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Trends in Cognitive Sciences

Review

Tag and capture: how salient experiences target and rescue nearby events in memory

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The long-term fate of a memory is not exclusively determined by the events occurring at the moment of encoding. Research at the cellular, circuit, and behavioral levels is beginning to reveal how neurochemical activations in the moments surrounding an event can retroactively and proactively rescue weak memory for seemingly mundane experiences. We review emerging evidence showing enhancement of weakly formed memories encoded minutes to hours before or after a related motivationally relevant experience. We discuss proposed neurobiological mechanisms for strengthening weak memories formed in temporal proximity to a strong event, and how this knowledge could be leveraged to improve memory for information that is prone to forgetting.

Highlights

Emotional arousal and novelty trigger neuromodulatory processes that prioritize meaningful information in long-term memory.

Emerging research reveals that the enhancing property of salient experiences can rescue memory for weak events encoded in a critical time-window before or after the salient experience.

A neurobiological model of long-term memory, known as synaptic tag-and-capture, and its behavioral counterpart, behavioral tagging, provide a mechanistic framework for investigating how salient events generate a time-window for memory preservation. This emerging research offers avenues to transform weak experiences into durable long-term memory through the judicious use of salient experiences placed around the time of weak learning.

Implications for improving memory for education, and optimizing treatment for affective disorders with an acknowledged learning and memory component, are discussed.

The penumbra of memory

> Nothing sorts out memory from ordinary moments. It is only later that they claim remembrance, when they show their scars (La Jatée)

The continuous deluge of sensory information we encounter in everyday life presents a challenge for our long-term memory systems. What information should we remember, and what information is reasonable to forget? Humans have a remarkable ability to retain memories of important episodes in our lives, whether they be positive (e.g., wedding day), negative (e.g., car accident), or simply unexpected (e.g., a surprise visit). These salient experiences are often better remembered with more vivid detail and with stronger confidence than are ordinary, mundane events [1–3]. These long-term memory enhancements rely on a cascade of endogenous neurochemical processes that ensure that meaningful events are preferentially processed at each stage of memory (encoding, consolidation, retrieval) [4–6]. In short, our memory systems prioritize information associated with salient events (i.e., emotion, novelty, surprise), and selectively retain and stabilize memories relevant to our subjective sense of wellbeing.

Remembering key details of the past is adaptive insofar as it helps to guide our behavior in response to stimuli, people, or situations associated with significant experiences [7–9]. From the perspective of an adaptive memory system, however, remembering only those details that are motivationally significant at that moment may prove insufficient to appropriately guide future behavior. It is equally important to remember even seemingly ordinary experiences surrounding the event in space and time because this would allow us to build a more robust model. Consider for example an animal that narrowly escapes a hidden predator. If the animal hopes to avoid this predator in the future, it is beneficial to remember not only the precise location of where the predator was encountered but also the route that led them there in the first place, and the best route of escape if encountered again.

Exciting advances in the neuroscience of learning and memory are starting to account for memory enhancements based on temporal proximity to a strong learning event. Specifically, there is

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evidence at the molecular/cellular, circuit, and behavioral levels that a weakly formed memory encoded minutes to hours before or after a salient event can be transformed into a durable long-term memory [10–13]. These findings hold explanatory power for understanding memory prioritization for related mundane information that acquires new meaning through its temporal association to a more salient related experience.

In the following we review evidence for how salient experiences generate a memory preservation time-window (a 'penumbra' [5,14]) of up to several hours, and how this process shapes the selectivity and structure of long-term memory. We first highlight recent models that provide a neurobehavioral framework for understanding how recent events that would otherwise be forgotten are captured in long-term memory by neural processes engaged by salient experiences in temporal proximity. We then build upon these models and integrate them with other frameworks of emotional memory to describe not only which specific details are enhanced by a proximal salient experience but also how these operations are tailored to balance memory specificity and generalization. We also propose how these neurobiological models can be leveraged to benefit real-world memory and the treatment of affective disorders.

