Trends in Neurosciences

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Review

Prediction Error and Memory Reactivation: How Incomplete Reminders Drive Reconsolidation

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Memories are readily distorted. What conditions allow memories to be altered? Converging evidence implicates prediction error, or surprise, as a key mechanism that renders memories malleable. Recent reconsolidation studies have used incomplete reminders to elicit prediction error; retrieval cues that partially replicate an encoding experience allow memories to be distorted, updated, and strengthened. Here, we review diverse evidence that incomplete reminders govern human memory updating, ranging from classical conditioning to naturalistic episodes. Through the unifying theme of predictive coding, we discuss evidence from reconsolidation theory and nonmonotonic plasticity. We argue that both animal and human reconsolidation research can benefit from critically examining prediction error and incomplete reminders. These findings bear implications for pathological fear memories, false memories, misinformation, and education.

Highlights

Past experience drives our expectations about future events. When new information contradicts past experience, memories are updated and possibly distorted.

Reconsolidation studies have used incomplete reminders to elicit prediction errors and partially reinstate encoding experiences.

Human memory studies have demonstrated that surprising and incomplete reminders influence many types of memory, from simple associations to naturalistic episodes.

Incomplete reminders can produce memory distortion, updating, and strengthening. We critically consider how these diverse effects parallel, and sometimes contradict, prediction errors in reinforcement learning.

Parametrically modulating the strength of expectation and memory reactivation can cast light on the effects of incomplete reminders. Reconsolidation research at multiple levels of analysis stands to benefit from a critical examination of incomplete reminders.

Prediction, Learning, and Incomplete Reminders

The record of our past experiences is not always faithful; memories are easily distorted. For decades, cognitive research on false memory has demonstrated that misinformation and imagined scenarios can develop into vivid false memories [1]. However, the same processes that distort memories can sometimes be beneficial. Memories can be adaptively updated, allowing us to learn from error and integrate old and new information. The broader question that arises is: what are the conditions that allow memories to be changed?

Through the process of **reconsolidation** (see Glossary), memories can be reactivated, temporarily destabilized, and altered. Recent reconsolidation research conducted both in animal models and humans has implicated **prediction error**, or surprise, as a key mechanism that drives memory change. Broadly, a prediction error is a surprising mismatch between expectation (based on prior experiences) and reality. Intuitively, the idea that surprise governs memory change makes sense; when we encounter information that contradicts a previous learning experience, our memories are adaptively updated.

Many reconsolidation studies have used **incomplete reminders** to generate prediction errors (these are somewhat comparable to omission of an expected reward). Retrieval cues that replicate part, but not all, of an encoding experience allow memories to be weakened, strengthened, and updated by new information (Figure 1, Key Figure). Yet, the underlying mechanisms of these effects remain elusive; few studies have parametrically manipulated expectation, surprise, and **memory reactivation**. These parameters are essential to understanding the effects of prediction error. In this review, we critically discuss the relationship between incomplete reminders and prediction error. We argue that human memory studies offer valuable insights about the effects of incomplete reminders, uncovering future directions for reconsolidation research across multiple levels of analysis.

Human and animal memory studies have expanded the concept of prediction error [2] to many domains, including memory for context [3,4], pairs of images [5,6], temporal delays [7], stimulus se-

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quences [8], narrative videos [9], and knowledge updating [10]. We highlight the far-reaching implications of memory updating: attenuating pathological fear and drug memories, counteracting misinformation, understanding eyewitness testimony, and creating more effective learning and teaching strategies. By synthesizing and contrasting evidence from reconsolidation theory and the **nonmonotonic plasticity hypothesis**, we offer guidelines for future reconsolidation research that can uncover the neural mechanisms of memory malleability. Through the overarching theme of prediction error, we critically discuss how incomplete reminders influence many forms of human memory, ranging from classical conditioning to naturalistic episodes.

Incomplete Reminders Drive Reconsolidation

How do surprising reminders influence memories? The concept of **predictive coding** was first characterized by computational models of **reinforcement learning** [11,12] and dopaminergic reward learning [13,14]. In reinforcement learning models, large prediction errors induce greater changes to memory, strengthening or weakening associations depending on whether the surprising outcome was positive or negative [15]. In the context of memory research, prediction error has been linked to new encoding [2,16] as well as memory updating [17]. In this review, we aim to discuss the role of expectation and surprise beyond the realm of reward learning; for an overview of reinforcement learning and the dopaminergic system, we refer readers to other reviews [15,18,19].

Below, we overview mechanisms of memory change, with a particular emphasis on reconsolidation studies that have used incomplete reminders. As described above, omitting an expected outcome can elicit surprise; incomplete reminders can be considered one subtype of prediction error. We characterize how animal studies of prediction error and reconsolidation relate to human memory research, reviewing diverse behavioral evidence of memory updating and distortion. In particular, we critically discuss how incomplete reminders may modulate plasticity through expectation and memory reactivation. This discussion is broadly shaped by predictive coding in memory. We argue that expectation, surprise, and reactivation are all critical components of memory change.

Reconsolidation of Associative Memories

According to reconsolidation theory, a reminder can reactivate and temporarily destabilize an established long-term memory trace (Figure 2) [20,21]. Following a period of lability, the memory is reconsolidated, or re-stabilized, through a time-dependent process of protein synthesis that takes several hours. Reconsolidation studies have typically used a canonical three-session structure: Encoding, Reactivation, and Test (Figure 3A). Critically, the Reactivation session includes interference of some kind; typically, a protein synthesis inhibitor or interfering new learning. Delays between each session ensure that there is enough time for the memory to be consolidated and reconsolidated. The three-session reconsolidation paradigm has been translated to many human memory studies: electroconvulsive shock [22], nitrous oxide (an NMDA-receptor antagonist) [23], interfering information [9,24,25], the β-blocker propranolol [26,27], or the anesthetic propofol [28] have all been used to suppress or distort memories after reactivation with an incomplete reminder.

However, not all reminders destabilize memories. Multiple animal studies of reconsolidation have demonstrated that prediction error is a critical prerequisite for reconsolidation, particularly when an expected outcome is omitted (Figure 2) [17,29–31]. In classical conditioning paradigms, an unreinforced conditioned stimulus is an incomplete reminder (e.g., a tone presented without the accompanying shock). Recently, several human memory studies also uncovered evidence that incomplete reminders drive reconsolidation [9,32–34]. In humans, cueing an expected shock but then omitting it can render fear memories vulnerable to the effects of β-adrenergic receptor antagonists, reducing affective and physiological responses to the conditioned stimulus (CS) [35]. Extinction training is also more effective after an incomplete reminder for image–shock

Glossary

Incomplete reminders: reminders that reinstate part of the encoding experience, but not all of it. This may involve omitting an expected outcome, providing contextual cues, or partially obscuring the memoranda. Incomplete reminders can elicit surprise and violate expectations.

Intrusions: a common dependent variable in memory paradigms. Intrusions are false memories that arise from source misattribution. Examples include words from a newly learned list intruding into recall of an old list, or integrating details from two videos into one episode.

