clearly reflected in the challenge of determining the specific reactivation conditions, reactivation stimuli, and individual genetic factors required to destabilize and update human

memories both in a laboratory and clinical setting. The following sections delve deeper into the boundary conditions that strongly influence the likelihood of reactivated memories to destabilize and enter a modifiable state. A comprehensive understanding of these various factors will be essential to resolve current controversies in this field and move us closer to exploiting the mechanisms of reactivation-induced memory updating for therapeutic purposes in humans.

5. Boundaries on memory destabilization and updating

As noted, often the inability to demonstrate reactivation-induced memory updating is the result of boundary conditions on memory destabilization. That is, characteristics of the memory, such as the age or strength of the memory, can prevent it from destabilizing upon reactivation. For example, Milekic and Alberini (2002) trained rats on an inhibitory avoidance task and observed that only those exposed to memory reactivation 2–7 days following training were impaired when given anisomycin following reactivation. When memory was reactivated 14–28 days following training, post-reactivation anisomycin had no effect on performance (Milekic and Alberini, 2002). Similar effects have been observed for inhibitory avoidance memory in mice (Boccia et al., 2006), fear memory in fish (Eisenberg and Dudai, 2004), rats (Einarsson and Nader, 2012) and mice (Frankland et al., 2006; Suzuki et al., 2004), passive avoidance in chicks (Litvin and Anokhin, 2000), morphine place preference in rats (Robinson and Franklin, 2010), and object memory in rats (Winters et al., 2009). These findings suggest that the passage of time leads to changes in underlying memory storage mechanisms that enable older memories to resist reactivation-induced destabilization.

There is also evidence that extensive training or stronger encoding enables the resultant memory to resist destabilization. Indeed, rodents trained with a greater number of CS-foot shock pairings have been shown to have intact fear memory despite post-reactivation administration of anisomycin, suggesting that the memory did not destabilize (Suzuki et al., 2004; S.-H. Wang et al., 2009). Similarly, strongly encoded object memories were shown to resist the impairing effects of post-reactivation administration of the NMDA receptor antagonist MK-801 (Winters et al., 2009). These studies suggest that molecular mechanisms associated with enhanced memory encoding can also prevent reactivation-induced destabilization.

5.1. Neurobiological mechanisms of boundary conditions

The existence of boundary conditions on memory destabilization suggests that there are neurobiological mechanisms that enable memory stability in the presence of reminder cues. This may serve to protect reactivated memories from potentially maladaptive updating, such as unwanted erasure or the development of false memories through the inappropriate incorporation of inaccurate or unrelated information. Indeed, a delicate balance between accurate and inaccurate information integration would seem to be a basic requirement of such an updating mechanism for it to serve an adaptive purpose in maintaining memory relevance. Although occasional modification of long held or strongly encoded memories might still be required, it makes intuitive sense that such significant determinants of behavior should be safeguarded relative to those that are less salient or more recently acquired. It is, therefore, perhaps not so surprising that reconsolidation or reactivation-induced memory modification effects are not always easily replicated.

One mechanism that has been suggested to underlie resistance to destabilization is changes in NMDA receptor subunit composition following strong fear conditioning training (Holehonnur et al., 2016; Wang et al., 2009). NMDA receptors have been implicated in both memory destabilization and reconsolidation, their involvement in which is dependent upon the composition of the NR2 subunit. That is, GluN2B- and GluN2A-containing NMDA receptors have dissociable roles in modulating fear and object memory destabilization and reconsolidation, respectively (Milton et al., 2013; Wideman et al., 2021). It has been shown that repeated tone-foot shock pairings established strong fear memories that were resistant to reactivation-induced destabilization, as demonstrated by a lack of impairing effect of post-reactivation BLA infusions of anisomycin (Wang et al., 2009). This resistance to destabilization was accompanied by a reduction in the number of GluN2B-containing NMDA receptors in the BLA (Wang et al., 2009). A follow-up study reported similar findings that strong fear memories that were resistant to reactivation-induced destabilization were associated with an increased ratio of GluN2A/N2B in the BLA (Holehonnur et al., 2016). They then demonstrated that weak fear memories, which readily destabilize, could become resistant to destabilization if the ratio of N2A/N2B subunit composition was increased following training.

There is also evidence that changes in GluN2B subunit protein expression in the time following learning serve to protect remote object memories from destabilization (Wideman et al., 2021). That is, 24 h following learning there was an increase in expression of GluN2B subunit proteins in PRh and at this time point it was determined that GluN2B-containing NMDA receptors had a functional role in object memory destabilization. However, at 48 h following learning, GluN2B subunit protein levels returned to baseline and this corresponded with increased resistance to destabilization and a limited role for GluN2B-containing NMDA receptors in overcoming boundary conditions to promote destabilization (Wideman et al., 2021). Thus, it appears that the downregulation of mechanisms involved in destabilization, such as GluN2B-containing NMDA receptors, may serve to stabilize memory traces such that they become resistant to reactivation-induced destabilization (Finnie and Nader, 2012; Zhang et al., 2018).

Changes in synaptic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors may also underlie memory stability during destabilization. Within the lateral amygdala, GluA2 subunit-containing (i.e. calcium-impermeable) AMPA receptors were removed from the synapse and replaced with GluA2-lacking (i.e. calcium-permeable) AMPA receptors during fear memory retrieval (Hong et al., 2013). Blocking either the endocytosis of calcium-impermeable AMPA receptors or NMDA receptor activity, which are both necessary processes for this transient AMPA receptor exchange, impeded fear memory destabilization (Hong et al., 2013). This strongly suggests that the exchange of AMPA receptor subtypes is critical for changing a stable long-term memory to an unstable form (Hong et al., 2013). Although the role of AMPA receptors has not been discussed in direct relation to boundary conditions, the absence of the AMPA receptor subtype exchange may contribute to resistance to destabilization.

Another neural mechanism that has been posited to underlie resistance to destabilization is elevated levels of amyloid beta (Aβ) during the formation of strong auditory fear memories (Finnie and Nader, 2020). That is, there was a selective increase in $A\beta_{42}$ in young rats following strong auditory fear conditioning training (10 foot shocks) compared to weakly trained rats (1 foot shock; Finnie and Nader, 2020). To determine whether Aβ was involved in establishing resistance to destabilization, a γ-secretase inhibitor was infused into the BLA to prevent the cleavage of Aβ from amyloid precursor protein (APP) following training. Inhibiting Aβ production following learning appeared to prevent the establishment of boundary conditions, as strongly encoded fear memories were readily destabilized upon reactivation in rats infused with the γ-secretase inhibitor (Finnie and Nader, 2020). This effect was then reversed with administration of endogenous Aβ, suggesting that Aβ production following learning may act to stabilize the memory trace and in doing so, reduce the likelihood of destabilization. The potential role of Aβ in memory stability has implications for understanding reduced cognitive flexibility with aging and those with Alzheimer's disease, both of which are associated with elevated levels of Aβ. In this case, the presence of boundary conditions may be associated with the inability to update memories with new and relevant information such that they are not accurately maintained over time.

5.2. Overcoming boundary conditions

5.2.1. Reactivation parameters favouring destabilization

Boundary conditions must be overcome so that older and stronger memories can be updated to guide behaviors accurately in changing environments; in such cases, the updating information likely needs to be highly salient or obvious to activate the neural mechanisms necessary to override these boundary conditions. Accordingly, several studies have demonstrated that explicit new information presented along with reminder cues at the time of memory reactivation can overcome boundary conditions and promote destabilization. Morris et al. (2006) reported that strongly encoded spatial memories in rats were susceptible to disruption by post-reactivation intra-hippocampal anisomycin only when rats encoded new spatial information at the time of memory reactivation. Similarly, presentation of a salient contextual change at the time of memory reactivation was necessary to promote destabilization of strongly encoded or remote object memories in rats (Winters et al., 2009). In this study, the previously learned objects were briefly presented to serve as a reminder for the object memory, and the texture of the floor of the apparatus was changed. Only when this context change was introduced were memories susceptible to disruption by post-reactivation administration of MK-801 (Winters et al., 2009). Numerous additional studies support the notion that memories are more readily destabilized when reactivated under conditions that are different from those of the original learning episode (Exton-McGuinness et al., 2015; Fernández et al., 2016; Finnie and Nader, 2012; Jarome et al., 2015; Krawczyk et al., 2017; Pedreira et al., 2004; Rossato et al., 2007). That is, there must be sufficient mismatch (or prediction error) between reactivation and the original learning event to reliably engage destabilization mechanisms in rodents (Exton-McGuinness et al., 2014; Jarome et al., 2015; Morris et al., 2006; Pedreira et al., 2004; Reichelt et al., 2013; Winters et al., 2009) and humans (Chen et al., 2021; Das et al., 2018a, 2018b; Forcato et al., 2016; Gotthard and Gura, 2018; Li et al., 2021; Schiller et al., 2010; Sevenster et al., 2013, 2014; Sinclair and Barense, 2018) for subsequent memory updating. In addition to contextual changes, other forms of surprise during reactivation include adding a new object (Rossato et al., 2007), changing object location (Choi et al., 2010; Kwapis et al., 2019), or temporal changes in an associative pairing presentation (Agustina López et al., 2016; Díaz-Mataix et al., 2013). Differences in the type of memory, degree of unexpectedness, and valence of the unexpected information across studies likely explain why certain neuromodulators are recruited for various types of memory modification.

5.2.2. Neuromodulators and memory destabilization

Research investigating the neurobiological basis of memory destabilization promoted by the presentation of new or unexpected information at the time of memory reactivation has demonstrated that acetylcholine (ACh) and dopamine (DA) have important roles in modulating destabilization to overcome boundary conditions. Given evidence of its involvement in cognitive functions involved in new learning, such as attention and arousal (Hasselmo and McGaughy, 2004; Sarter and Bruno, 1997), as well as signaling unexpected outcomes (Sturgill et al., 2020), it has been hypothesized that ACh signaling in response to novelty at the time of reactivation plays a role in promoting destabilization (Stiver et al., 2017, 2015). In a series of studies using the SOR task, where the floor of the apparatus was changed during the reactivation session to promote destabilization, it was found that inhibiting muscarinic receptors in PRh of rats prevented novelty-induced destabilization of remote object memories, suggesting that when a reactivation session contains new information, ACh acting at muscarinic receptors is an important signal for promoting object memory destabilization (Stiver et al., 2015). This was further evidenced by the finding that activation of muscarinic receptors in PRh with the muscarinic receptor agonist oxotremorine prior to reactivation in the absence of the floor change mimicked the effect of novelty and was sufficient to promote destabilization of remote object memories (Stiver et al., 2015). Similarly, it has recently been shown that inhibiting muscarinic receptors in the dHPC prevented novelty-induced destabilization of strongly encoded object location memories (Huff et al., 2021).

Studies have since shown that the modulatory role of ACh in novelty-induced object memory destabilization is likely through its activity at the M_1-muscarinic receptor subtype, as inhibition of M_1, but not M_2, receptors in PRh prevented novelty-induced destabilization in rats (Stiver et al., 2017). Furthermore, in the absence of explicit novelty during reactivation, activation of M_1-receptors within PRh (Stiver et al., 2017), or the dHPC (Huff et al., 2021), facilitates destabilization of remote object memories or strongly encoded object location memories, respectively. It appears that M_1-receptor activation by ACh may be directly involved in triggering memory destabilization at the synaptic level through activation of the ubiquitin proteasome system (UPS), which degrades synaptic proteins and has previously been implicated in destabilization of other forms of memory (Choi et al., 2010; Jarome et al., 2016, 2011; Lee et al., 2008; Orsi et al., 2019; Ortiz et al., 2019). Inhibition of the UPS in PRh was found to prevent both novelty-induced destabilization and M_1-receptor induced destabilization in rats, suggesting that the UPS is required for object memory destabilization and may become activated downstream of M_1-receptors (Stiver et al., 2017). The mechanism through which M_1-receptors lead to activation of the UPS at the time of memory reactivation likely involves the second messenger protein inositol 1,4,5-triphosphate (IP_3), which when inhibited from binding to its receptors in PRh prevents both novelty- and M_1-receptor induced destabilization (Stiver et al., 2017). When bound to its receptors on the endoplasmic reticulum (ER), IP_3 can mobilize intracellular calcium stores (Felder, 1995), and this increased intracellular calcium may regulate changes in UPS activity through calcium-calmodulin dependent protein kinase II (CaMKII; Djakovic et al., 2009; Jarome and Helmstetter, 2014).

Interestingly, CaMKII has been implicated in fear memory destabilization (Jarome et al., 2016), where it is thought to be activated following calcium influx through NMDA receptors at the time of reactivation. Recent work has found that NMDA receptors, specifically GluN2B-containing NMDA receptors, in PRh are also involved in object memory destabilization but only in the absence of boundary conditions (Wideman et al., 2021). That is, inhibition of GluN2B-containing NMDA receptors had no effect on novelty- or M_1-induced destabilization of remote object memories (Wideman et al., 2021). Thus, despite GluN2B-containing NMDA receptors and M_1-receptors having similar downstream mechanisms for promoting synaptic destabilization, ACh activity at M_1-receptors appears to have a specialized role in facilitating destabilization of resistant memories reactivated in the presence of salient novel information.