Synaptic tag-and-capture: a neurobiological mechanism of memory stabilization

Because many of our ordinary experiences are redundant, and therefore do not require much in the way of updating of knowledge, it makes sense that memories for details of these experiences are eventually forgotten [15]. On the other hand, a variety of mechanisms bolster the retention of behaviorally relevant information [16,17]. Of course, we cannot always anticipate when a meaningful event will occur, nor do we always fully appreciate the meaning of a moment until it later acquires importance. A neurobiological model of long-term memory consolidation, known as synaptic tag-and-capture (STC) [18], provides a valuable framework for understanding how an initially weak memory trace can become stabilized in long-term memory by a more salient event. The STC model is based on the finding that weak synaptic potentiation creates the conditions for long-term potentiation (LTP, a surrogate of long-term memory), but only if weak potentiation is accompanied by stronger neural activity within the same neural ensemble and within a critical time-window of several minutes up to several hours [10,19–21]. The basic premise for STC can be broken down as described in the following section (Figure 1).

Weak potentiation induces a local 'tag' at the synapse that is set by glutamatergic transmission. Although these local tags are only sufficient to create a short-term memory trace, they are also sensitive to potentiation from another source (heterosynaptic stimulation) on the order of a few hours. Robust potentiation through a strong input to the same neural ensemble upregulates the availability of plasticity-related proteins (PRPs) that stabilize local tags induced by the weak event. If the PRPs are released while the local tag is still transiently active, the local tag will 'capture' the PRPs, thereby strengthening memory at the site of weak stimulation via protein synthesis-dependent late LTP. Further neurobiological research on the spatial and temporal dynamics of the tag-and-capture mechanism has revealed its synaptic locus. For instance, weakly stimulated synapses compete for the limited availability of PRPs such that synapses linked closer together within the same dendritic compartment (as opposed to across dendritic branches) 'win out' in capturing available PRPs [22]. This spatial component suggests that the efficiency of long-term memory storage is induced via tag-and-capture at the level of neighboring synaptic clusters [23].

Crucially, weak potentiation that sets a transient local synaptic tag can be transformed by late-LTP if strong potentiation occurs either before or after the tag is set [24], sometimes referred to as 'strong-before-weak' or 'weak-before-strong', respectively. Thus, synaptic tag-and-capture provides a framework to understand how weakly encoded, or mundane, experiences can