Memory reactivation: recall or reinstatement of an established memory trace. Incomplete reminders likely produce neural reactivation of the missing information. Reactivating a memory with a reminder is a critical component of the reconsolidation process, initiating a period of memory destabilization.

Nonmonotonic plasticity hypothesis (NMPH): the hypothesis that there is a nonlinear relationship between the strength of neural activation/reactivation and plasticity. When a memory is weakly reactivated, it does not become labile. Moderate reactivation induces optimal synaptic weakening, inducing plasticity. Strong reactivation strengthens synaptic connections.

Prediction error: a signal that represents the degree to which an outcome contradicts expectations. Prediction error reflects a sense of surprise or expectancy violation. This signal quantifies the discrepancy between expectation and reality, driving learning from error to improve future predictions. In reinforcement learning, prediction error is quantified as a discrete error signal with 'valence' (positive or negative) and 'magnitude' (strength).

Predictive coding: a broad theoretical framework of cognition that describes how the brain draws on past experience to make predictions. New experiences affirm or violate those predictions, and the brain refines its models to make better predictions in the future.

Reconsolidation: the neural process by which an established long-term memory trace can be reactivated with a reminder and temporarily destabilized. During this period of lability, the memory trace can be disrupted, modified, or pairs [36] or aversive sounds [37]. These findings support the idea that incomplete reminders allow memories to be updated.

Incomplete reminders have also been implicated in reconsolidation of nonfearful associative memories (e.g., two stimulus images paired together; Figure 1). In one such paradigm, participants learned associations between pairs of nonsense words [38,39]. Later, participants were reminded of the associations: they reviewed the word cues and reported the paired associates. Critically, some trials were incomplete, abruptly ending before the participant could report the paired associate. These incomplete reminders disrupted memories, whereas complete trials did not. In variants of this paradigm, incomplete reminders modified memories by increasing forgetting [38], or updating memories with new words from an interfering list [24]. Recent functional magnetic resonance imaging (fMRI) versions of this paradigm have contrasted complete and incomplete reminders of image–word associations. Incomplete reminders were associated with activation in the left hippocampus that predicted subsequent memory updating with interference information [34]. When incomplete reminders were presented without subsequent interference, memory retention was enhanced after a 15-day delay [40]. This memory retention benefit was also associated with broad changes in brain network connectivity, as analyzed using graph theory.

Although these studies of human memory updating parallel findings from the animal reconsolidation literature, it is important to note that direct evidence for cellular reconsolidation processes in humans is lacking. Some studies have produced inconsistent and contradictory results [41,42], and alternative mechanisms are possible (Box 1). Overall, however, these studies demonstrate that surprising and incomplete reminders can selectively update associative memories in humans.

Reconsolidation Theory Applied to Complex Episodic Memories

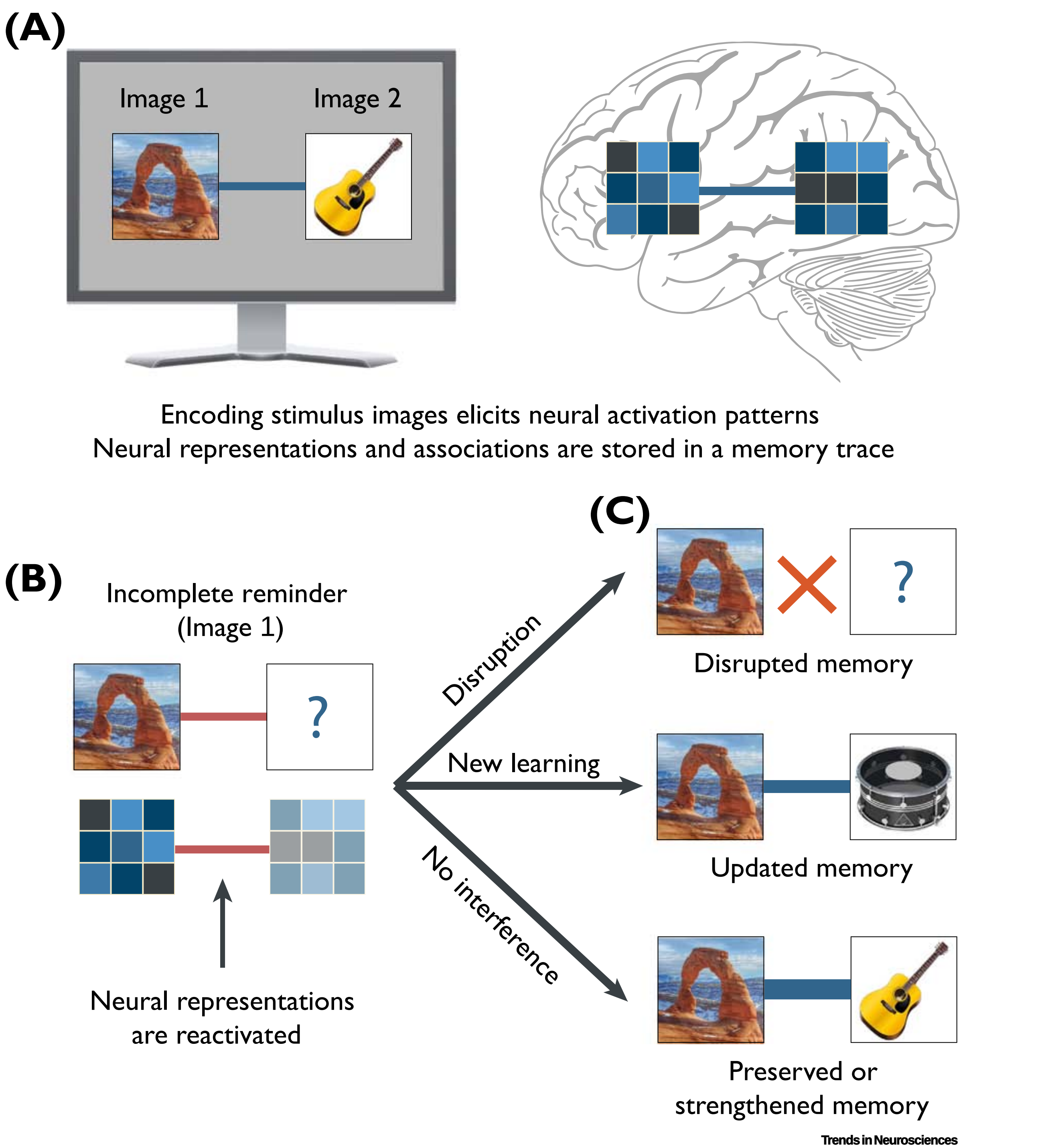
If incomplete reminders are a critical factor driving reconsolidation of associative memories, then they should influence memory change in other domains as well. We recently developed a novel paradigm to investigate whether incomplete reminders drive updating of temporally extended episodic memories [9] (Figure 3). We used videos that featured narrative action–outcome events (e.g., a baseball batter hitting a home run) (Figure 3A). By interrupting these video clips immediately before the expected outcome (e.g., the baseball batter stopped mid-swing), we were able to violate the action–outcome contingency and elicit a feeling of surprise, analogous to the incomplete reminders previously used in rodent [17,29,30] and human [33,35,38] memory updating studies.