This M_1-mediated pathway involved in overcoming boundary conditions to destabilize resistant object memories has also been found to be necessary for object memory updating in rats (Jardine et al., 2020). Inhibiting M_1-receptors, IP_3 receptors, CaMKII, or the UPS within PRh was sufficient to prevent object memory destabilization and subsequent updating with new contextual information presented during the post-reactivation window (Jardine et al., 2020). This study further highlighted not only the importance of ACh-mediated memory destabilization, but the functional role this process likely plays for updating and maintaining long-term memories.

Other forms of novelty at the time of reactivation, such as a novel object, have also been found to more readily destabilize object memories (Rossato et al., 2007). While this study did not investigate boundary conditions per se, they found that object memories were more likely to destabilize if a novel object was presented with the reminder object at the time of reactivation, likely because the reactivation session served as an opportunity for memory updating (Rossato et al., 2007). The authors hypothesized that DA was involved in initiating destabilization under these conditions as the presentation of the novel object likely caused a prediction error, or a violation of previous expectations. Indeed, when

D1/D5 receptors were inhibited in dorsal CA1 it prevented novelty-induced object memory destabilization in rats (Rossato et al., 2015).

Other studies have similarly reported that novelty or an unexpected outcome at the time of reactivation can more readily destabilize memories and that this form of destabilization depends on DA. One study found that memory for an appetitive goal-tracking task could be destabilized following a reactivation session in which stimuli were presented in the absence of reward and this effect required DA signaling in the ventral tegmental area (VTA; Reichelt et al., 2013). Unexpected omission of a reward can generate a negative prediction error signal, which is regulated by phasic DA activity in the VTA (Takahashi et al., 2009). While the VTA was not found to be the site of appetitive memory destabilization, this study demonstrated that DA signaling from the VTA in response to the events at the time of reactivation is involved in mediating destabilization of reward-associated memories in other brain regions (Reichelt et al., 2013). The BLA, which receives DA innervation from the VTA, has been implicated in appetitive memory destabilization, as inhibition of D1 and D2 receptors in the amygdala prior to reactivation where reward was withheld, prevented appetitive memory destabilization (Merlo et al., 2015).

While these studies provide evidence that DA signaling in response to new or unexpected information at the time of reactivation is necessary for memory destabilization, DA alone does not appear to be sufficient to promote destabilization. In recent work with rats, it was found that increasing the strength of foot shock during auditory fear conditioning training created a strong fear memory that resisted destabilization following reactivation, even when DA signaling was enhanced (Flavell and Lee, 2019). That is, activating D1 receptors pharmacologically prior to reactivation was not sufficient to promote destabilization. However, destabilization could be pharmacologically induced by nootropic nefiracetam and this was dependent upon DA signaling. When D1 receptors were inhibited, this prevented nefiracetam from initiating destabilization of strong fear memories (Flavell and Lee, 2019). These results suggest that while DA signaling is necessary for destabilization, it is not sufficient on its own to promote destabilization. This contrasts with the role of ACh, which was found to be both necessary and sufficient to promote destabilization of strong or remote object memories (Stiver et al., 2017, 2015). Interestingly, nefiracetam interacts with a number of neuromodulators of memory and cognition and has been shown to enhance ACh signaling (Sakurai et al., 1998). Thus, the results of the study by Flavell and Lee (2019) subtly hint that DA may modulate destabilization through its interaction with other neuromodulators of memory destabilization, such as ACh.

A recent study further delineated the role of these two neuromodulator systems for reactivation-based memory modification. In a functional magnetic resonance imaging (fMRI) study in humans, familiar video clips were replayed and abruptly stopped in order to elicit prediction error during memory reactivation with the goal of assessing neural processes that facilitated episodic memory updating (Sinclair et al., 2021). When participants were asked to recall details about the video clips in a subsequent test phase, it was found that prediction error during memory reactivation facilitated the incorporation of false information into the reactivated memory. Prediction error during reactivation seemed to direct hippocampal functioning to readily modify, rather than merely preserve, the episodic memory. Interestingly, this effect was supported by basal forebrain and HPC connectivity, as opposed to hippocampal connectivity with the VTA (Sinclair et al., 2021). This study further supports the idea that prediction error during memory reactivation signals the opportunity to update memory and it suggests that the basal forebrain, a major source of ACh in the brain, modulates the resultant episodic memory updating within the HPC. Furthermore, it is notable that an increase of false memories of the video clips was the key indicator of memory updating in this paradigm, which reinforces the notion that resilience to memory destabilization could be an adaptive mechanism to protect episodic memories from inaccurate modifications.

While research investigating the neuromodulators of memory destabilization is ongoing, the current evidence suggests that long-term memory storage involves a number of mechanisms dedicated to maintaining a careful balance between protecting memories from destabilization to avoid disruption and overcoming boundary conditions to allow for relevant updating (Fig. 3). As we continue to appreciate the behavioural factors at the time of reactivation that can trigger these neuromodulators to either limit or initiate destabilization, our ability to destabilize memories in both research and clinical settings will vastly improve.

6. Conclusions and outstanding questions

We have attempted a thorough and balanced review of the literature regarding reactivation-induced memory modification in humans and non-human animals. This represents a vast and growing array of studies across species and memory types. While not an exhaustive review of all research in this field, the weight of evidence presented here strongly favours the interpretation that some form of mechanism(s) operates within the brain to facilitate memory change upon reactivation. However, and crucially, evidence for this process is not always readily forthcoming, and we propose that this reflects a critical feature of such a process rather than calling into question the existence thereof. Although the behavioural requirements and neurobiological mechanisms underlying this process remain to be comprehensively described, great strides have been made in recent years to this end. It is apparent that highly specific reactivation conditions must be met to render consolidated long-term memories modifiable during or following reactivation. These conditions typically include some form of prediction error or salient novelty that likely signals the opportunity for updating reactivated memories with relevant information. The importance of salient novelty at the time of reactivation has been demonstrated in both human and non-human studies, and these behavioural stimuli appear to be essential for activating neuromodulatory systems that could be key to the synaptic destabilization process. Careful consideration of reactivation parameters could allow researchers to selectively modify a target memory, but a slight variation in the features of a reactivation episode could signal for the formation of a new memory rather than the modification of an old memory (Gershman et al., 2017). A delicate balance of re-exposure and unexpectedness determines the engagement of memory modification processes and, even then, memory reconsolidation and new learning mechanisms could be working cohesively to update an old memory with newly relevant information (Clem and Schiller, 2016). We are far from a comprehensive understanding of these various factors, but increasingly systematic and targeted work should continue to reveal how these important features of this complex process interact to regulate memory destabilization and modifiability. It should not come as a surprise that such a process would be a complex one, given the importance of balancing adaptive memory updating with the need to avoid maladaptive integration of novel inaccuracies during the dynamic process of long-term memory storage.

Several outstanding questions are raised by this literature. In addition to continuing to specify the behavioural conditions that promote memory destabilization and updating, it will be essential to evaluate the generalizability of these effects across memory types and brain regions. Similarly, do neuromodulators, such as ACh and DA, play overlapping or complementary roles in these processes, and do these roles apply broadly or only to certain types of memory storage? Additionally, although some studies have effectively probed the specificity of memory updating (Exton-McGuinness et al., 2019; Kindt et al., 2009), this feature is generally absent from many investigations, and it will be important to document conditions that result in highly specific versus broader modifications to stored information. Do these effects differ depending on the nature of memories being targeted (e.g., aversive versus declarative memory)? The feasibility of exploiting these processes for actual

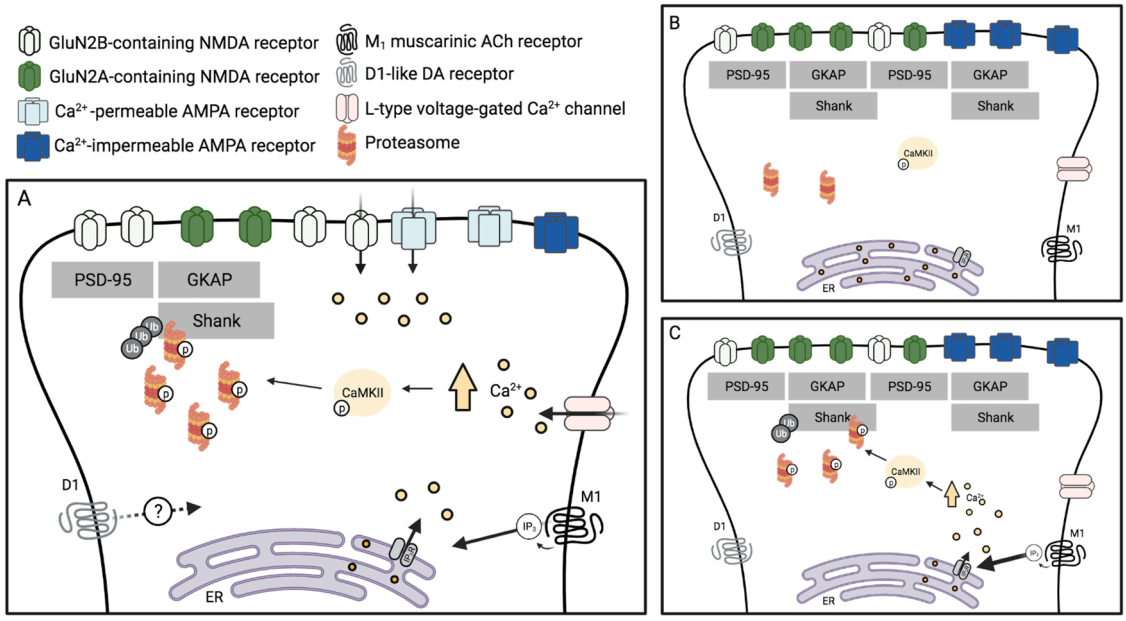

Fig. 3. Diagram of memory destabilization mechanisms in a post-synaptic neuron. A) A recent memory more readily destabilizes during memory reactivation. Both NMDA and AMPA glutamatergic receptors seem to play an important role in destabilization of recent memories. Activation of GluN2B subunit-containing, but not GluN2A-containing, NMDA receptors is required for destabilization of fear memory and object memory. As a memory becomes resistant to destabilization, more GluN2A-containing NMDA receptors are present in the synapse compared to the GluN2B-containing NMDA receptors. Moreover, during retrieval of some memories, there is a switch in GluA2 subunit-containing (i.e. calcium-impermeable) AMPA receptors and GluA2-lacking (i.e. calcium-permeable), wherein calcium-impermeable AMPA receptors are removed from the synapse via endocytosis and calcium-permeable are added to the synapse. This switch in AMPA receptor subtypes is required for memory destabilization. Furthermore, activation of L-type voltage-gated calcium channels (LVGCC) is necessary for destabilization of fear memory, likely because they provide an important influx of calcium that results in important calcium-related cellular responses for destabilization, such as the recruitment of calcium-calmodulin dependent protein kinase II (CaMKII). CaMKII also appears to have an important role in facilitating memory destabilization. It has been shown that CaMKII functioning is critical for the destabilization of fear memory and object memory, and it has been proposed that CaMKII phosphorylates and activates proteasomes of the ubiquitin proteasome system (UPS) to degrade certain post-synaptic density proteins, such as Shank and GKAP. M_1-muscarinic receptors and D1-like receptors seems to play a neuromodulatory role in memory destabilization. Blocking M_1 receptor activation prevents destabilization of object memories and blocks object memory updating, apparently through inositol 1,4,5-triphosphate (IP_3)-mediated release of calcium stores from the endoplasmic reticulum (ER). D1-like receptor functioning also appears to be critical for the destabilization of fear memories, appetitive memories and object memories. There is evidence that D1-like receptor activation is required for memory destabilization, but the link between D1-like receptors and downstream destabilization mechanisms requires further investigation. B) A relatively remote or strong memory does not readily destabilize upon reactivation, possibly because of changes in the synapse that decrease the likelihood of engaging mechanisms of destabilization. Resistance to destabilization seems to be characterized by an increased ratio of GluN2A/GluN2B-containing receptors, and GluN2A-containing receptors are specialized for memory reconsolidation rather than destabilization. C) Introducing novelty during memory reactivation can override boundary conditions to memory destabilization. It is theorized that these boundary conditions can be overcome by targeted activation of muscarinic receptors for at least some types of memories. Specifically, activating M_1 receptors directly with drugs or indirectly via novelty presentation can promote destabilization of remote object memories, despite changes to glutamatergic receptors at the synapse. This may be accomplished by triggering the release of intracellular calcium from ER stores and consequently recruiting the UPS for synaptic protein degradation. Moreover, D1-like receptor activation is critical for memory destabilization, but recent findings suggest that activating these receptors pharmacologically does not promote destabilization of strong memories. The involvement of DA in the destabilization of strongly encoded memories requires further characterization. Other receptor types, including LVGCCs, have secondary cascades that potentially link to downstream CaMKII activity, so it is also worth exploring these receptors as potential upstream mechanisms for triggering memory destabilization to overcome boundary conditions. The potential contributions of other neuromodulatory transmitters to this process remain to be investigated.

treatments in mental disorders characterized by maladaptive or inflexible memories will require continued assessment in various contexts. Many such conditions (e.g., PTSD, phobias, age-related cognitive inflexibility) are linked to underlying learning and memory processes that have likely been influenced strongly by the various boundary conditions referred to widely in the reconsolidation literature. Moreover, the complexity of most human memories, as opposed to those produced in controlled laboratory settings, will likely necessitate careful consideration of the procedures used to produce targeted memory modification in the clinical environment. Thus, a greater understanding of the conditions and neurobiological underpinnings of this process is essential. Answers to these and related questions will bring us closer to understanding the complex and dynamic process of long-term memory storage and modification in the brain and ultimately enable us to harness these mechanisms for the treatment of numerous mental and emotional disorders driven by maladaptive and inflexible memories.