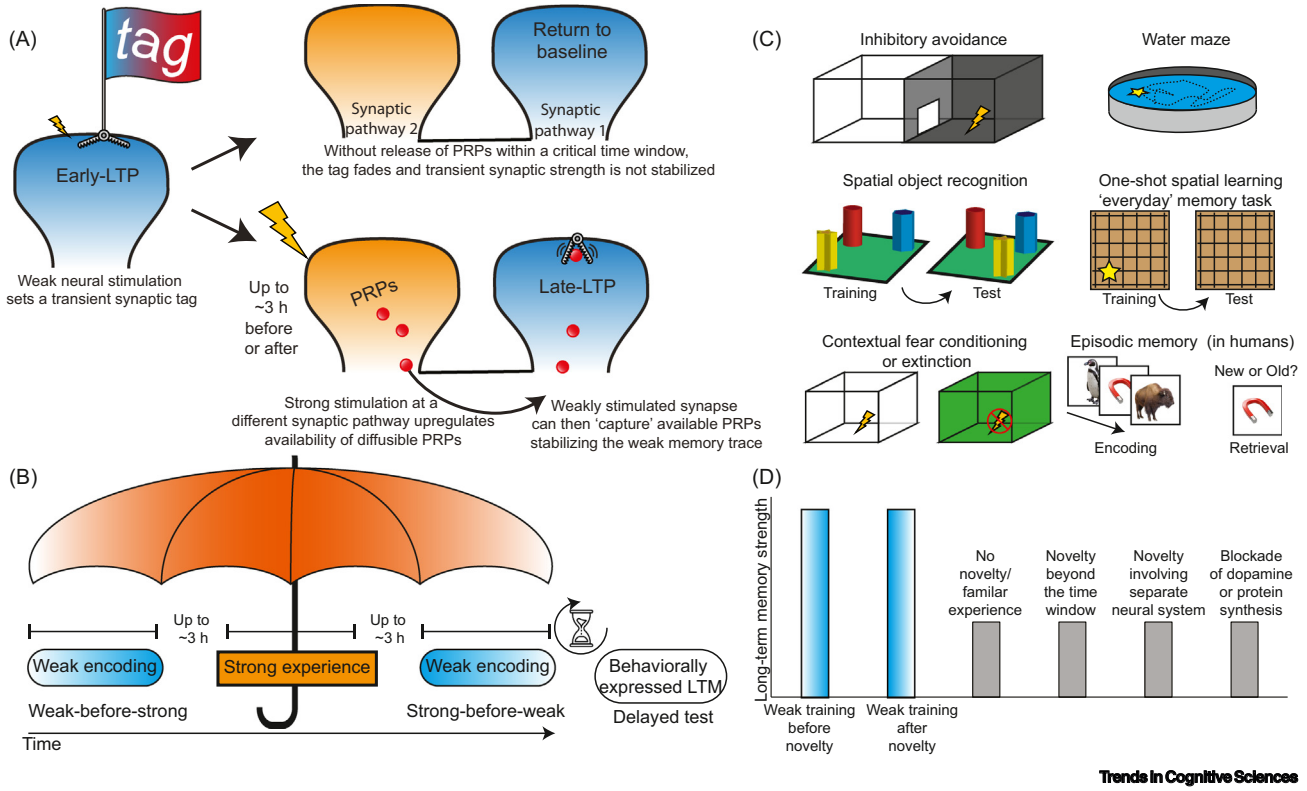

Figure 1. Tag-and-capture at the cellular and behavioral level. (A) Simplified schematic of synaptic tag-and-capture at the cellular level. Weak stimulation at a synaptic pathway (early-LTP) sets a tag insufficient to produce a long-term memory (late-LTP). Strong stimulation in a different synaptic pathway, from the same neural ensemble, induces the release of plasticity-related proteins (PRPs). These PRPs are now accessible and can be 'captured' by the weakly stimulated synaptic pathway. (B) The behavioral tagging hypothesis proposes that strong experiences serve as potentiating events that bolster memory for weakly learned experiences encoded before or after the strong event. (C) Commonly used laboratory tasks to test behavioral tagging mostly utilize hippocampus-dependent learning, including tests of episodic memory in humans. (D) Several boundary conditions and pharmacological manipulations interfere with proactive and retroactive enhancements of memory generated via novelty, establishing the behavioral tagging hypothesis as a testable phenomenon. Abbreviations: LTM, long-term memory; LTP, long-term potentiation.

nonetheless become enduring memories if they occur within the penumbra of a strong event. Notably, the candidate cellular and molecular processes underlying STC were initially identified from *in vitro* experimentation on hippocampal slices. Emerging research has extended this STC model *in vivo* showing that particular events upregulate the availability of PRPs and influence the behavioral expression of weakly formed memories learned close in time.

Evidence for tag-and-capture using behavioral manipulations

Although there was initial speculation about the behavioral implications of STC, it took nearly 10 years from the publication of the groundbreaking discovery by Frey and Morris [18] until this mechanistic framework was tested in a behavioral framework, referred to as 'behavioral tagging'. Behavioral tagging experiments follow a similar time-dependent framework as STC. Animals undergo weak training that relies on a well-characterized neural substrate, typically a task that relies fundamentally on hippocampal processing. Like weak synaptic potentiation, weak training is sufficient to produce a short-term memory but is insufficient to produce a long-term memory that can be expressed in behavior. However, if weak training is accompanied close in time (before or after) by an unrelated salient experience that engages the same neural substrate as the training protocol, then memory for weak training is enhanced.

Most research examining behavioral tagging has focused on exposure to novelty, which constitutes a strong potentiating experience that induces the release of PRPs that stabilize memory formation. Novelty influences memory encoding and consolidation via engagement of the neurotransmitters dopamine (DA) and norepinephrine (NE) [25,26]. The role of novelty in facilitating behavioral tagging dovetails with studies showing that dopaminergic D1/D5 receptors and β-adrenoceptors help to stabilize long-term memory for salient events [27]. Further, the effects of novelty in behavioral tagging aligns with years of research implicating these neuromodulatory systems in enhancing the consolidation of motivationally relevant information [5,6,28,29].