In the encoding session, participants viewed the full-length target video clips [9] (Figure 3B). The next day, we reactivated their memories by presenting the target videos again; however, we presented half of the videos in full-length form (complete reminder), and half in interrupted form (incomplete reminder). We found that interrupting videos during reactivation made memories susceptible to subsequent interference from a new set of semantically related videos, producing false memories (Figure 3C). In other words, incomplete reminders increased **intrusions**, defined as details from an interference video that were mistakenly attributed to the corresponding target video. Furthermore, in an item analysis, we found that videos that were rated more surprising when interrupted produced more intrusions (Figure 3D). Importantly, participants in a control group received interference before reactivation. We found that memory reactivation was a prerequisite for memory change, such that in the control group, there were fewer intrusions, and the incomplete reminders did not influence memory (Figure 3C). Lastly, in in a separate sample, we modified the timing of our paradigm to test key predictions about the time course of protein degradation and synthesis involved in reconsolidation (Box 1). In accordance with reconsolidation theory, our memory updating effects only occurred when there were sufficient delays between reactivation, interference, and test.

strengthened. After several hours, the memory is reconsolidated, and stabilized once more.
Reinforcement learning: a computational framework for learning, based on choosing actions to maximize reward. Prediction error alters the likelihood of choosing actions again in the future.
Temporal Context Model (TCM): a model of human memory updating that explains intrusions without making assumptions about synaptic reconsolidation processes. According to the TCM, reminders reinstate the encoding context, linking new learning to the same contextual factors and producing source confusion.
Testing effect: this cognitive phenomenon demonstrates that incomplete reminders, which allow retrieval practice, strengthen memories more effectively than restudying the material.

Key Figure

Conceptual Overview of How Incomplete Reminders Can Produce Memory Change



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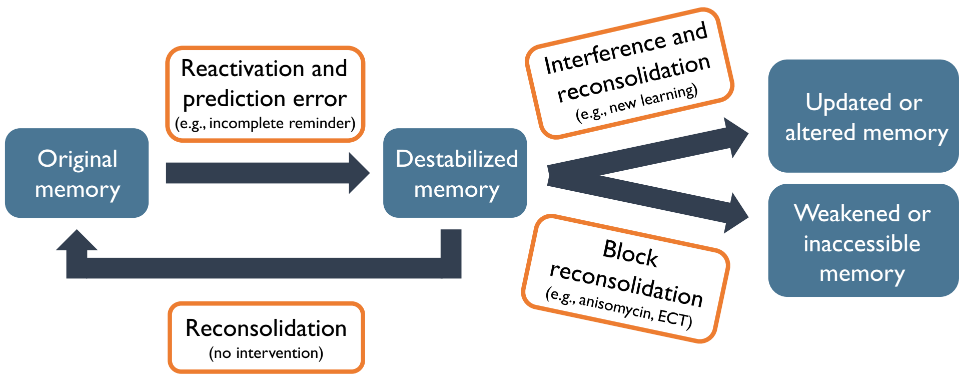


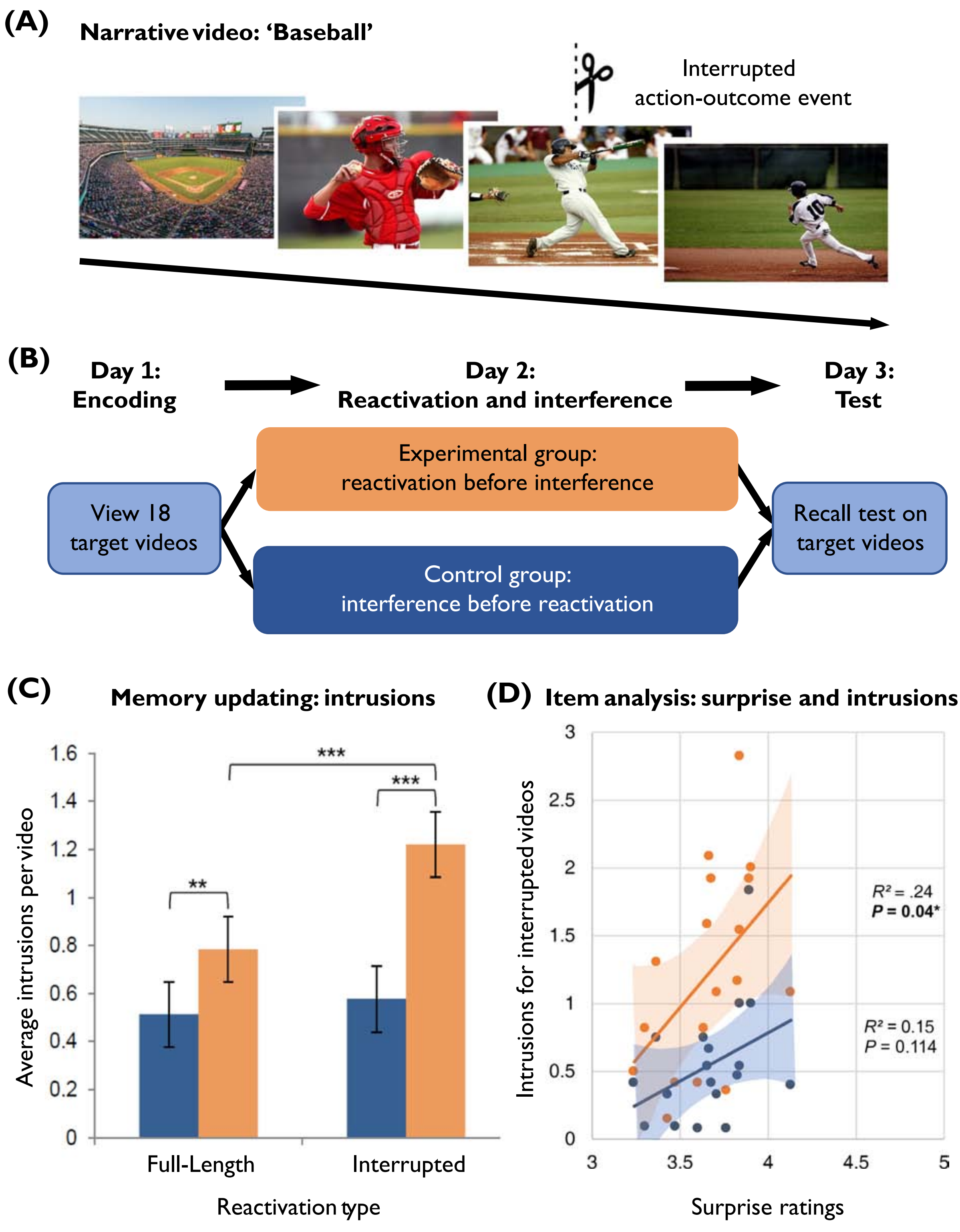
Figure 2. Overview of Reconsolidation Mechanisms. An established long-term memory is destabilized when reactivated in conjunction with a prediction error. If interference (e.g., pharmacological intervention or new learning) occurs during the critical window of destabilization, the memory is reconsolidated in an altered form. Alternatively, if the reconsolidation process is completed without interference, the memory is preserved or strengthened. Abbreviation: ECT, electroconvulsive therapy.