Declaration of interest

None.

Acknowledgements

This work was supported by a Discovery Grant from the Natural Sciences and Engineering Research Council (NSERC) of Canada (Grant #400176) to BDW. Figs. 1 and 3 were created with BioRender.com.

References

Agren, T., 2014. Human reconsolidation: a reactivation and update. Brain Res. Bull. 105, 70–82. https://doi.org/10.1016/j.brainresbull.2013.12.010.

Agren, T., Engman, J., Frick, A., Björkstrand, J., Larsson, E.M., Furmark, T., Fredrikson, M., 2012. Disruption of reconsolidation erases a fear memory trace in the human amygdala. Science 337 (6101), 1550–1552. https://doi.org/10.1126/science.1223006.

Agren, T., Furmark, T., Eriksson, E., Fredrikson, M., 2012. Human fear reconsolidation and allelic differences in serotonergic and dopaminergic genes. Transl. Psychiatry 2, e76. https://doi.org/10.1038/tp.2012.5.

Agren, T., Björkstrand, J., Fredrikson, M., 2017. Disruption of human fear reconsolidation using imaginal and in vivo extinction. Behav. Brain Res. 319, 9–15. https://doi.org/10.1016/j.bbr.2016.11.014.

Agustina López, M., Jimena Santos, M., Cortasa, S., Fernández, R.S., Carbó Tano, M., Pedreira, M.E., 2016. Different dimensions of the prediction error as a decisive factor for the triggering of the reconsolidation process. Neurobiol. Learn. Mem. 136, 210–219. https://doi.org/10.1016/j.nlm.2016.10.016.

Allison, S.L., Fagan, A.M., Morris, J.C., Head, D., 2016. Spatial navigation in preclinical Alzheimer's disease. J. Alzheimer's Dis. 52 (1), 77–90. https://doi.org/10.3233/JAD-150855.

Anokhin, K.V., Tiunova, A.A., Rose, S.P.R., 2002. Reminder effects - reconsolidation or retrieval deficit? Pharmacological dissection with protein synthesis inhibitors following reminder for a passive-avoidance task in young chicks. Eur. J. Neurosci. 15 (11), 1759–1765. https://doi.org/10.1046/j.1460-9568.2002.02023.x.

Antypa, D., Rodrigues Cabrita, D., Vuilleumier, P., Rimmele, U., 2019. Cortisol suppression after memory reactivation impairs later memory performance. Psychoneuroendocrinology 106, 226–232. https://doi.org/10.1016/j.psyneuen.2019.03.035.

Assini, F.L., Duzzioni, M., Takahashi, R.N., 2009. Object location memory in mice: pharmacological validation and further evidence of hippocampal CA1 participation. Behav. Brain Res. 204, 206–211. https://doi.org/10.1016/j.bbr.2009.06.005.

Asthana, M.K., Brunhuber, B., Mühlberger, A., Reif, A., Schneider, S., Herrmann, M.J., 2016. Preventing the return of fear using reconsolidation update mechanisms depends on the met-allele of the brain derived neurotrophic factor Val66met polymorphism. Int. J. Neuropsychopharmacol. 19 (6), 1–9. https://doi.org/10.1093/ijnp/pyv137.

Balderas, I., Rodriguez-Ortiz, C.J., Bermudez-Rattoni, F., 2013. Retrieval and reconsolidation of object recognition memory are independent processes in the perirhinal cortex. Neuroscience 253, 398–405. https://doi.org/10.1016/j.neuroscience.2013.09.001.

Baldi, E., Bucherelli, C., 2005. The inverted "u-shaped" dose-effect relationships in learning and memory: modulation of arousal and consolidation. Nonlinear Biol. Toxicol. Med. 3 (1), 9–21. https://doi.org/10.2201/nonlin.003.01.002.

Barak, S., Goltseker, K., 2021. Targeting the reconsolidation of licit drug memories to prevent relapse: focus on alcohol and nicotine. Int. J. Mol. Sci. 22 (8) https://doi.org/10.3390/ijms22084090.

Barker, G.R.I., Warburton, E.C., 2011. When is the hippocampus involved in recognition memory? J. Neurosci. 31 (29), 10721–10731. https://doi.org/10.1523/JNEUROSCI.6413-10.2011.

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 (1), 4660. https://doi.org/10.1038/s41467-018-07128-7.

Bernardi, R.E., Lattal, K.M., Berger, S.P., 2006. Postretrieval propranolol disrupts a cocaine conditioned place preference. NeuroReport 17 (13), 1443–1447. https://doi.org/10.1097/01.wnr.0000233098.20655.26.

Bernardi, R.E., Ryabinin, A.E., Berger, S.P., Lattal, K.M., 2009. Post-retrieval disruption of a cocaine conditioned place preference by systemic and intrabasolateral amygdala 2- and 1-adrenergic antagonists. Learn. Mem. 16 (12), 777–789. https://doi.org/10.1101/lm.1648509.

Berridge, C.W., Waterhouse, B.D., 2003. The locus coeruleus-noradrenergic system: modulation of behavioral state and state-dependent cognitive processes. Brain Res. Rev. 42 (1), 33–84. https://doi.org/10.1016/S0165-0173(03)00143-7.

Björkstrand, J., Agren, T., Frick, A., Engman, J., Larsson, E.M., Furmark, T., Fredrikson, M., 2015. Disruption of memory reconsolidation erases a fear memory trace in the human amygdala: An 18-month follow-up. PLoS One 10 (7), 1–8. https://doi.org/10.1371/journal.pone.0129393.

Björkstrand, J., Agren, T., Åhs, F., Frick, A., Larsson, E.M., Hjorth, O., Fredrikson, M., 2016. Disrupting reconsolidation attenuates long-term fear memory in the human amygdala and facilitates approach behavior. Curr. Biol. 26 (19), 2690–2695. https://doi.org/10.1016/j.cub.2016.08.022.

Björkstrand, J., Agren, T., Åhs, F., Frick, A., Larsson, E.M., Hjorth, O., Fredrikson, M., 2017. Think twice, it's all right: long lasting effects of disrupted reconsolidation on brain and behavior in human long-term fear. Behav. Brain Res. 324, 125–129. https://doi.org/10.1016/j.bbr.2017.02.016.

Boccia, M.M., Blake, M.G., Acosta, G.B., Baratti, C.M., 2006. Post-retrieval effects of icv infusions of hemicholinium in mice are dependent on the age of the original memory. Learn. Mem. 13 (3), 376–381. https://doi.org/10.1101/lm.150306.

Bos, M.G.N., Beckers, T., Kindt, M., 2014. Noradrenergic blockade of memory reconsolidation: a failure to reduce conditioned fear responding. Front. Behav. Neurosci. 8, 412. https://doi.org/10.3389/fnbeh.2014.00412.

Bos, M.G.N., Schuijer, J., Lodestijn, F., Beckers, T., Kindt, M., 2014. Stress enhances reconsolidation of declarative memory. Psychoneuroendocrinology 46, 102–113. https://doi.org/10.1016/j.psyneuen.2014.04.011.

Bouton, M.E., 2002. Context, ambiguity, and unlearning: sources of relapse after behavioral extinction. Biol. Psychiatry 52 (10), 976–986. https://doi.org/10.1016/S0006-3223(02)01546-9.

Bozon, B., Davis, S., Laroche, S., 2003. A requirement for the immediate early gene zif268 in reconsolidation of recognition memory after retrieval. Neuron 40 (4), 695–701. https://doi.org/10.1016/S0896-6273(03)00674-3.

Bredy, T.W., Barad, M., 2008. The histone deacetylase inhibitor valproic acid enhances acquisition, extinction, and reconsolidation of conditioned fear. Learn. Mem. 15 (1), 39–45. https://doi.org/10.1101/lm.801108.

Bridge, D.J., Paller, K.A., 2012. Neural correlates of reactivation and retrieval-induced distortion. J. Neurosci. 32 (35), 12144–12151. https://doi.org/10.1523/JNEUROSCI.1378-12.2012.

Brown, R., Kulik, J., 1977. Flashbulb memories. Cognition 5 (1), 73–99. https://doi.org/10.1016/0010-0277(77)90018-X.

Brown, T.E., Lee, B.R., Sorg, B.A., 2008. The NMDA antagonist MK-801 disrupts reconsolidation of a cocaine-associated memory for conditioned place preference but not for self-administration in rats. Learn. Mem. 15 (12), 857–865. https://doi.org/10.1101/lm.1152808.

Brunet, A., Saumier, D., Liu, A., Streiner, D.L., Tremblay, J., Pitman, R.K., 2018. Reduction of PTSD symptoms with pre-reactivation propranolol therapy: a randomized controlled trial. Am. J. Psychiatry 175 (5), 427–433. https://doi.org/10.1176/appi.ajp.2017.17050481.

Buzsáki, G., Moser, E.I., 2013. Memory, navigation and theta rhythm in the hippocampal-entorhinal system. Nat. Neurosci. 16 (2), 130–138. https://doi.org/10.1038/nn.3304.

Cahill, E.N., Milton, A.L., 2019. Neurochemical and molecular mechanisms underlying the retrieval-extinction effect. Psychopharmacology 236, 111–132. https://doi.org/10.1007/s00213-018-5121-3.

Cai, D., Pearce, K., Chen, S., Glanzman, D.L., 2012. Reconsolidation of long-term memory in aplysia. Curr. Biol. 22 (19), 1783–1788. https://doi.org/10.1016/j.cub.2012.07.038.

Chalkia, A., Weermeijer, J., Van Oudenhove, L., Beckers, T., 2019. Acute but not permanent effects of propranolol on fear memory expression in humans. Front. Hum. Neurosci. 13, 51. https://doi.org/10.3389/fnhum.2019.00051.

Chalkia, A., Schroyens, N., Leng, L., Vanhasbroeck, N., Zenses, A.K., Van Oudenhove, L., Beckers, T., 2020. No persistent attenuation of fear memories in humans: a registered replication of the reactivation-extinction effect. Cortex 129, 496–509. https://doi.org/10.1016/j.cortex.2020.04.017.

Chan, J.C.K., LaPaglia, J.A., 2013. Impairing existing declarative memory in humans by disrupting reconsolidation. Proc. Natl. Acad. Sci. USA 110 (23), 9309–9313. https://doi.org/10.1073/pnas.1218472110.

Chen, W., Li, J., Zhang, X., Dong, Y., Shi, P., Luo, P., Zheng, X., 2021. Retrieval-extinction as a reconsolidation-based treatment for emotional disorders:Evidence from an extinction retention test shortly after intervention. Behav. Res. Ther. 139 (February), 103831 https://doi.org/10.1016/j.brat.2021.103831.

Choi, J.-H., Kim, J.-E., Kaang, B.-K., 2010. Protein synthesis and degradation are required for the incorporation of modified information into the pre-existing object-location memory. Mol. Brain 3. https://doi.org/10.1186/1756-6606-3-1.

Clem, R.L., Schiller, D., 2016. New learning and unlearning: strangers or accomplices in threat memory attenuation? Trends Neurosci. 39 (5), 340–351. https://doi.org/10.1016/j.tins.2016.03.003.

Coccoz, V., Maldonado, H., Delorenzi, A., 2011. The enhancement of reconsolidation with a naturalistic mild stressor improves the expression of a declarative memory in humans. Neuroscience 185, 61–72. https://doi.org/10.1016/j.neuroscience.2011.04.023.

Cofresí, R.U., Lewis, S.M., Chaudhri, N., Lee, H.J., Monfils, M.H., Gonzales, R.A., 2017. Postretrieval extinction attenuates alcohol cue reactivity in rats. Alcohol. Clin. Exp. Res. 41 (3), 608–617. https://doi.org/10.1111/acer.13323.

Coughlan, G., Laczó, J., Hort, J., Minihane, A.-M., Hornberger, M., 2018. Spatial navigation deficits - overlooked cognitive marker for preclinical Alzheimer disease? Nat. Rev. Neurol. 14, 496–506. https://doi.org/10.1038/s41582-018-0031-x.

Das, R.K., Lawn, W., Kamboj, S.K., 2015. Rewriting the valuation and salience of alcohol-related stimuli via memory reconsolidation. Transl. Psychiatry 5 (9), e645. https://doi.org/10.1038/tp.2015.132.

Das, R.K., Hindocha, C., Freeman, T.P., Lazzarino, A.I., Curran, H.V., Kamboj, S.K., 2015. Assessing the translational feasibility of pharmacological drug memory reconsolidation blockade with memantine in quitting smokers. Psychopharmacology 232 (18), 3363–3374. https://doi.org/10.1007/s00213-015-3990-2.

Das, R.K., Gale, G., Hennessy, V., Kamboj, S.K., 2018a. A prediction error-driven retrieval procedure for destabilizing and rewriting maladaptive reward memories in hazardous drinkers. J. Vis. Exp. (131), e56097 https://doi.org/10.3791/56097.

Das, R.K., Walsh, K., Hannaford, J., Lazzarino, A.I., Kamboj, S.K., 2018b. Nitrous oxide may interfere with the reconsolidation of drinking memories in hazardous drinkers in a prediction-error-dependent manner. Eur. Neuropsychopharmacol. 28 (7), 828–840. https://doi.org/10.1016/j.euroneuro.2018.05.001.

Davis, R.E., Hirtzel, M.S., 1970. Environmental control of ECS-produced retrograde amnesia in goldfish. Physiol. Behav. 5 (10), 1089–1092. https://doi.org/10.1016/0031-9384(70)90193-9.