Although most research has focused on hippocampus-dependent memory, an important feature of synaptic tag-and-capture is that it may be a general property of synapses across multiple neural systems [30]. In terms of hippocampus-dependent memory, exploration of a novel environment, which is known to engage the hippocampus, retroactively and proactively improves weak memory in other hippocampus-dependent tasks such as the water maze [31], spatial object recognition [32], contextual fear conditioning [30] and contextual fear extinction [33,34], and episodic-like 'everyday' spatial memory [35–37] (Figure 1). However, effects consistent with behavioral tagging have also been observed for conditioned taste aversion supported by the insula cortex [38]. Crucially, weakly learned conditioned taste aversion is improved by novelty that likewise engages the insula cortex, such as exposure to a different novel flavor, whereas weak taste aversion memory is not enhanced by novelty exploration, which does not engage insula cortex [30]. This dependence on the overlap between the neural systems engaged by the weak and strong events is a unique prediction of the STC model [10]. These findings show that tag-and-capture requires consideration of the overlap in networks between the salient event and temporally proximal learning demands. Notably, the overwhelming preponderance of evidence from rodent studies involves hippocampus-dependent learning; more work will be necessary to confirm whether or not the hippocampus is a crucial component of behavioral tagging.

What separates tag-and-capture from other mechanisms of memory maintenance?

What determines whether memory enhancements via temporal proximity to a salient event meet the criteria for a *per se* tag-and-capture mechanism? One primary condition to be met is that the strong event is sufficient to induce release of neurotransmitters, primarily DA. For example, blocking D1/D5 receptors at around the time of novelty exploration thwarts enhancement of weakly learned memories encoded before or after [30,37,39,40]. Likewise, systemic injections of dopaminergic agonists [39] or stimulation of dopaminergic neurons projecting to the hippocampus [36,41] promotes behavioral tagging-like effects on weak training if delivered in a critical time-window, even in the absence of novelty exposure. Importantly, the source of dopamine projections to the hippocampus may be a crucial factor for these effects [13]. Takeuchi *et al.* [36] provided important evidence that the locus coeruleus (LC) provides strong dopaminergic projections to the hippocampus that promotes the enhancement of memory observed using a behavioral tagging framework. Interestingly, inactivation of the ventral tegmental area (VTA), long considered to be a chief source mediating novelty-associated memory enhancements [5], did not prevent these effects. Likewise, memory enhancements were not prevented by blocking β-adrenoreceptor activity. These findings suggested that behavioral tagging involves DA, and not NE, released in the hippocampus from the LC. However, other evidence indicates a role for both DA and NE released in the hippocampus from both VTA and LC [39,41]. Questions surrounding the role of different neuromodulatory signals, where they originate, and whether they mediate unique aspects of memory consolidation in the hippocampus, constitute areas of ongoing investigation.

The second crucial condition that must be met for behavioral tagging to occur relates to the time interval between the weak and strong event. Evidence from *in vivo* and *in vitro* STC protocols

determined an asymmetric time-window of up to 1 h for a synaptic tag to decay to baseline when it is set before strong stimulation (weak-before-strong protocol) and 2–3 h afterward [18,22,24]. In behavioral experiments, there seems to be a 'sweet-spot' between weak and strong learning of about 30 minutes to 2 h, and no effect if the strong event occurs outside a time-window of 3 h. The nature of the time-window is not entirely clear but is generally related to the time it would take for early-LTP to decay to baseline [42]. The time-window may depend on several factors, including whether hippocampal DA originates from the VTA or the LC, and whether there is corelease of DA and NE, which is perhaps determined by the nature of the novel event; that is, whether novelty is related to or unrelated to prior experience [13] (Box 1). Another possibility, so far untested, is that the time-window of memory preservation varies based on the neural system – and hence the type of memory – that is engaged by weak and strong events.