Overall, we found that surprise destabilized memories for narrative videos, producing selective updating with new, semantically related information. These results conceptually extend the findings discussed in the above section, demonstrating that incomplete reminders drive dynamic updating of complex, temporally extended naturalistic memories, allowing relevant new information to be incorporated.

The items-in-a-basket paradigm, developed by Hupbach and colleagues, is another example of how incomplete reminders can influence episodic memories, producing intrusions. Participants were shown a series of objects (List 1) in a distinctive blue basket [25]. A day later, memory of the event was reactivated with one of several reminders, and then participants learned a new list of objects (List 2). Some participants returned to the encoding context and were shown the blue basket (without the List 1 objects inside) as a reminder of the List 1 learning session. When these participants later recalled the two lists, they reported intrusions, erroneously attributing List 2 items to List 1 [25]. Intrusions emerged only after a delay, and only List 1 memories were updated (i.e., List 1 items were not mistakenly attributed to List 2, but rather List 2 items were mistakenly attributed to List 1) [43]. Memory updating only occurred when there was an incomplete reminder that also reinstated the spatial context of encoding (i.e., the blue basket without the corresponding objects), comparable with the incomplete reminders used in other studies [9,17,33,38]. Providing a complete reminder, such as presenting the List 1 objects again, produced fewer intrusions [44].

Other paradigms have also demonstrated updating of naturalistic episodic memories. Although the studies described below were not designed to directly compare the effect of complete and incomplete reminders, they provide evidence consistent with the notion that incomplete reminders drive memory updating. For instance, memory reactivation followed by electroconvulsive shock [22] or propofol-induced deep sedation [28] disrupted memory for slide shows with negative emotional narratives. These studies used incomplete reminders to reactivate

Figure 1. (A) Encoding an association between two stimuli, Image 1 and Image 2. Here, we depict memory representations as patterns of neural activation, and the horizontal line as the association between them. (B) An incomplete reminder, Image 1 presented alone, reactivates memory for the association, reinstating neural representations. (C) The memory trace is susceptible to change in three ways. 'Disruption', such as through pharmacological intervention that impairs reconsolidation, weakens the memory. 'New learning', or exposure to interference, updates memories and produces intrusions (e.g., learning to associate the arch with the drum, instead of the guitar). If 'no interference' occurs after an incomplete reminder, the memory for the association between the images is strengthened (depicted by a thicker line).



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Box 1. Do Intrusions Result from Reconsolidation or Contextual Interference?

Reconsolidation theory posits that reactivation allows an existing memory trace to be destabilized and updated. However, alternative theories explain memory change through contextual reinstatement and Hebbian association [41,60]. According to the **Temporal Context Model (TCM)**, reactivating an old memory reinstates the mental context from the original encoding at the same time that the new memory trace is being formed. The old and new information is thus bridged by the common context, producing intrusions. Computational models of the TCM replicate the asymmetric pattern of intrusions from the items-in-a-basket paradigm [60].

In an fMRI version of the items-in-a-basket paradigm, participants learned two lists of object images [61]. When participants learned the new, interfering list of objects, neural reactivation of the encoding context (background scene images) was associated with intrusions. However, although this finding highlights the importance of contextual factors, it does not rule out reconsolidation; contextual reinstatement may be part of the reconsolidation process. Conversely, a recent study systematically varied contextual factors in the items-in-a-basket paradigm and found that retrieval context at test did not influence intrusions [62]. Although these findings show that intrusions cannot be explained by contextual interference at 'final retrieval' (Day 3 session), this paradigm does not rule out contextual reinstatement during memory 'reactivation' (Day 2 session).

One way to test competing predictions of these two accounts is to manipulate the timing of encoding, reactivation, and test. Reconsolidation theory predicts that intrusions should be delay-dependent, because protein synthesis required to re-stabilize a memory takes several hours [63,64]. Several studies have indeed found that intrusions do not emerge until after a delay between reactivation and test [43]. However, when there is no delay between reactivation and test, it is possible that participants can use a recall-to-reject strategy to avoid reporting intrusions. We tested competing hypotheses of reconsolidation theory and the TCM by manipulating the delay between reactivation and interference [9]. Because the protein degradation that destabilizes a memory trace requires a 3–10 minute delay [65–67], we interleaved memory reactivation and interference, leaving insufficient time for the memory destabilization that is necessary for reconsolidation. Under these conditions, TCM predicts increased intrusions, because experiencing reactivation and interference closer together in time should maximize contextual associations. In accordance with reconsolidation, we found that interleaving reactivation and interference reduced intrusions and eliminated the effect of incomplete reminders. In general, however, reconsolidation is not the only process that can produce intrusions in human memory; contextual reinstatement can also produce memory updating. Reconsolidation and contextual associations are not mutually exclusive.

memories: participants were reminded of the slide show stories with one partially obscured image from the narrative.

Furthermore, episodic memories for disturbing videos with negative emotional content (e.g., a graphic car accident) can be influenced by a visuospatial interference task (the computer game Tetris) [45]. Playing Tetris after memory reactivation dramatically reduced the occurrence of flashback-like intrusive memories in the following week. Critically, memories were reactivated by a single frame from each video taken the moment immediately before the climactic traumatic event. These incomplete reminders were not designed to be surprising, but they may have reactivated memories for the narrative outcome, similar to the interrupted action–outcome events in our paradigm [9]. Similarly, another recent study found that visuospatial interference disrupted episodic memories for videos with positive emotional content [46], but only after a reminder that elicited prediction error by adding new information.

In the real world, a retrospective investigation found that memories for a natural disaster were weakened following the experience of a second, milder disaster [47]. Youth who experienced both Hurricane Katrina and Hurricane Gustav (a similar, but less severe storm) forgot more details of Hurricane Katrina over time than their peers who experienced only Hurricane Katrina. The

Figure 3. Violating Expectation about Narrative Videos Destabilizes Episodic Memories. (A) Example frames from a video in the stimulus set. The narrative video shows a baseball batter hitting a home run. The 'Interrupted' version of this video ended while the batter was mid-swing, thus disrupting a salient action-outcome sequence and eliciting a feeling of surprise. (B) Overview of the 3-day reconsolidation paradigm. On Day 1, participants encoded 18 narrative videos. On Day 2, we reactivated memories by replaying the target videos, half 'full-length' and half 'interrupted'. During the Interference Phase, participants viewed 18 new videos. On Day 3, we assessed memory for the target videos with a structured interview test. (C) In the Experimental group, mismatch reactivation increased 'intrusions', false memories from the interference videos. (D) Videos that were rated more surprising when interrupted (by an independent sample) produced more intrusions. Each point represents a target video. Error bars/bands depict 95% confidence intervals. * P <0.05, ** P <0.01, and *** P <0.001. Adapted from [9].

authors argue that the second hurricane may have functioned as a milder, incomplete reminder of the previous experience, attenuating the memory of the first hurricane.