Davis, R.E., Klinger, P.D., 1969. Environmental control of amnesic effects of various agents in goldfish. Physiol. Behav. 4 (2), 269–271. https://doi.org/10.1016/0031-9384(69)90092-4.

Dawson, R.G., McGaugh, J.L., 1969. Electroconvulsive shock effects on a reactivated memory trace: Further examination. Science 166 (3904), 525–527. https://doi.org/10.1126/science.166.3904.525.

De Beukelaar, T.T., Woolley, D.G., Wenderoth, N., 2014. Gone for 60 seconds: reactivation length determines motor memory degradation during reconsolidation. Cortex 59, 138–145. https://doi.org/10.1016/j.cortex.2014.07.008.

De Beukelaar, T.T., Woolley, D.G., Alaerts, K., Swinnen, S.P., Wenderoth, N., 2016. Reconsolidation of motor memories is a time-dependent process. Front. Hum. Neurosci. 10, 408. https://doi.org/10.3389/fnhum.2016.00408.

Debiec, J., LeDoux, J.E., 2004. Disruption of reconsolidation but not consolidation of auditory fear conditioning by noradrenergic blockade in the amygdala. Neuroscience 129 (2), 267–272. https://doi.org/10.1016/j.neuroscience.2004.08.018.

Debiec, J., LeDoux, J.E., Nader, K., 2002. Cellular and systems reconsolidation in the hippocampus. Neuron 36 (3), 527–538. https://doi.org/10.1016/S0896-6273(02)01001-2.

Deng, J., Shi, L., Yuan, K., Yao, P., Chen, S., Que, J., Lu, L., 2020. Propranolol-induced inhibition of unconditioned stimulus-reactivated fear memory prevents the return of fear in humans. Transl. Psychiatry 10 (1). https://doi.org/10.1038/s41398-020-01023-w.

DeVietti, T.L., Holliday, J.H., 1972. Retrograde amnesia produced by electroconvulsive shock after reactivation of a consolidated memory trace: a replication. Science 29 (3), 137–138. https://doi.org/10.1126/science.160.3827.554.

Di Ciano, P., Everitt, B.J., 2004. Conditioned reinforcing properties of stimuli paired with self-administered cocaine, heroin or sucrose: implications for the persistence of addictive behaviour. Neuropharmacology 47, 202–213. https://doi.org/10.1016/j.neuropharm.2004.06.005.

Díaz-Mataix, L., Chacon Ruiz Martinez, R., Schafe, G.E., Ledoux, J.E., Doyère, V., Author, C.B., 2013. Detection of a temporal error triggers reconsolidation of amygdala-dependent memories. Curr. Biol. 23 (6), 467–472. https://doi.org/10.1016/j.cub.2013.01.053.

Djakovic, S.N., Schwarz, L.A., Barylko, B., DeMartino, G.N., Patrick, G.N., 2009. Regulation of the proteasome by neuronal activity and calcium/calmodulin-dependent protein kinase II. J. Biol. Chem. 284 (39), 26655–26665. https://doi.org/10.1074/jbc.M109.021956.

Dongaonkar, B., Hupbach, A., Gomez, R., Nadel, L., 2013. Effects of psychosocial stress on episodic memory updating. Psychopharmacology 226 (4), 769–779. https://doi.org/10.1007/s00213-013-2998-8.

Duvarci, S., Nader, K., 2004. Characterization of fear memory reconsolidation. J. Neurosci. 24 (42), 9269–9275. https://doi.org/10.1523/JNEUROSCI.2971-04.2004.

Eichenbaum, H., Dudchenko, P., Wood, E., Shapiro, M., Tanila, H., 1999. The hippocampus, memory, and place cells: is it spatial memory or a memory space? Neuron 23, 209–226. ⟨http://cogs200.pbworks.com/f/Eichenbaum99Hippocampus.pdf⟩.

Einarsson, E.Ö., Nader, K., 2012. Involvement of the anterior cingulate cortex in formation, consolidation, and reconsolidation of recent and remote contextual fear memory. Learn. Mem. 19 (10), 449–452. https://doi.org/10.1101/lm.027227.112.

Eisenberg, M., Dudai, Y., 2004. Reconsolidation of fresh, remote, and extinguished fear memory in medaka: Old fears don't die. Eur. J. Neurosci. 20 (12), 3397–3403. https://doi.org/10.1111/j.1460-9568.2004.03818.x.

Eisenberg, M., Kobilo, T., Berman, D.E., Dudai, Y., 2003. Stability of retrieved memory: inverse correlation with trace dominance. Science 301 (5636), 1102–1104. https://doi.org/10.1126/science.1086881.

Elsey, 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 (8), 797–848. https://doi.org/10.1037/bul0000152.

Elsey, J.W.B., Filmer, A.I., Galvin, H.R., Kurath, J.D., Vossoughi, L., Thomander, L.S., Kindt, M., 2020. Reconsolidation-based treatment for fear of public speaking: a systematic pilot study using propranolol. Transl. Psychiatry 10 (1), 179. https://doi.org/10.1038/s41398-020-0857-z.

Ennaceur, A., Delacour, J., 1988. A new one-trial test for neurobiological studies of memory in rats. 1: behavioral data. Behav. Brain Res. 31 (1), 47–59. https://doi.org/10.1016/S0166-4328(05)80315-8.

Escosteguy-Neto, J.C., Varela, P., Correa-Neto, N.F., Coelho, L.S., Onaivi, E.S., Santos-Junior, J.G., 2016. Reconsolidation and update of morphine-associated contextual memory in mice. Neurobiol. Learn. Mem. 130, 194–201. https://doi.org/10.1016/j.nlm.2016.02.015.

Exton-Mcguinness, M.T.J., Milton, A.L., 2018. Reconsolidation blockade for the treatment of addiction: challenges, new targets, and opportunities. Learn. Mem. 25 (9), 492–500. https://doi.org/10.1101/lm.046771.117.

Exton-McGuinness, M.T.J., Patton, R.C., Sacco, L.B., Lee, J.L.C., 2014. Reconsolidation of a well-learned instrumental memory. Learn. Mem. 21 (9), 468–477. https://doi.org/10.1101/lm.035543.114.

Exton-McGuinness, M.T.J., Lee, J.L.C., Reichelt, A.C., 2015. Updating memories -the role of prediction errors in memory reconsolidation. Behav. Brain Res. 278, 375–384. https://doi.org/10.1016/j.bbr.2014.10.011.

Exton-McGuinness, M.T.J., Drame, M.L., Flavell, C.R., Lee, J.L.C., 2019. On the resistance to relapse to cocaine-seeking following impairment of instrumental cocaine memory reconsolidation. Front. Behav. Neurosci. 13, 242. https://doi.org/10.3389/fnbeh.2019.00242.

Felder, C.C., 1995. Muscarinic acetylcholine receptors: signal transduction through multiple effectors. FASEB J. 9 (8), 619–625. https://doi.org/10.1096/fasebj.9.8.7768353.

Feng, P., Zheng, Y., Feng, T., 2016. Resting-state functional connectivity between amygdala and the ventromedial prefrontal cortex following fear reminder predicts fear extinction. Soc. Cogn. Affect. Neurosci. 11 (6), 991–1001. https://doi.org/10.1093/scan/nsw031.

Fernández, 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. https://doi.org/10.1016/j.neubiorev.2016.06.004.

Ferrara, N.C., Jarome, T.J., Cullen, P.K., Orsi, S.A., Kwapis, J.L., Trask, S., Helmstetter, F. J., 2019. GluR2 endocytosis-dependent protein degradation in the amygdala mediates memory updating. Sci. Rep. 9 (1), 5180. https://doi.org/10.1038/s41598-019-41526-1.

Ferrer Monti, R.I., Giachero, M., Alfei, J.M., Bueno, A.M., Cuadra, G., Molina, V.A., 2016. An appetitive experience after fear memory destabilization attenuates fear retention: involvement GluN2B-NMDA receptors in the Basolateral Amygdala Complex. Learn. Mem. 23 (9), 465–478. https://doi.org/10.1101/lm.042564.116.

Finnie, P.S.B., Nader, K., 2012. The role of metaplasticity mechanisms in regulating memory destabilization and reconsolidation. Neurosci. Biobehav. Rev. 36, 1667–1707. https://doi.org/10.1016/j.neubiorev.2012.03.008.

Finnie, P.S.B., Nader, K., 2020. Amyloid beta secreted during consolidation prevents memory malleability. Curr. Biol. 30 (10), 1934–1940. https://doi.org/10.1016/j.cub.2020.02.083.

Flavell, C.R., Lee, J.L.C., 2019. Dopaminergic D1 receptor signalling is necessary, but not sufficient for cued fear memory destabilisation. Psychopharmacology 236 (12), 3667–3676. https://doi.org/10.1007/s00213-019-05338-5.

Flavell, C.R., Lambert, E.A., Winters, B.D., Bredy, T.W., 2013. Mechanisms governing the reactivation-dependent destabilization of memories and their role in extinction. Front. Behav. Neurosci. 7, 214. https://doi.org/10.3389/fnbeh.2013.00214.

Forcato, C., Burgos, V.L., Argibay, P.F., Molina, V.A., Pedreira, M.E., Maldonado, H., 2007. Reconsolidation of declarative memory in humans. Learn. Mem. 14 (4), 295–303. https://doi.org/10.1101/lm.486107.

Forcato, C., Argibay, P.F., Pedreira, M.E., Maldonado, H., 2009. Human reconsolidation does not always occur when a memory is retrieved: the relevance of the reminder structure. Neurobiol. Learn. Mem. 91, 50–57. https://doi.org/10.1016/j.nlm.2008.09.011.

Forcato, C., Rodríguez, M.L.C., Pedreira, M.E., Maldonado, H., 2010. Reconsolidation in humans opens up declarative memory to the entrance of new information. Neurobiol. Learn. Mem. 93, 77–84. https://doi.org/10.1016/j.nlm.2009.08.006.

Forcato, C., Rodríguez, M.L.C., Pedreira, M.E., 2011. Repeated labilization-reconsolidation processes strengthen declarative memory in humans. PLoS One 6 (8), e23305. https://doi.org/10.1371/journal.pone.0023305.

Forcato, C., Fernández, 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 (4), e61688. https://doi.org/10.1371/journal.pone.0061688.

Forcato, C., Bavassi, L., De Pino, G., Fernández, R.S., Villarreal, M.F., Pedreira, M.E., 2016. Differential left hippocampal activation during retrieval with different types of reminders: an fMRI study of the reconsolidation process. PLoS One 11 (3), e0151381. https://doi.org/10.1371/journal.pone.0151381.

Frankland, P.W., Ding, H.-K., Takahashi, E., Suzuki, A., Kida, S., Silva, A.J., 2006. Stability of recent and remote contextual fear memory. Learn. Mem. 13 (4), 451–457. https://doi.org/10.1101/lm.183406.

Fricchione, J., Greenberg, M.S., Spring, J.D., Wood, N.E., Mueller-Pfeiffer, C., Milad, M. R., Orr, S.P., 2016. Delayed extinction fails to reduce skin conductance reactivity to fear-conditioned stimuli. Psychophysiology 53 (9), 1343–1351. https://doi.org/10.1111/psyp.12687.

Gale, G., Walsh, K., Hennessy, V.E., Stemerding, L.E., Ni, K.S., Thomas, E., Das, R.K., 2020. Long-term behavioural rewriting of maladaptive drinking memories via reconsolidation-update mechanisms. Psychol. Med. 1–11. https://doi.org/10.1017/S0033291720001531.

Garry, M., Manning, C.G., Loftus, E.F., Sherman, S.J., 1996. Imagination inflation: Imagining a childhood event inflates confidence that it occurred. Psychon. Bull. Rev. 3 (2), 208–214. https://doi.org/10.3758/BF03212420.

Germeroth, L.J., Carpenter, M.J., Baker, N.L., Froeliger, B., LaRowe, S.D., Saladin, M.E., 2017. Effect of a brief memory updating intervention on smoking behavior. JAMA Psychiatry 74 (3), 214–223. https://doi.org/10.1001/jamapsychiatry.2016.3148.

Gershman, S.J., Monfils, M.H., Norman, K.A., Niv, Y., 2017. The computational nature of memory modification. ELife 6, 1–41. https://doi.org/10.7554/eLife.23763.

Gisquet-Verrier, P., Lynch Iii, 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 (33), 11623–11633. https://doi.org/10.1523/JNEUROSCI.1386-15.2015.

Golkar, A., Bellander, M., Olsson, A., Öhman, A., 2012. Are fear memories erasable? -reconsolidation of learned fear with fear relevant and fearirrelevant stimuli. Front. Behav. Neurosci. 6, 80. https://doi.org/10.3389/fnbeh.2012.00080.

Golkar, A., Tjaden, C., Kindt, M., 2017. Vicarious extinction learning during reconsolidation neutralizes fear memory. Behav. Res. Ther. 92, 87–93. https://doi.org/10.1016/j.brat.2017.02.004.

Gordon, W.C., 1977a. Similarities of recently acquired and reactivated memories in interference. Am. J. Psychol. 90 (2), 231–242. https://doi.org/10.2307/1422045.

Gordon, W.C., 1977b. Susceptibility of a reactivated memory to the effects of strychnine: a time-dependent phenomenon. Physiol. Behav. 18 (1), 95–99. https://doi.org/10.1016/0031-9384(77)90099-3.