Arousal-mediated memory consolidation

There is a notable similarity between retroactive effects of behavioral tagging (i.e., weak-before-strong) and post-encoding influences of arousal on implicit and declarative memory [4,43]. Specifically, pioneering work by McGaugh and colleagues showed that neuromodulation of the basolateral amygdala after a memory is formed can affect the consolidation of that memory. Post-training modulation can involve adrenal stress hormone release, amphetamines [44], and even caffeine [45]. Given widespread projections from the amygdala to the rest of the brain, arousal-activated stress hormones can affect multiple forms of memory supported by a variety of brain systems [46].

One important factor of arousal-mediated consolidation, which may distinguish it from behavioral tagging, concerns the lack of specificity of memories enhanced by post-training amygdala modulation. That is, arousal can produce global (i.e., non-specific) enhancements of memory. In humans, post-encoding arousal non-specifically affects declarative memory for prior information

Box 1. What constitutes novelty *per se*?

Novelty assumes a broad definition in psychological research. There are recent efforts to distinguish between different forms of novelty to help to refine the operational definition of an overused term. One suggested distinction is between events that are related to prior experience, referred to as 'common novelty', and events unrelated to prior experience that necessitate formation of new knowledge structures, referred to as 'distinct novelty' [13]. Although both forms of novelty involve DA and upregulate the availability of plasticity-related proteins, there is evidence that 'common novelty' involves the VTA–hippocampus system, whereas 'distinct novelty' involves the LC–hippocampus system. These systems have different temporal dynamics in their ability to rescue weak memories encoded within the penumbra of the novel event. Specifically, DA-releasing LC neurons that target the hippocampus induce a broader time-window than those projecting from VTA. Further, optogenetic stimulation of the LC, but not of the VTA, in mice mimics the effects of novelty exploration and improves episodic-like spatial memory retention for location of food reward [36].

This distinction between different types of novelty may have implications for leveraging the mnemonic effects of behavioral tagging for education and other applications. Specifically, if, as proposed, distinct novelty is a more effective driver of behavioral tagging [13], then the repeated use of only slight variations of a novel event may be less efficient over time (i.e., a novel experience that is nonetheless similar to past experience). Instead, more effective novel experiences would be those that share little in common with past experience and therefore necessitate the formation of new knowledge structures and memory representations. As a practical matter, consistently providing distinct novel experiences would be challenging to maintain in real-world situations over the long term.

Another important question regarding the use of novelty (or emotion, for that matter) is the quality and quantity of novelty that is necessary to trigger upregulation of PRPs. Five minutes of unexpected exploration of an unfamiliar open field has proved to be sufficient to produce reliable behavioral tagging effects in rodents. Laboratory experiments in humans have frequently used novel stimuli (pictures, sounds) that acquire novelty status by virtue of simply being unfamiliar in the context of the experiment. This seems to be sufficient to induce novelty-associated memory effects. Interestingly, however, simply encoding novel objects may not be sufficient to induce behavioral tagging effects in rodents [76]. There is currently not enough research focused on the necessary threshold or the types of experiences sufficient to produce enhancements in memory for information encoded close in time.

[47] or enhances memory for emotional material but not neutral material [48]. Thus, a general increase in arousal appears to be non-selective with regards to the type of learning that is enhanced, distinguishing this mechanism from a putative tag-and-capture mechanism where the prerequisite is that the two events share overlapping neural ensembles. Interestingly, in humans acute stress induction post-encoding versus pre-encoding appears to have divergent effects on improving item versus associative memory, respectively [49], indicating some level of specificity in terms of post-training amygdala modulation. Post-encoding stress has also been shown to selectively benefit memory for neutral information that was encoded in the same room, suggesting that contextual information can also dictate retroactive memory enhancements [50]. In addition, there is evidence that post-encoding acute stress induction improves episodic memory for information that happened to generate high activation in the medial temporal lobe (MTL) during encoding, suggesting that post-encoding arousal interacts with the strength of encoding [51]. Perhaps the central distinguishing factor is that arousal-mediated consolidation is amygdala-dependent, whereas behavioral tagging is framed as a general mechanism of long-term memory that relies on repeated activation in an overlapping neural substrate involved in supporting different forms of memory [10,30]. Simply put, most demonstrations in support of the behavioral tagging hypothesis in animal models involve the hippocampus and are not dependent on the basolateral amygdala.