However, other evidence suggests that incomplete reminders may not universally drive memory modification. In a real-world memory paradigm, participants wore cameras while taking a museum tour [48]. Later, participants reviewed photos taken on the tour and viewed new interference images. When photos were presented in the same order as previously experienced on the tour, memory reactivation enhanced both accuracy and false recognition of museum locations. However, when the temporal order of the photographs was scrambled, accuracy and false recognition was reduced. Notably, both of these conditions involved photos as incomplete reminders of the tour, but disrupting the temporal structure of the event reduced memory updating. This finding may relate to contextual associations between encoding and retrieval (Box 1).

Taken together, the evidence reviewed above illustrates how incomplete reminders influence episodic memory change, both in the laboratory and in the real world. Reconsolidation theory has inspired many human memory paradigms; numerous studies, including ones beyond the scope of this review, have shown that reactivation can impair, distort, and update human memories [21,49]. These findings expand and cohere with concepts from animal reconsolidation research, demonstrating the diverse effects of incomplete reminders. However, the mechanisms of incomplete reminders remain unclear; are incomplete reminders effective because they produce surprise? Is there a signal encoding the strength of these prediction errors? Below, we discuss limitations of research on prediction error and reconsolidation, and highlight both complementary evidence and competing predictions from research on nonmonotonic plasticity.

Refining Reconsolidation Research by Characterizing Prediction Error

A key limitation of existing reconsolidation research is that incomplete reminders purportedly generate prediction errors, but the resulting surprise is not well defined. Is any surprising reminder sufficient to trigger reconsolidation, or is there something unique about incomplete reminders? Incomplete reminders may lead a subject to actively retrieve missing information, reactivating and destabilizing a memory trace. Memory disruption could also be explained by interference, rather than destabilization. An incomplete reminder may disrupt memory if the subject fails to accurately retrieve the missing information, instead adding erroneous information to the memory. Conversely, correctly retrieving the missing information could strengthen a memory trace.

Some evidence suggests that using incomplete reminders to elicit prediction error may be more effective than other methods of violating expectations. In a study seeking to modify alcohol-related associations in addicts, prediction errors of omission (alcohol is unexpectedly removed), but not value (alcohol is unexpectedly bitter) facilitated memory updating [50]. However, to some extent, any attempt at memory reactivation is an incomplete reminder, because it is impossible to perfectly replicate the encoding experience. Past studies have used incomplete reminders to violate expectations, but have yet to quantify the strength of the prediction error and relate it to memory change. Importantly, neither human nor animal studies of incomplete reminders have demonstrated any quantifiable neural prediction error that is parametrically related to memory change.

Predictive coding can explain why surprising and incomplete reminders facilitate memory change: prediction error weakens existing memory associations, allowing new information that follows the surprise to modify a memory trace. However, what if there is no interfering information after a surprise? Large prediction errors should weaken memory, pruning the inaccurate association. Yet, reconsolidation research in both humans and rodents [40,51–53] has shown that reactivating a memory with an incomplete reminder can paradoxically strengthen the original memory trace, as long as the memory is reconsolidated without disruption. This phenomenon parallels evidence from classic cognitive psychology. The **testing effect** describes how providing an incomplete reminder cue, such as a word without its associate, boosts long-term memory retention far more than simply restudying the complete material [54,55]. These effects contradict some predictions of reinforcement learning, because prediction error leads to memory strengthening instead of weakening. However, other models like the **nonmonotonic plasticity hypothesis (NMPH)** can augment the predictive coding framework and explain why incomplete reminders can both distort and enhance memories.

Nonmonotonic Plasticity

The NMPH is a model of memory change that draws on evidence from computational models and mechanisms of synaptic plasticity. According to the NMPH, there is a U-shaped, nonlinear relationship between the strength of memory reactivation and the degree of memory change (Figure 4B) [56,57]. Weak reactivation fails to influence memory, moderate reactivation weakens synaptic associations, and strong reactivation strengthens synaptic associations. This process can reduce competition among interfering items by pruning connections.

In some cases, the NMPH accords with the predictive coding framework. Recent fMRI studies have linked prediction error to the NMPH by measuring changes to item-specific neural representations [4,5]. Following repeated exposure to a pair of associated images, neural representations of those two images became more alike. However, violating the association with a novel pairing elicited a prediction error and led neural representations of the originally paired images to differentiate [5]. Stronger prediction errors were parametrically related to more neural differentiation, driving memory distortion and reducing future competition among items. Similarly, another paradigm demonstrated that following a contextual prediction error (images from an unexpected semantic category in a sequence), associative memories were weakened or 'pruned' and neural representations were distorted [4].

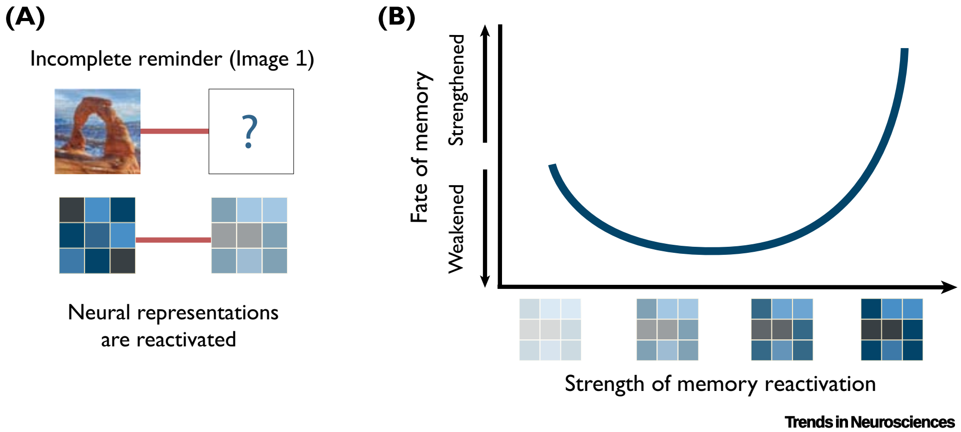

Figure 4. Conceptual Overview of How Incomplete Reminders Reactivate Memory Representations. (A) An incomplete reminder (Image 1 presented without the associate, Image 2) reactivates a memory trace, reinstating neural patterns that represent the stimuli. (B) The nonmonotonic plasticity hypothesis predicts that the strength of memory reactivation (depicted as the opacity of the neural pattern) determines the fate of a memory. At weak levels of memory reactivation, the memory trace is not affected. Moderate levels of memory reactivation weaken memories, and strong levels of memory reactivation strengthen memories.