Gordon, W.C., Spear, N.E., 1973. Effect of reactivation of a previously acquired memory on the interaction between memories in the rat. J. Exp. Psychol. 99 (3), 349–355. https://doi.org/10.1037/h0035301.

Gotthard, G.H., Gura, H., 2018. Visuospatial word search task only effective at disrupting declarative memory when prediction error is present during retrieval. Neurobiol. Learn. Mem. 156, 80–85. https://doi.org/10.1016/j.nlm.2018.11.003.

Gräff, J., Joseph, N.F., Horn, M.E., Samiei, A., Meng, J., Seo, J., Tsai, L.H., 2014. Epigenetic priming of memory updating during reconsolidation to attenuate remote fear memories. Cell 156, 261–276. https://doi.org/10.1016/j.cell.2013.12.020.

Grégoire, L., Greening, S.G., 2019. Opening the reconsolidation window using the mind's eye: extinction training during reconsolidation disrupts fear memory expression following mental imagery reactivation. Cognition 183, 277–281. https://doi.org/10.1016/j.cognition.2018.12.001.

Hardwicke, T.E., Taqi, M., Shanks, D.R., 2016. Postretrieval new learning does not reliably induce human memory updating via reconsolidation. Proc. Natl. Acad. Sci. USA 113 (19), 5206–5211. https://doi.org/10.1073/pnas.1601440113.

Hasselmo, M.E., McGaughy, J., 2004. High acetylcholine levels set circuit dynamics for attention and encoding and low acetylcholine levels set dynamics for consolidation. Prog. Brain Res. 145, 207–231. https://doi.org/10.1016/S0079-6123(03)45015-2.
Haubrich, J., Crestani, A.P., Cassini, L.F., Santana, F., Sierra, R.O., De O Alvares, L., Quillfeldt, 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. https://doi.org/10.1038/npp.2014.174.
Herszage, J., Censor, N., 2017. Memory reactivation enables long-term prevention of interference. Curr. Biol. 27 (10), 1529–1534.e2. https://doi.org/10.1016/j.cub.2017.04.025.
Herszage, J., Sharon, H., Censor, N., 2021. Reactivation-induced motor skill learning. Proc. Natl. Acad. Sci. U.S.A. 118 (23), 1–6. https://doi.org/10.1073/PNAS.2102242118.
Holehonnur, R., Phensy, A.J., Kim, L.J., Milivojevic, M., Vuong, D., Daison, D.K., Ploski, J.E., 2016. Increasing the GluN2A/GluN2B ratio in neurons of the mouse basal and lateral amygdala inhibits the modification of an existing fear memory trace. J. Neurosci. 36 (36), 9490–9504. https://doi.org/10.1523/JNEUROSCI.1743-16.2016.
Hong, I., Kim, J., Kim, J., Lee, S., Ko, H., Nader, K., Choi, S., 2013. AMPA receptor exchange underlies transient memory destabilization on retrieval. Proc. Natl. Acad. Sci. U.S.A. 110 (20), 8218–8223. https://doi.org/10.1073/pnas.1221113110.
Hu, J., Wang, W., Homan, P., Wang, P., Zheng, X., Schiller, D., 2018. Reminder duration determines threat memory modification in humans. Sci. Rep. 8 (1), 1–10. https://doi.org/10.1038/s41598-018-27252-0.
Huang, F., Zou, G., Li, C., Meng, H., Liu, X., Yang, Z., 2020. A novelty-retrieval-extinction paradigm leads to persistent attenuation of remote fear memories. Sci. Rep. 10 (1), 3319. https://doi.org/10.1038/s41598-020-60176-2.
Huff, A.E., McGraw, S.D., Winters, B.D., 2021. Muscarinic (M1) cholinergic receptor activation within the dorsal hippocampus promotes destabilization of strongly encoded object location memories. Hippocampus November, 1–12. https://doi.org/10.1002/hipo.23396.
Hupbach, A., 2015. Retrieval practice does not safeguard memories from interference-based forgetting. Learn. Motiv. 49, 23–30. https://doi.org/10.1016/j.lmot.2015.01.004.
Hupbach, A., Dorskind, J.M., 2014. Stress selectively affects the reactivated components of a declarative memory. Behav. Neurosci. 128 (5), 614–620. https://doi.org/10.1037/bne0000006.
Hupbach, A., Gomez, R., Hardt, O., Nadel, L., 2007. Reconsolidation of episodic memories: a subtle reminder triggers integration of new information. Learn. Mem. 14 (1–2), 47–53. https://doi.org/10.1101/lm.365707.
Hupbach, A., Hardt, O., Gomez, R., Nadel, L., 2008. The dynamics of memory: context-dependent updating. Learn. Mem. 15 (8), 574–579. https://doi.org/10.1101/lm.1022308.
Hupbach, A., Gomez, R., Nadel, L., 2011. Episodic memory updating: the role of context familiarity. Psychon. Bull. Rev. 18 (4), 787–797. https://doi.org/10.3758/s13423-011-0117-6.
Hupbach, A., Gomez, R., Nadel, L., 2013. Episodic memory reconsolidation: an update. In: Alberini, C.M. (Ed.), Memory Reconsolidation. Elsevier Academic Press, pp. 233–247. https://doi.org/10.1016/B978-0-12-386892-3.00011-1.
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 (5), 1635–1643. https://doi.org/10.1523/JNEUROSCI.4736-10.2011.
James, E.L., Bonsall, M.B., Hoppitt, L., Tunbridge, E.M., Geddes, J.R., Milton, A.L., Holmes, E.A., 2015. Computer game play reduces intrusive memories of experimental trauma via reconsolidation-update mechanisms. Psychol. Sci. 26 (8), 1201–1215. https://doi.org/10.1177/0956797615583071.
Jardine, K.H., Wideman, C.E., MacGregor, C., Sgarbossa, C., Orr, D., Mitchnick, K.A., Winters, B.D., 2020. Activation of cortical M1 muscarinic receptors and related intracellular signaling is necessary for reactivation-induced object memory updating. Sci. Rep. 10 (1), 9209. https://doi.org/10.1038/s41598-020-65836-x.
Jarome, T.J., Helmstetter, F.J., 2014. Protein degradation and protein synthesis in long-term memory formation. Front. Mol. Neurosci. 7, 61. https://doi.org/10.3389/fnmol.2014.00061.
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 (9), e24349. https://doi.org/10.1371/journal.pone.0024349.
Jarome, T.J., Ferrara, N.C., Kwapis, J.L., Helmstetter, F.J., 2015. Contextual information drives the reconsolidation-dependent updating of retrieved fear memories. Neuropsychopharmacology 40, 3044–3052. https://doi.org/10.1038/npp.2015.161.
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. https://doi.org/10.1016/j.nlm.2016.01.001.
Johnson, D.C., Casey, B.J., 2015. Extinction during memory reconsolidation blocks recovery of fear in adolescents. Sci. Rep. 5, 8863. https://doi.org/10.1038/srep08863.
Jones, B., Bukoski, E., Nadel, L., Fellous, J.-M., 2012. Remaking memories: reconsolidation updates positively motivated spatial memory in rats. Learn. Mem. 19, 91–98. https://doi.org/10.1101/lm.023408.111.
Judge, M.E., Quartermain, D., 1982. Characteristics of retrograde amnesia following reactivation of memory in mice. Physiol. Behav. 28 (4), 585–590. https://doi.org/10.1016/0031-9384(82)90034-8.
Karpicke, J.D., Roediger, H.L., 2008. The critical importance of retrieval for learning. Science 319 (5865), 966–968. https://doi.org/10.1126/science.1152408.
Kelly, Á., Laroche, S., Davis, S., 2003. Activation of mitogen-activated protein kinase/extracellular signal-regulated kinase in hippocampal circuitry is required for consolidation and reconsolidation of recognition memory. J. Neurosci. 23 (12), 5354–5360. https://doi.org/10.1523/JNEUROSCI.23-12-05354.2003.
Khalaf, O., Gräff, J., 2019. Reactivation of recall-induced neurons in the infralimbic cortex and the basolateral amygdala after remote fear memory attenuation. Front. Mol. Neurosci. 12 (April) https://doi.org/10.3389/fnmol.2019.00070.
Khalaf, O., Resch, S., Dixsaut, L., Gorden, V., Glauser, L., Gräff, J., 2018. Reactivation of recall-induced neurons contributes to remote fear memory attenuation. Science 360, 1239–1242. https://doi.org/10.1126/science.aas9875.
Kida, S., Josselyn, S.A., De Ortiz, S.P., Kogan, J.H., Chevere, I., Masushige, S., Silva, A.J., 2002. CREB required for the stability of new and reactivated fear memories. Nat. Neurosci. 5 (4), 348–355. https://doi.org/10.1038/nn819.
Kim, J., Kwon, J.-T., Kim, H.-S., Josselyn, S.A., Han, J.-H., 2013. Memory recall and modifications by activating neurons with elevated CREB. Nat. Neurosci. 17 (1), 65–72. https://doi.org/10.1038/nn.3592.
Kim, R., Moki, R., Kida, S., 2011. Molecular mechanisms for the destabilization and restabilization of reactivated spatial memory in the Morris water maze. Mol. Brain 4, 9. https://doi.org/10.1186/1756-6606-4-9.
Kindt, M., 2018. The surprising subtleties of changing fear memory: a challenge for translational science. Philos. Trans. R. Soc. B Biol. Sci. 373 (1742), 20170033 https://doi.org/10.1098/rstb.2017.0033.
Kindt, M., Soeter, M., 2013. Reconsolidation in a human fear conditioning study: a test of extinction as updating mechanism. Biol. Psychol. 92 (1), 43–50. https://doi.org/10.1016/j.biopsycho.2011.09.016.
Kindt, M., Soeter, M., 2018. Pharmacologically induced amnesia for learned fear is time and sleep dependent. Nat. Commun. 9 (1), 1316. https://doi.org/10.1038/s41467-018-03659-1.
Kindt, M., van Emmerik, A., 2016. New avenues for treating emotional memory disorders: towards a reconsolidation intervention for posttraumatic stress disorder. Ther. Adv. Psychopharmacol. 6 (4), 283–295. https://doi.org/10.1177/2045125316644541.
Kindt, M., Soeter, M., Vervliet, B., 2009. Beyond extinction: erasing human fear responses and preventing the return of fear. Nat. Neurosci. 12 (3), 256–258. https://doi.org/10.1038/nn.2271.
Kitamura, H., Johnston, P., Johnson, L., Strodl, E., 2020. Boundary conditions of post-retrieval extinction: a direct comparison of low and high partial reinforcement. Neurobiol. Learn. Mem. 174 (July), 107285 https://doi.org/10.1016/j.nlm.2020.107285.
Klingmüller, A., Caplan, J.B., Sommer, T., 2017. Intrusions in episodic memory: reconsolidation or interference? Learn. Mem. 24 (5), 216–224. https://doi.org/10.1101/lm.045047.117.
Krawczyk, M.C., Fernández, R.S., Pedreira, M.E., Boccia, M.M., 2017. Toward a better understanding on the role of prediction error on memory processes: from bench to clinic. Neurobiol. Learn. Mem. 142, 13–20. https://doi.org/10.1016/j.nlm.2016.12.011.
Kredlow, M.A., Unger, L.D., Otto, M.W., 2016. Harnessing reconsolidation to weaken fear and appetitive memories: a meta-analysis of post-retrieval extinction effects. Psychol. Bull. 142 (3), 314–336. https://doi.org/10.1037/bul0000034.
Kroes, M.C.W., Strange, B.A., Dolan, R.J., 2010. B-adrenergic blockade during memory retrieval in humans evokes a sustained reduction of declarative emotional memory enhancement. J. Neurosci. 30 (11), 3959–3963. https://doi.org/10.1523/JNEUROSCI.5469-09.2010.
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. https://doi.org/10.1016/j.nlm.2013.09.007.
Kwapis, J.L., Jarome, T.J., Ferrara, N.C., Helmstetter, F.J., 2017. Updating procedures can reorganize the neural circuit supporting a fear memory. Neuropsychopharmacology 42 (10), 1688–1697. https://doi.org/10.1038/npp.2017.23.
Kwapis, J.L., Alaghband, Y., Keiser, A.A., Dong, T.N., Michael, C.M., Rhee, D., Wood, M.A., 2019. Aging mice show impaired memory updating in the novel OUL updating paradigm. Neuropsychopharmacology 45, 337–346. https://doi.org/10.1038/s41386-019-0438-0.
Lancaster, C.L., Monfils, M.-H., Telch, M.J., 2020. Augmenting exposure therapy with pre-extinction fear memory reactivation and deepened extinction: a randomized controlled trial. Behav. Res. Ther. 135, 103730 https://doi.org/10.1016/j.brat.2020.103730.
Lee, J.L.C., 2008. Memory reconsolidation mediates the strengthening of memories by additional learning. Nat. Neurosci. 11 (11), 1264–1266. https://doi.org/10.1038/nn.2205.
Lee, J.L.C., 2009. Reconsolidation: maintaining memory relevance. Trends Neurosci. 32 (8), 413–420. https://doi.org/10.1016/j.tins.2009.05.002.
Lee, J.L.C., 2010. Memory reconsolidation mediates the updating of hippocampal memory content. Front. Behav. Neurosci. 4, 168. https://doi.org/10.3389/fnbeh.2010.00168.
Lee, J.L.C., Everitt, B.J., 2008. Appetitive memory reconsolidation depends upon NMDA receptor-mediated neurotransmission. Neurobiol. Learn. Mem. 90, 147–154. https://doi.org/10.1016/j.nlm.2008.02.004.
Lee, J.L.C., Everitt, B.J., Thomas, K.L., 2004. Independent cellular processes for hippocampal memory consolidation and reconsolidation. Science 304 (5672), 839–843. https://doi.org/10.1126/science.1095760.
Lee, J.L.C., Di Ciano, P., Thomas, K.L., Everitt, B.J., 2005. Disrupting reconsolidation of drug memories reduces cocaine-seeking behavior. Neuron 47, 795–801. https://doi.org/10.1016/j.neuron.2005.08.007.