Carryover effects

Emotional experiences have a lasting impact on mental processing that may carry forward in time to affect how subsequent neutral experiences are encoded. Tambini and colleagues [52] found that human subjects who encoded a block of emotional pictures showed improved memory for neutral items encoded up to ~33 minutes afterwards, as compared to when the encoding order was reversed. Brain states measured in patterns of low-frequency correlations in background connectivity between the amygdala and the rest of the brain, including the anterior hippocampus, were recapitulated between emotional and neutral item encoding. A lingering neural state biasing subsequent encoding is a possible alternative explanation for the effects of a strong-before-weak tag-and-capture protocol. However, the asymmetry in which the emotional carryover effect biases subsequent encoding, but does not retroactively boost neutral memory, suggests distinct neural mechanisms.

Evidence of behavioral tagging human research: extending models of rescuing mundane memories

Recent findings from human behavioral and imaging research have examined how salient events (novelty and emotion) affect memory for other events learned close in time. These results have helped to refine models of synaptic/behavioral tagging. Events that trigger activity in the dopaminergic midbrain (substantia nigra/VTA) or LC have been shown to increase hippocampus-dependent long-term memory, which has helped to bridge findings from animal neuroscience and human psychology research [53,54]. For example, directly associating neutral information with reward [55], punishment [56,57], an aversive stimulus [58], or a novel event [59] enhances episodic memory by enhancing encoding-related activity in the MTL.

An early study in humans framed according to the STC hypothesis showed that exposure to a series of novel pictures enhanced memory for subsequently encoded words, as compared to words encoded after a series of familiar pictures [59]. Another study showed that merely 5 minutes of exploring an unfamiliar immersive virtual reality (VR) environment, as compared to a familiar environment, increased free recall for words encoded immediately after exploration [60]. Although these proactive memory enhancements induced by novelty exposure are generally well situated in a behavioral tagging framework, they did not investigate one of the strongest features of the STC hypothesis: memory enhancements utilizing a weak-before-strong protocol.

In humans, the weak-before-strong protocol was applied in a clever experiment in a population of elementary school children in Argentina [61]. In this study, children first heard a short story, and then several minutes later experienced either a novel and interactive music lesson or a familiar music lesson. Children who experienced a novel music lesson exhibited better 24 h memory performance for the unrelated story that they heard earlier, as compared to children who experienced a familiar music lesson. In accordance with the timing parameters of behavioral tagging, exposure to novelty did not improve memory for a story read 4 h before novelty. A similar finding was obtained for a visuospatial memory (Rey–Osterrieth complex figure test) encoded 1 h before or after a novel science lesson in school children aged 12–15 years [62], and memory persisted for up to 45 days. Similar evidence was garnered for enhancement of free recall for words encoded 45 minutes before exploration of a novel VR environment [63], albeit memory enhancements were limited to children and adolescents with attention-deficit/hyperactivity disorder, but not a typically developing group. However, another study did not find retroactive enhancements for words encoded before novel VR exploration [64].

Selective retroactive memory enhancements

According to the evidence reviewed thus far, behavioral tagging might appear to produce non-specific global improvements for weak memories encoded in the penumbra of the strong event, regardless of the content of learning. However, research in humans challenges this assumption of non-specificity. We recently conducted experiments using a hybrid Pavlovian fear conditioning and episodic memory design that revealed the behavioral specificity of a putative behavioral tagging mechanism [65,66]. In this protocol, the conditioned stimuli consisted of different pictures from two different non-overlapping semantic categories (i.e., animals, tools). Initially, participants simply viewed trial-unique exemplars from the two categories without any association between the picture and reinforcement or outcome. After a short break, new pictures from one category were paired with a shock to the wrist whereas new pictures from the other category were never shocked – in other words, Pavlovian fear conditioning. Afterward, subjects viewed additional unique pictures from the same categories without any shocks. A surprise recognition memory test was administered immediately after learning, 6 h later, or 24 h later to test whether fear conditioning to a specific category retroactively and proactively boosted memory for semantically related exemplars.