However, in other cases the NMPH diverges from reinforcement learning, the basis for the predictive coding framework [58]. According to the NMPH, the strength of memory reactivation can modulate plasticity regardless of whether or not there is explicit feedback about a learned association (e.g., reward or punishment). Through this process, the NMPH can explain why incomplete reminders can sometimes strengthen memory: if an association is well learned, then a retrieval cue strongly reactivates memory for the missing associate. Even when the missing associate is not presented again, the subject recalls it, which ultimately strengthens the memory. At the same time that the subject recalls the missing associate, spreading neural activity also moderately reactivates related items that compete during retrieval [58]. The moderate reactivation weakens connections to the related items, thus decreasing their competition during future retrieval. Together, these processes strengthen the target association and bolster memory over time. This account is still compatible with evidence that incomplete reminders can distort memories; when interference follows an incomplete reminder, these new associations can disrupt the memory trace, explaining how memories can be weakened or distorted. Overall, the NMPH can potentially explain why incomplete reminders can strengthen and weaken memories. With traditional measures of prediction error, it is difficult to quantify the degree of surprise elicited by an incomplete reminder, because the subject does not receive a reward or other feedback. Importantly, the NMPH model focuses on the strength of memory reactivation without explicitly computing a prediction error term; this approach could be extended to studying the effects of incomplete reminders in reconsolidation paradigms.

Future Perspectives: Modulating Expectation and Memory Reactivation

Accumulating evidence from many domains of memory research illustrates that incomplete reminders allow memories to be altered. In recent years, predictive coding has strongly influenced animal and human reconsolidation research. Numerous studies have used incomplete reminders to elicit surprise, demonstrating that these prediction errors increase memory malleability. Human memory studies have translated this approach to complex and naturalistic memories, and have produced findings that echo those obtained from simpler memories and lower levels of analysis. However, past research has not fully explored the mechanisms of these incomplete reminders (see Outstanding Questions). We argue that both animal and human reconsolidation research stands to benefit from critically examining the effects of prediction error and memory reactivation, going beyond simply contrasting complete and incomplete reminders.

Moving forward, parametric modulations offer the greatest power to characterize the strength of surprise and memory reactivation, casting light on the mechanisms of reconsolidation. Systematically manipulating the strength of the expectation, or the established memory, can produce variability in the strength of prediction error elicited by an incomplete reminder. Previously, we found that memory updating was linearly related to the degree of surprise produced by an incomplete reminder [9]. However, because we designed our stimulus set to elicit surprise, there was a limited range of prediction error strength. One recent study of prediction error and knowledge updating quantified expectation and surprise through confidence ratings, a promising avenue for future research [10]. Future reconsolidation studies (both in humans and animals) could modulate expectation strength by varying the number of encoding trials, salience, schema-consistency, or semantic relatedness of stimuli.

Neural measures of memory reactivation are also essential. Although existing studies have shown promising nonmonotonic behavioral findings [56] and patterns of neural reactivation consistent with segments of the U-shaped curve predicted by nonmonotonic plasticity [4,5], the full spectrum of memory reactivation has yet to be demonstrated in one study. One promising method involves real-time fMRI. A recent study used real-time fMRI neurofeedback to create a positive

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feedback loop that encouraged participants to amplify contextual reinstatement during memory retrieval [59]. When multivariate neural activity better resembled the mental context from encoding, recall was better. Real-time fMRI could be used to optimize parametric designs; with an experimental task that dynamically adapts to a subject's neural responses, one could sample a broad range of prediction error or memory reactivation strength. In animal studies, targeted stimulation could be used to enhance or suppress memory reactivation after an incomplete reminder. For future research, parametric modulations of expectation and memory reactivation can cast light on the mechanisms of memory change.

Concluding Remarks

In this review, we argue that incomplete reminders drive memory malleability, allowing memories to be distorted, strengthened, or adaptively updated with new information. Here, we bridge evidence from multiple levels of analysis to highlight how incomplete reminders broadly influence memory, ranging from classical conditioning to naturalistic episodes. We critically discuss past findings from the reconsolidation literature by drawing on tenets of predictive coding and nonmonotonic plasticity, theoretical perspectives that can be complementary despite key differences. In particular, we recommend that reconsolidation research can benefit from parametric measures of prediction error and memory reactivation. We argue that incomplete reminders elicit surprise and promote memory reactivation, enabling memories to be distorted, updated, or strengthened. Moving forward, research on memory change has far-reaching implications (Box 2) for clinical treatment

Box 2. Applications of Prediction Error and Memory Updating

Changing Pathological Fear Memories

Research on prediction error and memory updating has promising implications for treating pathological fear memories [30,68]. Reconsolidation-inspired treatments have disrupted fear memories with beta-blockers [26,35,69], electroconvulsive shock [22], computer game play [45], or a new experience [47]. Extinction training is also more effective after an incomplete reminder of image-shock pairs [36] or aversive sounds [37]. However, some reconsolidation studies have produced inconsistent and contradictory results [41], and there is evidence that affect modulates memory strength and resilience [70,71]. Moreover, some evidence from computational models [72] suggests that very strong prediction errors may backfire, preventing extinction because the learner infers a new latent cause. Further investigation is necessary to understand how prediction error influences reconsolidation of fear memories.

Educational Contexts

Research on prediction error and memory updating can inspire ways to improve memory. Prediction error is a critical part of learning from mistakes, and reconsolidation allows established memories to be modified. Furthermore, when memories are destabilized and then reconsolidated without external interference, the memory trace is strengthened, comparable with the well-established benefits of retrieval practice and the testing effect in cognitive psychology [40,49,51]. Repeated strengthening through reconsolidation can make a memory resistant to future pharmacological disruptions, although this effect appears to be selective for more recent [52] and stronger memories [73]. Likewise, integrating and updating memories can improve the way that we draw connections among related experiences and knowledge. In the classroom, exercises that feature incomplete reminders may facilitate integration of old and new information. By drawing on mechanisms of prediction error and memory updating, we may be able to reinforce memories in classrooms, aging populations, and everyday life.

Counteracting Misinformation

Memories can be updated to correct mistakes and improve accuracy. The 'misinformation effect' is the phenomenon whereby misleading, incorrect information received long after encoding can distort memory [74]. Strikingly, misinformation persists even after the source is discredited or the participant is re-exposed to the correct information. These false memories bear profound implications for eyewitness testimony; uncovering the memory-altering effects of surprising and incomplete reminders can inform police and courtroom practices to better preserve the accuracy of eyewitness memories.

Moreover, the misinformation effect is broadly applicable to current events, including fake news [75] and vaccine skepticism [76]. Understanding the mechanisms of memory change is crucial for preventing and undoing erroneous learning [77]. Interventions that elicit prediction error may prove more effective at overcoming misinformation by driving memory updating with accurate content.