Lee, J.L.C., Milton, A.L., Everitt, B.J., 2006a. Cue-induced cocaine seeking and relapse are reduced by disruption of drug memory reconsolidation. J. Neurosci. 26 (22), 5881–5887. https://doi.org/10.1523/JNEUROSCI.0323-06.2006.

Lee, J.L.C., Milton, A.L., Everitt, B.J., 2006b. Reconsolidation and extinction of conditioned fear: inhibition and potentiation. J. Neurosci. 26 (39), 10051–10056. https://doi.org/10.1523/JNEUROSCI.2466-06.2006.

Lee, J.L.C., Nader, K., Schiller, D., 2017. An update on memory reconsolidation updating. Trends Cogn. Sci. 21 (7), 531–545. https://doi.org/10.1016/j.tics.2017.04.006.

Lee, S.-H., Choi, J.-H., Le, N., Lee, H.-R., Kim, J.-I., Yu, N.-K., Kaang, B.-K., 2008. Synaptic protein degradation underlies destabilization of retrieved fear memory. Science 319, 1253–1256. https://doi.org/10.1126/science.1153019.

Lee, S.-H., Kwak, C., Shim, J., Kim, J.-E., Choi, S.-L., Kim, H.F., Kaang, B.-K., 2012. A cellular model of memory reconsolidation involves reactivation-induced destabilization and restabilization at the sensorimotor synapse in Aplysia. Proc. Natl. Acad. Sci. U.S.A 109 (35), 14200–14205. https://doi.org/10.1073/pnas.1211997109.

Lester, A.W., Moffat, S.D., Wiener, J.M., Barnes, C.A., Wolbers, T., 2017. The aging navigational system. Neuron 95 (5), 1019–1035. https://doi.org/10.1016/j.neuron.2017.06.037.

Lewis, D.J., 1979. Psychobiology of active and inactive memory. Psychol. Bull. 86 (5), 1054–1083. https://doi.org/10.1037/0033-2909.86.5.1054.

Lewis, P.A., Bendor, D., 2019. How targeted memory reactivation promotes the selective strengthening of memories in sleep. Curr. Biol. 29 (18), R906–R912. https://doi.org/10.1016/j.cub.2019.08.019.

Li, J., Chen, W., Caoyang, J., Wu, W., Jie, J., Xu, L., Zheng, X., 2017. Moderate partially reduplicated conditioned stimuli as retrieval cue can increase effect on preventing relapse of fear to compound stimuli. Front. Hum. Neurosci. 11 (November) https://doi.org/10.3389/fnhum.2017.00575.

Li, J., Chen, W., Caoyang, J., Hu, Y., Yang, Y., Xu, L., Zheng, X., 2019. Role of prediction error in destabilizing fear memories in retrieval extinction and its neural mechanisms. Cortex 121, 292–307. https://doi.org/10.1016/j.cortex.2019.09.003.

Li, J., Wei, C., Hu, Y., Caoyang, J., Zheng, X., 2021. Effects of prediction error and acute stress on retrieval-extinction of fear memories of different strengths. Acta Psychol. Sin. 53 (6), 587–602. https://doi.org/10.3724/sp.j.1041.2021.00587.

Lim, C.-S., Kim, J.-I., Kwak, C., Lee, J., Jang, E.H., Oh, J., Kaang, B.-K., 2018. β-Adrenergic signaling is required for the induction of a labile state during memory reconsolidation. Brain Res. Bull. 141, 50–57. https://doi.org/10.1016/j.brainresbull.2018.04.011.

Lin, X., Deng, J., Yuan, K., Wang, Q., Liu, L., Bao, Y., Lu, L., 2021. Neural substrates of propranolol-induced impairments in the reconsolidation of nicotine-associated memories in smokers. Transl. Psychiatry 11 (1). https://doi.org/10.1038/s41398-021-01566-6.

Litvin, O.O., Anokhin, K.V., 2000. Mechanisms of memory reorganization during retrieval of acquired behavioral experience in chicks: the effects of protein synthesis inhibition in the brain. Neurosci. Behav. Physiol. 30 (6), 671–678. https://doi.org/10.1023/A:1026698700139.

Liu, J.-F., Zhao, L., Xue, Y.-X., Shi, J., Suo, L., Luo, Y.-X., Lu, L., 2014. An unconditioned stimulus retrieval extinction procedure to prevent the return of fear memory. Biol. Psychiatry 76 (11), 895–901. https://doi.org/10.1016/j.biopsych.2014.03.027.

Loftus, E.F., Pickrell, J.E., 1995. The formation of false memories. Psychiatr. Ann. 25 (12), 720–725. https://doi.org/10.3928/0048-5713-19951201-07.

Lonergan, M., Olivera-Figueroa, L., Pitman, R.K., Brunet, A., 2013. Propranolol's effects on the consolidation and reconsolidation of long-term emotional memory in healthy participants: a meta-analysis. J. Psychiatry Neurosci. 38 (4), 222–231. https://doi.org/10.1503/jpn.120111.

Lukowiak, K., Fras, M., Smyth, K., Wong, C., Hittel, K., 2007. Reconsolidation and memory infidelity in Lymnaea. Neurobiol. Learn. Mem. 87 (4), 547–560. https://doi.org/10.1016/j.nlm.2006.12.002.

Luo, Y.-X., Xue, Y.-X., Liu, J.-F., Shi, H.-S., Jian, M., Han, Y., Lu, L., 2015. A novel UCS memory retrieval-extinction procedure to inhibit relapse to drug seeking. Nat. Commun. 6 (1), 7675. https://doi.org/10.1038/ncomms8675.

Luyten, L., Beckers, T., 2017. A preregistered, direct replication attempt of the retrieval-extinction effect in cued fear conditioning in rats. Neurobiol. Learn. Mem. 144, 208–215. https://doi.org/10.1016/j.nlm.2017.07.014.

Luyten, L., Schnell, A.E., Schroyens, N., Beckers, T., 2021. Lack of drug-induced post-retrieval amnesia for auditory fear memories in rats. BMC Biol. 19 (1), 17. https://doi.org/10.1186/s12915-021-00957-x.

MacLeod, S., Reynolds, M.G., Lehmann, H., 2018. The mitigating effect of repeated memory reactivations on forgetting. npj Sci. Learn. 3 (1) https://doi.org/10.1038/s41539-018-0025-x.

Maddox, S.A., Schafe, G.E., 2011. Epigenetic alterations in the lateral amygdala are required for reconsolidation of a Pavlovian fear memory. Learn. Mem. 18 (9), 579–593. https://doi.org/10.1101/lm.2243411.

Mamiya, N., Fukushima, H., Suzuki, A., Matsuyama, Z., Homma, S., Frankland, P.W., Kida, S., 2009. Brain region-specific gene expression activation required for reconsolidation and extinction of contextual fear memory. J. Neurosci. 29 (2), 402–413. https://doi.org/10.1523/JNEUROSCI.4639-08.2009.

Mamou, C.Ben, Gamache, K., Nader, K., 2006. NMDA receptors are critical for unleashing consolidated auditory fear memories. Nat. Neurosci. 9 (10), 1237–1239. https://doi.org/10.1038/nn1778.

Maples-Keller, J.L., Price, M., Jovanovic, T., Norrholm, S.D., Odenat, L., Post, L., Rothbaum, B.O., 2017. Targeting memory reconsolidation to prevent the return of fear in patients with fear of flying. Depress. Anxiety 34 (7), 610–620. https://doi.org/10.1002/da.22626.

Marin, M.F., Pilgrim, K., Lupien, S.J., 2010. Modulatory effects of stress on reactivated emotional memories. Psychoneuroendocrinology 35 (9), 1388–1396. https://doi.org/10.1016/j.psyneuen.2010.04.002.

McGaugh, J.L., 1966. Time-dependent processes in memory storage. Science 153 (3742), 1351–1358. https://doi.org/10.1126/science.153.3742.1351.

McGaugh, J.L., 1989. Involvement of hormonal of memory storage. Annu. Rev. Neurosci. 12 (1), 255–287.

McGaugh, J.L., 2000. Memory - a century of consolidation. Science 287 (5451), 248–251. https://doi.org/10.1126/science.287.5451.248.

Meir Drexler, S., Merz, C.J., Hamacher-Dang, T.C., Marquardt, V., Fritsch, N., Otto, T., Wolf, O.T., 2014. Effects of postretrieval-extinction learning on return of contextually controlled cued fear. Behav. Neurosci. 128 (4), 474–481. https://doi.org/10.1037/a0036688.

Merlo, E., Ratano, P., Ilioi, E.C., Robbins, M.A.L.S., Everitt, B.J., Milton, A.L., 2015. Amygdala dopamine receptors are required for the destabilization of a reconsolidating appetitive memory. eNeuro 2 (1). https://doi.org/10.1523/ENEURO.0024-14.2015.

Milekic, M.H., Alberini, C.M., 2002. Temporally graded requirement for protein synthesis following memory reactivation. Neuron 36 (3), 521–525. https://doi.org/10.1016/S0896-6273(02)00976-5.

Milekic, M.H., Brown, S.D., Castellini, C., Alberini, C.M., 2006. Persistent disruption of an established morphine conditioned place preference. J. Neurosci. 26 (11), 3010–3020. https://doi.org/10.1523/JNEUROSCI.4818-05.2006.

Miller, C.A., Marshall, J.F., 2005. Molecular substrates for retrieval and reconsolidation of cocaine-associated contextual memory. Neuron 47 (6), 873–884. https://doi.org/10.1016/j.neuron.2005.08.006.

Milton, A.L., Lee, J.L.C., Everitt, B.J., 2008. Reconsolidation of appetitive memories for both natural and drug reinforcement is dependent on β-adrenergic receptors. Learn. Mem. 15 (2), 88–92. https://doi.org/10.1101/lm.825008.

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 (3), 1109–1115. https://doi.org/10.1523/JNEUROSCI.3273-12.2013.

Misanin, J.R., Miller, R.R., Lewis, D.J., 1968. Retrograde amnesia produced by electroconvulsive shock after reactivation of a consolidated memory trace. Science 160 (3827), 554–555. https://doi.org/10.1126/science.160.3827.554.

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. https://doi.org/10.1126/science.1167975.

Morris, R.G.M., Frey, U., 1997. Hippocampal synaptic plasticity: role in spatial learning or the automatic recording of attended experience? Philos. Trans. R. Soc. B Biol. Sci. 352, 1489–1503. https://doi.org/10.1098/rstb.1997.0136.

Morris, R.G.M., Inglis, J., Ainge, J.A., Olverman, H.J., Tulloch, J., Dudai, Y., Kelly, P.A. T., 2006. Memory reconsolidation: sensitivity of spatial memory to inhibition of protein synthesis in dorsal hippocampus during encoding and retrieval. Neuron 50, 479–489. https://doi.org/10.1016/j.neuron.2006.04.012.

Muffato, V., Hilton, C., Meneghetti, C., De Beni, R., Wiener, J.M., 2019. Evidence for age-related deficits in object-location binding during place recognition. Hippocampus 29 (10), 971–979. https://doi.org/10.1002/hipo.23099.

Mumby, D.G., Gaskin, S., Glenn, M.J., Schramek, T.E., Lehmann, H., 2002. Hippocampal damage and exploratory preferences in rats: memory for objects, places, and contexts. Learn. Mem. 9, 49–57. https://doi.org/10.1101/lm.41302.

Murai, T., Okuda, S., Tanaka, T., Ohta, H., 2007. Characteristics of object location memory in mice: behavioral and pharmacological studies. Physiol. Behav. 90, 116–124. https://doi.org/10.1016/j.physbeh.2006.09.013.

Myers, K.M., Davis, M., 2007. Mechanisms of fear extinction. Mol. Psychiatry 12 (2), 120–150. https://doi.org/10.1038/sj.mp.4001939.

Nadel, L., Hupbach, A., Gomez, R., Newman-Smith, K., 2012. Memory formation, consolidation and transformation. Neurosci. Biobehav. Rev. 36 (7), 1640–1645. https://doi.org/10.1016/j.neubiorev.2012.03.001.

Nader, K., 2003. Memory traces unbound. Trends Neurosci. 26 (2), 65–72. https://doi.org/10.1016/S0166-2236(02)00042-5.

Nader, K., 2016. Reconsolidation and the dynamic nature of memory. In: Giese, K.P., Radwanska, K. (Eds.), Novel Mechanisms of Memory. Springer International Publishing, Cham, pp. 1–20. https://doi.org/10.1007/978-3-319-24364-1_1.

Nader, K., Hardt, O., 2009. A single standard for memory: the case for reconsolidation. Nat. Rev. Neurosci. 10, 224–234. https://doi.org/10.1038/nrn2590.

Nader, K., Schafe, G.E., LeDoux, J.E., 2000a. Fear memories require protein synthesis in the amygdala for reconsolidation after retrieval. Nature 406 (6797), 722–726. https://doi.org/10.1038/35021052.