Outstanding Questions

Reconsolidation studies have shown that prediction error drives memory change. Do the same neural mechanisms underlie cognitive phenomena like the testing effect and misinformation effect?

What are the mechanisms of incomplete reminders? Do incomplete reminders render memories malleable because they elicit surprise, reactivate memories, or lead the subject to complete the memory with information missing from the reminder, which can introduce erroneous information?

How do the neural responses to incomplete reminders compare with prediction errors in reward learning? Is there an error signal that quantifies the surprise elicited by an incomplete reminder?

Is there a nonmonotonic relationship between the strength of memory reactivation and reconsolidation effects? Can the strength of reactivation be dissociated from the strength of surprise, such as by quantifying neural pattern reinstatement and prediction error signals?

How do incomplete or surprising reminders and retrieval cues impact the accuracy of eyewitness testimony? Are incomplete reminders the most effective way to modify pathological fear and drug memories?

How do we learn from error when we encounter misinformation and retractions? In educational contexts, can incomplete reminders enhance knowledge updating and integration?

of pathological fear and drug memories, eyewitness testimony, misinformation, and educational practices.

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References

1. Loftus, E.F. (2005) Planting misinformation in the human mind: A 30-year investigation of the malleability of memory. *Learn. Mem.* 12, 361–366
2. Henson, R.N. and Gagnepain, P. (2010) Predictive, interactive multiple memory systems. *Hippocampus* 20, 1315–1326
3. Jarome, T.J. *et al.* (2015) Contextual information drives the reconsolidation-dependent updating of retrieved fear memories. *Neuropsychopharmacology* 40, 3044–3052
4. Kim, G. *et al.* (2014) Pruning of memories by context-based prediction error. *Proc. Natl. Acad. Sci. U. S. A.* 111, 8997–9002
5. Kim, G. *et al.* (2017) Neural differentiation of incorrectly predicted memories. *J. Neurosci.* 37, 2022–2031
6. Long, N.M. *et al.* (2016) Hippocampal mismatch signals are modulated by the strength of neural predictions and their similarity to outcomes. *J. Neurosci.* 36, 12677–12687
7. Díaz-Mataix, L. *et al.* (2013) Detection of a temporal error triggers reconsolidation of amygdala-dependent memories. *Curr. Biol.* 23, 467–472
8. Chen, J. *et al.* (2015) Prediction strength modulates responses in human area CA1 to sequence violations. *J. Neurophysiol.* 114, 1227–1238
9. Sinclair, A.H. and Barense, M.D. (2018) Surprise and destabilize: Prediction error influences episodic memory reconsolidation. *Learn. Mem.* 25, 369–381
10. Pine, A. *et al.* (2018) Knowledge acquisition is governed by striatal prediction errors. *Nat. Commun.* 9, 1673
11. Rescorla, R.A. and Wagner, A.R. (1972) A theory of pavlovian conditioning: Variations in the effectiveness of reinforcement and nonreinforcement. In *Classical conditioning II: Current research and theory* (Black, A.H. and Prokasy, W.F., eds), pp. 64–99, Appleton-Century-Crofts
12. Gluck, M.A. and Bower, G.H. (1988) From conditioning to category learning: an adaptive network model. *J. Exp. Psychol. Gen.* 117, 227–247
13. Bayer, H.M. and Glimcher, P.W. (2005) Midbrain dopamine neurons encode a quantitative reward prediction error signal. *Neuron* 47, 129–141
14. Schultz, W. *et al.* (1997) A neural substrate of prediction and reward. *Science* 275, 1593–1599
15. Sutton, R. and Barto, A. (2018) *Reinforcement learning: An introduction*, 2nd edn. MIT Press
16. Greve, A. *et al.* (2017) Does prediction error drive one-shot declarative learning? *J. Mem. Lang.* 94, 149–165
17. Exton-Mcguinness, M.T.J. *et al.* (2015) Updating memories—the role of prediction errors in memory reconsolidation. *Behav. Brain Res.* 278, 375–384
18. Watabe-Uchida, M. *et al.* (2017) Neural circuitry of reward prediction error. *Annu. Rev. Neurosci.* 40, 373–394
19. Gardner, M.P.H. *et al.* (2018) Rethinking dopamine as generalized prediction error. *Proc. R. Soc. B Biol. Sci.* 285, 20181645
20. Nader, K. and Einarsson, E.O. (2010) Memory reconsolidation: an update. *Ann. N. Y. Acad. Sci.* 1191, 27–41
21. Lee *et al.* (2017) An update on memory reconsolidation updating. *Trends Cogn. Sci.* 21, 531–545
22. Kroes, M.C.W. *et al.* (2013) An electroconvulsive therapy procedure impairs reconsolidation of episodic memories in humans. *Nat. Neurosci.* 17, 204–206
23. Das, R.K. *et al.* (2018) Nitrous oxide may interfere with the reconsolidation of drinking memories in hazardous drinkers in a prediction-error-dependent manner. *Eur. Neuropsychopharmacol.* 28, 828–840
24. Forcato, C. *et al.* (2010) Reconsolidation in humans opens up declarative memory to the entrance of new information. *Neurobiol. Learn. Mem.* 93, 77–84
25. Hupbach, A. *et al.* (2007) Reconsolidation of episodic memories: A subtle reminder triggers integration of new information. *Learn. Mem.* 14, 47–53
26. Schwabe, L. *et al.* (2012) Neural signature of reconsolidation impairments by propranolol in humans. *Biol. Psychiatry* 71, 380–386
27. Thomas, É. *et al.* (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
28. Galarza Vallejo, A. *et al.* (2019) Propofol-induced deep sedation reduces emotional episodic memory reconsolidation in humans. *Sci. Adv.* 5, eaav3801
29. Exton-McGuinness, M.T.J. *et al.* (2014) Reconsolidation of a well-learned instrumental memory. *Learn. Mem.* 21, 468–477
30. Krawczyk, M.C. *et al.* (2017) Toward a better understanding on the role of prediction error on memory processes: From bench to clinic. *Neurobiol. Learn. Mem.* 142, 13–20
31. Pedreira, M.E. *et al.* (2004) Mismatch between what is expected and what actually occurs triggers memory reconsolidation or extinction. *Learn. Mem.* 11, 579–585
32. Sevenster, D. *et al.* (2012) Retrieval per se is not sufficient to trigger reconsolidation of human fear memory. *Neurobiol. Learn. Mem.* 97, 338–345
33. Sevenster, D. *et al.* (2014) Prediction error demarcates the transition from retrieval, to reconsolidation, to new learning. *Learn. Mem.* 21, 580–584
34. Forcato, C. *et al.* (2016) Differential left hippocampal activation during retrieval with different types of reminders: An fMRI study of the reconsolidation process. *PLoS One* 11, e0151381
35. Sevenster, D. *et al.* (2013) Prediction error governs pharmacologically induced amnesia for learned fear. *Science* 339, 830–833
36. Schiller, D. *et al.* (2010) Preventing the return of fear in humans using reconsolidation update mechanisms. *Nature* 463, 49–53
37. Oyarzún, J.P. *et al.* (2012) Updating fearful memories with extinction training during reconsolidation: A human study using auditory aversive stimuli. *PLoS One* 7, e38849
38. Forcato, C. *et al.* (2009) Human reconsolidation does not always occur when a memory is retrieved: The relevance of the reminder structure. *Neurobiol. Learn. Mem.* 91, 50–57
39. Forcato, C. *et al.* (2007) Reconsolidation of declarative memory in humans. *Learn. Mem.* 14, 295–303
40. Bavassi, L. *et al.* (2019) Retrieval of retrained and reconsolidated memories are associated with a distinct neural network. *Sci. Rep.* 9, 784
41. Klingmüller, A. *et al.* (2017) Intrusions in episodic memory: reconsolidation or interference? *Learn. Mem.* 24, 216–224
42. Hardwicke, T.E. *et al.* (2016) Postretrieval new learning does not reliably induce human memory updating via reconsolidation. *Proc. Natl. Acad. Sci. U. S. A.* 113, 5206–5211
43. Hupbach, A. *et al.* (2009) Episodic memory reconsolidation: Updating or source confusion? *Memory* 17, 502–510
44. Hupbach, A. *et al.* (2013) Episodic memory reconsolidation: An update. In *Memory Reconsolidation* (Alberini, C.M., ed.), pp. 233–247, Elsevier Academic Press
45. James, E.L. *et al.* (2015) Computer game play reduces intrusive memories of experimental trauma via reconsolidation-update mechanisms. *Psychol. Sci.* 26, 1201–1215