Nader, K., Schafe, G.E., LeDoux, J.E., 2000b. The labile nature of consolidation theory. Nat. Rev. Neurosci. 1 (3), 216–219. https://doi.org/10.1038/35044580.

Nyberg, L., Habib, R., McIntosh, A.R., Tulving, E., 2000. Reactivation of encoding-related brain activity during memory retrieval. Proc. Natl. Acad. Sci. U.S.A. 97 (20), 11120–11124. https://doi.org/10.1073/pnas.97.20.11120.

Orsi, S.A., Devulapalli, R.K., Nelsen, J.L., McFadden, T., Surineni, R., Jarome, T.J., 2019. Distinct subcellular changes in proteasome activity and linkage-specific protein polyubiquitination in the amygdala during the consolidation and reconsolidation of a fear memory. Neurobiol. Learn. Mem. 157, 1–11. https://doi.org/10.1016/j.nlm.2018.11.012.

Ortiz, V., Calfa, G.D., Molina, V.A., Martijena, I.D., 2019. Resistance to fear memory destabilization triggers exaggerated emotional-like responses following memory reactivation. Prog. Neuro Psychopharmacol. Biol. Psychiatry 93, 197–204. https://doi.org/10.1016/j.pnpbp.2019.04.004.

Oyarzún, J.P., Lopez-Barroso, D., Fuentemilla, L., Cucurell, D., Pedraza, C., Rodriguez-Fornells, A., de Diego-Balaguer, R., 2012. Updating fearful memories with extinction training during reconsolidation: a human study using auditory aversive stimuli. PLoS One 7 (6), e38849. https://doi.org/10.1371/journal.pone.0038849.

Pachas, G.N., Gilman, J., Orr, S.P., Hoeppner, B., Carlini, S.V., Loebl, T., Evins, A.E., 2015. Single dose propranolol does not affect physiologic or emotional reactivity to smoking cues. Psychopharmacology 232 (9), 1619–1628. https://doi.org/10.1007/s00213-014-3797-6.

Pedreira, M.E., Maldonado, H., 2003. Protein synthesis subserves reconsolidation or extinction depending on reminder duration. Neuron 38 (6), 863–869. https://doi.org/10.1016/S0896-6273(03)00352-0.

Pedreira, M.E., Pérez-Cuesta, L.M., Maldonado, H., 2002. Reactivation and reconsolidation of long-term memory in the crab Chasmagnathus:protein synthesis requirement and mediation by NMDA-type glutamatergic receptors. J. Neurosci. 22 (18), 8305–8311. https://doi.org/10.1523/jneurosci.22-18-08305.2002.

Pedreira, M.E., Pérez-Cuesta, L.M., Maldonado, H., 2004. Mismatch between what is expected and what actually occurs triggers memory reconsolidation or extinction. Learn. Mem. 11 (5), 579–585. https://doi.org/10.1101/lm.76904.

Pérez, A.D.A., Popik, B., de Oliveira Alvares, L., 2020. Rewarding information presented during reactivation attenuates fear memory: methylphenidate and fear memory updating. Neuropharmacology 171, 108107. https://doi.org/10.1016/j.neuropharm.2020.108107.

Phelps, E.A., Delgado, M.R., Nearing, K.I., Ledoux, J.E., 2004. Extinction learning in humans: role of the amygdala and vmPFC. Neuron 43 (6), 897–905. https://doi.org/10.1016/j.neuron.2004.08.042.

Philippens, I.H.C.H.M., Draaisma, L., Baarends, G., Krugers, H.J., Vermetten, E., 2021. Ketamine treatment upon memory retrieval reduces fear memory in marmoset monkeys. Eur. Neuropsychopharmacol. 50, 1–11. https://doi.org/10.1016/j.euroneuro.2021.04.004.

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 (1), 785–793. https://doi.org/10.1101/lm.032714.113.

Pitman, R.K., Sanders, K.M., Zusman, R.M., Healy, A.R., Cheema, F., Lasko, N.B., Orr, S. P., 2002. Pilot study of secondary prevention of posttraumatic stress disorder with propranolol. Biol. Psychiatry 51 (2), 189–192. https://doi.org/10.1016/S0006-3223(01)01279-3.

Potts, R., Shanks, D.R., 2012. Can testing immunize memories against interference? J. Exp. Psychol.: Learn. Mem. Cogn. 38 (6), 1780–1785. https://doi.org/10.1037/a0028218.

Przybyslawski, J., Sara, S.J., 1997. Reconsolidation of memory after its reactivation. Behav. Brain Res. 84, 241–246. https://doi.org/10.1016/s0166-4328(96)00153-2.

Przybyslawski, J., Roullet, P., Sara, S.J., 1999. Attenuation of emotional and nonemotional memories after their reactivation: role of β adrenergic receptors. J. Neurosci. 19 (15), 6623–6628. https://doi.org/10.1523/jneurosci.19-15-06623.1999.

Reichelt, A.C., Exton-Mcguinness, M.T.J., Lee, J.L.C., 2013. Ventral tegmental dopamine dysregulation prevents appetitive memory destabilization. J. Neurosci. 33 (35), 14205–14210. https://doi.org/10.1523/JNEUROSCI.1614-13.2013.

Rimmele, U., Besedovsky, L., Lange, T., Born, J., 2015. Emotional memory can be persistently weakened by suppressing cortisol during retrieval. Neurobiol. Learn. Mem. 119, 102–107. https://doi.org/10.1016/j.nlm.2015.01.010.

Robinson, M.J.F., Franklin, K.B.J., 2007. Central but not peripheral beta-adrenergic antagonism blocks reconsolidation for a morphine place preference. Behav. Brain Res. 182 (1), 129–134. https://doi.org/10.1016/j.bbr.2007.05.023.

Robinson, M.J.F., Franklin, K.B.J., 2010. Reconsolidation of a morphine place preference: Impact of the strength and age of memory on disruption by propranolol and midazolam. Behav. Brain Res. 213, 201–207. https://doi.org/10.1016/j.bbr.2010.04.056.

Rodriguez-Ortiz, C.J., Garcia-DeLaTorre, P., Benavidez, E., Ballesteros, M.A., Bermudez-Rattoni, F., 2008. Intrahippocampal anisomycin infusions disrupt previously consolidated spatial memory only when memory is updated. Neurobiol. Learn. Mem. 89 (3), 352–359. https://doi.org/10.1016/j.nlm.2007.10.004.

Rossato, J.I., Bevilaqua, L.R.M., Medina, J.H., Izquierdo, I., Cammarota, M., 2006. Retrieval induces hippocampal-dependent reconsolidation of spatial memory. Learn. Mem. 13 (4), 431–440. https://doi.org/10.1101/lm.315206.

Rossato, J.I., Bevilaqua, L.R.M., Myskiw, J.C., Medina, J.H., Izquierdo, I., Cammarota, M., 2007. On the role of hippocampal protein synthesis in the consolidation and reconsolidation of object recognition memory. Learn. Mem. 14 (1–2), 36–46. https://doi.org/10.1101/lm.422607.

Rossato, J.I., Köhler, C.A., Radiske, A., Lima, R.H., Bevilaqua, L.R.M., Cammarota, M., 2015. State-dependent effect of dopamine D1/D5receptors inactivation on memory destabilization and reconsolidation. Behav. Brain Res. 285, 194–199. https://doi.org/10.1016/j.bbr.2014.09.009.

Rubin, R.D., 1976. Clinical use of retrograde amnesia produced by electroconvulsive shock. A conditioning hypothesis. Can. Psychiatr. Assoc. J. 21, 87–90.

Sakurai, T., Kato, T., Mori, K., Takano, E., Watabe, S., Nabeshima, T., 1998. Nefiracetam elevates extracellular acetylcholine level in the frontal cortex of rats with cerebral cholinergic dysfunctions: an in vivo microdialysis study. Neurosci. Lett. 246 (2), 69–72. https://doi.org/10.1016/S0304-3940(98)00244-4.

Sara, S.J., 2000. Strengthening the shaky trace through retrieval. Nat. Rev. Neurosci. 1 (3), 212–213. https://doi.org/10.1038/35044575.

Sara, S.J., 2010. Reactivation, retrieval, replay and reconsolidation in and out of sleep: connecting the dots. Front. Behav. Neurosci. 4, 185. https://doi.org/10.3389/fnbeh.2010.00185.

Sarter, M., Bruno, J.P., 1997. Cognitive functions of cortical acetylcholine: toward a unifying hypothesis. Brain Res. Rev. 23 (1–2), 28–46. https://doi.org/10.1016/S0165-0173(96)00009-4.

Schacter, D.L., Loftus, E.F., 2013. Memory and law: what can cognitive neuroscience contribute? Nat. Neurosci. 16 (2), 119–123. https://doi.org/10.1038/nn.3294.

Schiller, D., Monfils, M.H., Raio, C.M., Johnson, D.C., LeDoux, J.E., Phelps, E.A., 2010. Preventing the return of fear in humans using reconsolidation update mechanisms. Nature 463 (7277), 49–53. https://doi.org/10.1038/nature08637.

Schiller, D., Kanen, J.W., LeDoux, J.E., Monfils, M.H., Phelps, E.A., 2013. Extinction during reconsolidation of threat memory diminishes prefrontal cortex involvement. Proc. Natl. Acad. Sci. U.S.A. 110 (50), 20040–20045. https://doi.org/10.1073/pnas.1320322110.

Schmidt, P.I., Rosga, K., Schatto, C., Breidenstein, A., Schwabe, L., 2014. Stress reduces the incorporation of misinformation into an established memory. Learn. Mem. 21 (1), 5–8. https://doi.org/10.1101/lm.033043.113.

Schneider, A.M., Sherman, W., 1968. Amnesia: a function of the temporal relation of footshock to electroconvulsive shock. Science 159 (3811), 219–221. https://doi.org/10.1126/science.159.3811.219.

Schroyens, N., Beckers, T., Kindt, M., 2017. In search for boundary conditions of reconsolidation: a failure of fear memory interference. Front. Behav. Neurosci. 11, 65. https://doi.org/10.3389/fnbeh.2017.00065.

Schroyens, N., Alfei, J.M., Schnell, A.E., Luyten, L., Beckers, T., 2019. Limited replicability of drug-induced amnesia after contextual fear memory retrieval in rats. Neurobiol. Learn. Mem. 166, 107105 https://doi.org/10.1016/j.nlm.2019.107105.

Schroyens, N., Sigwald, E.L., Van Den Noortgate, W., Beckers, T., Luyten, L., 2021. Reactivation-dependent amnesia for contextual fear memories: evidence for publication bias. eNeuro 0108–20, 2020. https://doi.org/10.1523/ENEURO.0108-20.2020.

Schultz, W., Dickinson, A., 2000. Neuronal coding of prediction errors. Annu. Rev. Neurosci. 23 (1), 473–500. https://doi.org/10.1146/annurev.neuro.23.1.473.

Schwabe, L., Wolf, O.T., 2009. New episodic learning interferes with the reconsolidation of autobiographical memories. PLoS One 4 (10), e7519. https://doi.org/10.1371/journal.pone.0007519.

Schwabe, L., Wolf, O.T., 2010. Stress impairs the reconsolidation of autobiographical memories. Neurobiol. Learn. Mem. 94 (2), 153–157. https://doi.org/10.1016/j.nlm.2010.05.001.

Schwabe, L., Nader, K., Wolf, O.T., Beaudry, T., Pruessner, J.C., 2012. Neural signature of reconsolidation impairments by propranolol in humans. Biol. Psychiatry 71 (4), 380–386. https://doi.org/10.1016/j.biopsych.2011.10.028.

Schwabe, L., Nader, K., Pruessner, J.C., 2013. β-Adrenergic blockade during reactivation reduces the subjective feeling of remembering associated with emotional episodic memories. Biol. Psychol. 92 (2), 227–232. https://doi.org/10.1016/j.biopsycho.2012.10.003.

Schwabe, L., Nader, K., Pruessner, J.C., 2014. Reconsolidation of human memory: brain mechanisms and clinical relevance. Biol. Psychiatry 76 (4), 274–280. https://doi.org/10.1016/j.biopsych.2014.03.008.

Scully, I.D., Napper, L.E., Hupbach, A., 2017. Does reactivation trigger episodic memory change? A meta-analysis. Neurobiol. Learn. Mem. 142, 99–107. https://doi.org/10.1016/j.nlm.2016.12.012.

Sevenster, D., Beckers, T., Kindt, M., 2013. Prediction error governs pharmacologically induced amnesia for learned fear. Science 339 (6121), 830–833. https://doi.org/10.1126/science.1232458.

Sevenster, D., Beckers, T., Kindt, M., 2014. Prediction error demarcates the transition from retrieval, to reconsolidation, to new learning. Learn. Mem. 21 (11), 580–584. https://doi.org/10.1101/lm.035493.114.

Shiban, Y., Brütting, J., Pauli, P., Mühlberger, A., 2015. Fear reactivation prior to exposure therapy: does it facilitate the effects of VR exposure in a randomized clinical sample? J. Behav. Ther. Exp. Psychiatry 46, 133–140. https://doi.org/10.1016/j.jbtep.2014.09.009.

Sinclair, A.H., Barense, M.D., 2018. Surprise and destabilize: prediction error influences episodic memory reconsolidation. Learn. Mem. 25 (8), 369–381. https://doi.org/10.1101/lm.046912.117.

Sinclair, A.H., Barense, M.D., 2019. Prediction error and memory reactivation: how incomplete reminders drive reconsolidation. Trends Neurosci. 42 (10), 727–739. https://doi.org/10.1016/j.tins.2019.08.007.

Sinclair, A.H., Manalili, G.M., Brunec, I.K., Adcock, R.A., Barense, M.D., 2021. Prediction errors disrupt hippocampal representations and update episodic memories. PNAS 118 (51), e2117625118. https://doi.org/10.1073/pnas.2117625118/-/DCSupplemental.Published.

Soeter, M., Kindt, M., 2010. Dissociating response systems: erasing fear from memory. Neurobiol. Learn. Mem. 94 (1), 30–41. https://doi.org/10.1016/j.nlm.2010.03.004.

Soeter, M., Kindt, M., 2011. Disrupting reconsolidation: pharmacological and behavioral manipulations. Learn. Mem. 18 (6), 357–366. https://doi.org/10.1101/lm.2148511.

Soeter, M., Kindt, M., 2012a. Erasing fear for an imagined threat event. Psychoneuroendocrinology 37 (11), 1769–1779. https://doi.org/10.1016/j.psyneuen.2012.03.011.

Soeter, M., Kindt, M., 2012b. Stimulation of the noradrenergic system during memory formation impairs extinction learning but not the disruption of reconsolidation. Neuropsychopharmacology 37 (5), 1204–1215. https://doi.org/10.1038/npp.2011.307.

Soeter, M., Kindt, M., 2015. An abrupt transformation of phobic behavior after a post-retrieval amnesic agent. Biol. Psychiatry 78 (12), 880–886. https://doi.org/10.1016/j.biopsych.2015.04.006.

Spring, J.D., Wood, N.E., Mueller-Pfeiffer, C., Milad, M.R., Pitman, R.K., Orr, S.P., 2015. Prereactivation propranolol fails to reduce skin conductance reactivity to prepared

fear-conditioned stimuli. Psychophysiology 52 (3), 407–415. https://doi.org/10.1111/psyp.12326.
Squire, L.R., Slater, P.C., Chace, P.M., 1976. Reactivation of recent or remote memory before electroconvulsive therapy does not produce retrograde amnesia. Behav. Biol. 18 (3), 335–343. https://doi.org/10.1016/S0091-6773(76)92295-1.
St. Jacques, P.L., Schacter, D.L., 2013. Modifying memory. Psychol. Sci. 24 (4), 537–543. https://doi.org/10.1177/0956797612457377.
St. Jacques, P.L., Olm, C., Schacter, D.L., 2013. Neural mechanisms of reactivation-induced updating that enhance and distort memory. Proc. Natl. Acad. Sci. 110 (49), 19671–19678. https://doi.org/10.1073/pnas.1319630110.
Steinfurth, E.C.K., Kanen, J.W., Raio, C.M., Clem, R.L., Huganir, R.L., Phelps, E.A., 2014. Young and old Pavlovian fear memories can be modified with extinction training during. Learn. Mem. 21 (7), 338–341. https://doi.org/10.1101/lm.033589.113.
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 (4), 203–214. https://doi.org/10.1101/lm.037713.114.
Stiver, M.L., Cloke, J.M., Nightingale, N., Rizos, J., Messer, W.S., Winters, B.D., 2017. Linking muscarinic receptor activation to UPS-mediated object memory destabilization: Implications for long-term memory modification and storage. Neurobiol. Learn. Mem. 145, 151–164. https://doi.org/10.1016/j.nlm.2017.10.007.
Sturgill, J.F., Hegedus, P., Li, S.J., Chevy, Q., Siebels, A., Jing, M., Kepecs, A., 2020. Basal forebrain-derived acetylcholine encodes valence-free reinforcement prediction error. *BioRxiv*. ⟨https://doi.org/10.1101/2020.02.17.953141⟩.
Suris, A.M., Smith, J., Powell, C., North, C.S., 2013. Interfering with the reconsolidation of traumatic memory: Sirolimus as a novel agent for treating veterans with posttraumatic stress disorder. Ann. Clin. Psychiatry 25 (1), 33–40.
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 (20), 4787–4795. https://doi.org/10.1523/JNEUROSCI.5491-03.2004.
Takahashi, Y.K., Roesch, M.R., Stalnaker, T.A., Haney, R.Z., Calu, D.J., Taylor, A.R., Schoenbaum, G., 2009. The orbitofrontal cortex and ventral tegmental area are necessary for learning from unexpected outcomes. Neuron 62 (2), 269–280. https://doi.org/10.1016/j.neuron.2009.03.005.
Tay, K.R., Flavell, C.R., Cassini, L.F., Wimber, M., Lee, J.L.C., 2019. Postretrieval relearning strengthens hippocampal memories via destabilization and reconsolidation. J. Neurosci. 39 (6), 1109–1118. https://doi.org/10.1523/JNEUROSCI.2618-18.2018.
Taylor, F., Cahill, L., 2002. Propranolol for reemergent posttraumatic stress disorder following an event of retraumatization: a case study. J. Trauma. Stress 15 (5), 433–437. https://doi.org/10.1023/A:1020145610914.
Taylor, J.R., Olausson, P., Quinn, J.J., Torregrossa, M.M., 2009. Targeting extinction and reconsolidation mechanisms to combat the impact of drug cues on addiction. Neuropharmacology 56, 186–189. https://doi.org/10.1016/j.neuropharm.2008.07.027.
Telch, M.J., York, J., Lancaster, C.L., Monfils, M.H., 2017. Use of a brief fear memory reactivation procedure for enhancing exposure therapy. Clin. Psychol. Sci. 5 (2), 367–378. https://doi.org/10.1177/2167702617690151.
Thomas, É., Saumier, D., Pitman, R.K., Tremblay, J., Brunet, A., 2017. Consolidation and reconsolidation are impaired by oral propranolol administered before but not after memory (re)activation in humans. Neurobiol. Learn. Mem. 142, 118–125. https://doi.org/10.1016/j.nlm.2016.12.010.
Thompson, A., Lipp, O.V., 2017. Extinction during reconsolidation eliminates recovery of fear conditioned to fear-irrelevant and fear-relevant stimuli. Behav. Res. Ther. 92, 1–10. https://doi.org/10.1016/j.brat.2017.01.017.
Tollenaar, M.S., Elzinga, B.M., Spinhoven, P., Everaerd, W., 2009. Immediate and prolonged effects of cortisol, but not propranolol, on memory retrieval in healthy young men. Neurobiol. Learn. Mem. 91 (1), 23–31. https://doi.org/10.1016/j.nlm.2008.08.002.
Tronel, S., Milekic, M.H., Alberini, C.M., 2005. Linking new information to a reactivated memory requires consolidation and not reconsolidation mechanisms. PLoS Biol. 3 (9), 1630–1638. https://doi.org/10.1371/journal.pbio.0030293.
Tronson, N.C., Taylor, J.R., 2007. Molecular mechanisms of memory reconsolidation. Nat. Rev. Neurosci. 8 (4), 262–275. https://doi.org/10.1038/nrn2090.
Tronson, N.C., Wiseman, S.L., Olausson, P., Taylor, J.R., 2006. Bidirectional behavioral plasticity of memory reconsolidation depends on amygdalar protein kinase A. Nat. Neurosci. 9 (2), 167–169. https://doi.org/10.1038/nn1628.
Vaiva, G., Ducrocq, F., Jezequel, K., Averland, B., Lestavel, P., Brunet, A., Marmar, C.R., 2003. Immediate treatment with propranolol decreases posttraumatic stress disorder two months after trauma. Biol. Psychiatry 54 (9), 947–949. https://doi.org/10.1016/S0006-3223(03)00412-8.
Valjent, E., Corbillé, A.-G.G., Bertran-Gonsalez, J., Hervé, D., Girault, J.A., 2006. Inhibition of ERK pathway or protein synthesis during reexposure to drugs of abuse erases previously learned place preference. Proc. Natl. Acad. Sci. U.S.A. 103 (8), 2932–2937. https://doi.org/10.1073/pnas.0511030103.
Vermes, J.S., Ayres, R., Goés, A.S., Real, N., Del, Araújo, Á.C., Schiller, D., Corchs, F., 2020. Targeting the reconsolidation of traumatic memories with a brief 2-session imaginal exposure intervention in post-traumatic stress disorder. J. Affect. Disord. 276 (November 2019), 487–494. https://doi.org/10.1016/j.jad.2020.06.052.
Villain, H., Florian, C., Roullet, P., 2016. HDAC inhibition promotes both initial consolidation and reconsolidation of spatial memory in mice. Sci. Rep. 6, 27015. https://doi.org/10.1038/srep27015.
Vorhees, C.V., Williams, M.T., 2014. Assessing spatial learning and memory in rodents. ILAR J. 55 (2), 310–332. https://doi.org/10.1093/ilar/ilu013.
Walker, M.P., Stickgold, R., 2016. Understanding the boundary conditions of memory reconsolidation. Proc. Natl. Acad. Sci. USA 113 (28), E3991–E3992. https://doi.org/10.1073/pnas.1607964113.
Walker, M.P., Brakefield, T., Hobson, J.A., Stickgold, R., 2003. Dissociable stages of human memory consolidation and reconsolidation. Nature 425 (6958), 616–620. https://doi.org/10.1038/nature01930.
Walsh, K., Iskandar, G., Kamboj, S.K., Das, R.K., 2021. An assessment of rapamycin for weakening binge-eating memories via reconsolidation: a pre-registered, double-blind randomised placebo-controlled experimental study. Psychol. Med. 51 (1), 158–167. https://doi.org/10.1017/S003329171900312X.
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. https://doi.org/10.1038/nn.2350.
Wang, X.-Y., Zhao, M., Ghitza, U.E., Li, Y.-Q., Lu, L., 2008. Stress impairs reconsolidation of drug memory via glucocorticoid receptors in the basolateral amygdala. J. Neurosci. 28 (21), 5602–5610. https://doi.org/10.1523/JNEUROSCI.0750-08.2008.
Wheeler, M.E., Petersen, S.E., Buckner, R.L., 2000. Memory's echo: Vivid remembering reactivates sensory-specific cortex. Proc. Natl. Acad. Sci. USA 97 (20), 11125–11129. https://doi.org/10.1073/pnas.97.20.11125.
Wichert, S., Wolf, O.T., Schwabe, L., 2013. Updating of episodic memories depends on the strength of new learning after memory reactivation. Behav. Neurosci. 127 (3), 331–338. https://doi.org/10.1037/a0032028.
Wideman, C.E., Nguyen, J., Jeffries, S.D., Winters, B.D., 2021. Fluctuating NMDA receptor subunit levels in perirhinal cortex relate to their dynamic roles in object memory destabilization and reconsolidation. Int. J. Mol. Sci. 22, 67. https://doi.org/10.3390/ijms22010067.
Winters, B.D., Saksida, L.M., Bussey, T.J., 2008. Object recognition memory: neurobiological mechanisms of encoding, consolidation and retrieval. Neurosci. Biobehav. Rev. 32, 1055–1070. https://doi.org/10.1016/j.neubiorev.2008.04.004.
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 (9), 545–553. https://doi.org/10.1101/lm.1509909.
Winters, B.D., Saksida, L.M., Bussey, T.J., 2010. Implications of animal object memory research for human amnesia. Neuropsychologia 48, 2251–2261. https://doi.org/10.1016/j.neuropsychologia.2010.01.023.
Winters, B.D., Tucci, M.C., Jacklin, D.L., Reid, J.M., Newsome, J., 2011. On the dynamic nature of the engram: evidence for circuit-level reorganization of object memory traces following reactivation. J. Neurosci. 31 (48), 17719–17728. https://doi.org/10.1523/JNEUROSCI.2968-11.2011.
Wood, N.E., Rosasco, M.L., Suris, A.M., Spring, J.D., Marin, M.-F., Lasko, N.B., Pitman, R.K., 2015. Pharmacological blockade of memory reconsolidation in posttraumatic stress disorder: three negative psychophysiological studies. Psychiatry Res. 225 (1–2), 31–39. https://doi.org/10.1016/j.psychres.2014.09.005.
Wright, D.S., Bodinayake, K.K., Kwapis, J.L., 2020. Investigating memory updating in mice using the objects in updated locations task. Curr. Protoc. Neurosci. 91, e87 https://doi.org/10.1002/cpns.87.
Xue, Y.-X., Luo, Y.-X., Wu, P., Shi, H.-S., Xue, L.-F., Chen, C., Lu, L., 2012. A memory retrieval-extinction procedure to prevent drug craving and relapse. Science 336 (6078), 241–245. https://doi.org/10.1126/science.1215070.
Yang, Y., Jie, J., Li, J., Chen, W., Zheng, X., 2019. A novel method to trigger the reconsolidation of fear memory. Behav. Res. Ther. 122 (August), 103461 https://doi.org/10.1016/j.brat.2019.103461.
Zandonai, T., Benvegnù, G., Tommasi, F., Ferrandi, E., Libener, E., Ferraro, S., Chiamulera, C., 2021. A virtual reality study on postretrieval extinction of smoking memory reconsolidation in smokers. J. Subst. Abus. Treat. 125, 108317 https://doi.org/10.1016/j.jsat.2021.108317.
Zhang, J.J., Haubrich, J., Bernabo, M., Finnie, P.S.B., Nader, K., 2018. Limits on lability: boundaries of reconsolidation and the relationship to metaplasticity. Neurobiol. Learn. Mem. 154, 78–86. https://doi.org/10.1016/j.nlm.2018.02.018.