46. Gotthard, G.H. and 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
47. Weems, C.F. *et al.* (2014) Memories of traumatic events in childhood fade after experiencing similar less stressful events: Results from two natural experiments. *J. Exp. Psychol. Gen.* 143, 2046–2055
48. St. Jacques, P.L. and Schacter, D.L. (2013) Modifying memory: selectively enhancing and updating personal memories for a museum tour by reactivating them. *Psychol. Sci.* 24, 537–543
49. Fernández, R.S. *et al.* (2017) Does reconsolidation occur in natural settings? Memory reconsolidation and anxiety disorders. *Clin. Psychol. Rev.* 57, 45–58
50. Hon, T. *et al.* (2016) The effects of cognitive reappraisal following retrieval-procedures designed to destabilize alcohol memories in high-risk drinkers. *Psychopharmacology* 233, 851–861
51. Merlo, E. *et al.* (2015) Enhancing cognition by affecting memory reconsolidation. *Curr. Opin. Behav. Sci.* 4, 41–47
52. Forcato, C. *et al.* (2014) Strengthening a consolidated memory: The key role of the reconsolidation process. *J. Physiol. Paris* 108, 323–333
53. Tay, K.R. *et al.* (2019) Postretrieval relearning strengthens hippocampal memories via destabilization and reconsolidation. *J. Neurosci.* 39, 1109–1118
54. Roediger, H.L. and Karpicke, J.D. (2018) Reflections on the resurgence of interest in the testing effect. *Perspect. Psychol. Sci.* 13, 236–241
55. van den Broek, G. *et al.* (2016) Neurocognitive mechanisms of the "testing effect": A review. *Trends Neurosci. Educ.* 5, 52–66
56. Detre, G.J. *et al.* (2013) Moderate levels of activation lead to forgetting in the think/no-think paradigm. *Neuropsychologia* 51, 2371–2388
57. Newman, E.L. and Norman, K.A. (2010) Moderate excitation leads to weakening of perceptual representations. *Cereb. Cortex* 20, 2760–2770
58. Ritvo, V.J.H. *et al.* (2019) Nonmonotonic plasticity: How memory retrieval drives learning. *Trends Cogn. Sci.* 23, 726–742
59. deBettencourt, M.T. *et al.* (2019) Neurofeedback helps to reveal a relationship between context reinstatement and memory retrieval. *Neuroimage* 200, 292–301
60. Sederberg, P.B. *et al.* (2011) Human memory reconsolidation can be explained using the temporal context model. *Psychon. Bull. Rev.* 18, 455–468
61. Gershman, S.J. *et al.* (2013) Neural context reinstatement predicts memory misattribution. *J. Neurosci.* 33, 8590–8595
62. Capelo, A.M. *et al.* (2019) Exploring the role of context on the existing evidence for reconsolidation of episodic memory. *Memory* 27, 280–294
63. Nader, K. *et al.* (2000) Fear memories require protein synthesis in the amygdala for reconsolidation after retrieval. *Nature* 406, 722–726
64. Debiec, J. *et al.* (2002) Cellular and systems reconsolidation in the hippocampus. *Neuron* 36, 527–538
65. Bustos, S.G. *et al.* (2009) Disruptive effect of midazolam on fear memory reconsolidation: Decisive influence of reactivation time span and memory age. *Neuropsychopharmacology* 34, 446–457
66. Suzuki, A. *et al.* (2004) Memory reconsolidation and extinction have distinct temporal and biochemical signatures. *J. Neurosci.* 24, 4787–4795
67. Lee, S.-H. *et al.* (2008) Synaptic protein degradation underlies destabilization of retrieved fear memory. *Science* 319, 1253–1256
68. Kroes, M.C.W. *et al.* (2016) Translational approaches targeting reconsolidation. *Curr. Top. Behav. Neurosci.* 28, 197–230
69. Schwabe, L. *et al.* (2013) β-Adrenergic blockade during reactivation reduces the subjective feeling of remembering associated with emotional episodic memories. *Biol. Psychol.* 92, 227–232
70. Lázaro-Muñoz, G. and Diaz-Mataix, L. (2016) Manipulating human memory through reconsolidation: Stones left unturned. *AJOB Neurosci.* 7, 244–247
71. Golkar, A. *et al.* (2012) Are fear memories erasable? Reconsolidation of learned fear with fear-relevant and fear-irrelevant stimuli. *Front. Behav. Neurosci.* 6, 1–10
72. Gershman, S.J. *et al.* (2017) The computational nature of memory modification. *eLife* 6
73. Fernández, R.S. *et al.* (2016) The dynamic nature of the reconsolidation process and its boundary conditions: Evidence based on human tests. *Neurobiol. Learn. Mem.* 130, 202–212
74. Loftus, E.F. (2018) Eyewitness science and the legal system. *Annu. Rev. Law Soc. Sci.* 14, 1–10
75. Scheufele, D.A. and Krause, N.M. (2019) Science audiences, misinformation, and fake news. *Proc. Natl. Acad. Sci. U. S. A.* 116, 1–8
76. Pluviano, S. *et al.* (2017) Misinformation lingers in memory: Failure of three pro-vaccination strategies. *PLoS One* 12, e0181640
77. Benedict, T. *et al.* (2019) The influence of misinformation manipulations on evaluative conditioning. *Acta Psychol.* 194, 28–36