Indeed, recognition memory results showed selectively enhanced performance for pictures from the shocked category that were encoded before, during, and after fear conditioning, relative to pictures from the other category. These selective retroactive and proactive memory enhancements were only observed when the surprise memory test was administered after a delay, suggesting that such enhancements are consolidation-dependent. Moreover, selective retroactive enhancements were not observed if items encoded before fear conditioning were repeated three times to strengthen their encoding, consistent with the idea that synaptic tagging is a mechanism for strengthening weak memories that are prone to forgetting in the first place.

We have also found a consolidation-dependent selective retroactive memory enhancement using reward [67], suggesting these effects are not specific for negatively valenced events but instead represent a broader spectrum of motivationally significant events. Immersive VR paradigms also induce a novel and salient experience that may induce behavioral tagging effects on declarative memory. For instance, Bréchet *et al.* [68] first asked subjects to encode neutral objects in an indoor or outdoor environment. Subsequently, they encoded new objects in indoor or outdoor scenes in immersive VR. Crucially, only one context was made more immersive by including a virtual 'body' immersion that involved the presence of a physical hand, body, and legs. Subjects showed selective and retroactive enhancements in memory for items previously encoded in the context that was later associated with the immersive 'bodily self-consciousness' VR experience.

These findings are consistent with the bulk of the behavioral tagging research in rodents that incorporate novelty exploration, which is not aversive. The common element of the strong event may be that it necessarily induces arousal to some degree, regardless of valence. This dovetails with findings in behavioral tagging research in rodents that the release of NE and DA, which can be induced by a range of salient events, is a crucial mechanism necessary to stabilize weak memories [12,41]. Although this idea would not accord with findings from mice that behavioral tagging effects can persist despite blocking β-adrenoreceptor activity [36], it highlights the need for further neurobiological research to fully translate these models from rodents to humans. Finally, the finding of selective retroactive effects using immersive VR [68] may indicate the importance of the conceptual link between the weak and strong learning experience, and may explain the failure to find retroactive enhancements for unrelated material encoded before VR exploration [64].

Recent evidence in both the rodent and human literature provides support for interactions between tag-and-capture and systems-level consolidation [69]. For example, rodent models demonstrate that salient events, such as reward learning, undergo prioritized replay [70], a process thought to support systems-level consolidation. Although animal studies have yet to demonstrate that neural replay can support the types of temporal generalization seen in tag-and-capture, recent human data has shown that interactions between the hippocampus and sensory cortex associated with salient events support generalization [71,72] and, more importantly, retroactive memory benefits for conceptually related information [73].

Interestingly, within this systems-consolidation framework, individuals are thought to lose some specificity of each episodic event in favor of highlighting statistical regularities in the environment [69]. Thus, these models would predict that there may be some errors in identifying the specific elements of the encoding experience for information that undergoes retrograde memory enhancements. In line with these predictions, recent evidence suggests that retroactive memory enhancements for neutral items induced via threat conditioning are accompanied by source misattribution to the temporal context of the threat conditioning [65]. That is, participants who exhibited stronger retroactive biases in recognition memory were also more likely to mistakenly attribute those items to the moment of threat conditioning. Although this first demonstration of a trade-off between specificity and generalization is in line with systems-consolidation theory, more behavioral and neural evidence is necessary to fully confirm these predictions.

In summary, emerging findings in humans extend earlier work on behavioral tagging by showing that memory enhancements for weakly encoded items selectively generalize on the basis of category membership. This feature is consistent with the idea from STC that there must be neuronal overlap between the weak and strong learning experiences, as shown in fMRI studies of categorical fear learning whereby occipitotemporal regions preferential to particular object categories are modulated by aversive learning [74]. Consequently, behavioral tagging may be an even more adaptive mechanism than was originally conceptualized based on animal learning protocols because it promotes learning of representations and perhaps behaviors that generalize within but not across conceptual spaces.

What determines memory prioritization?

Although the evidence provided in the preceding section highlights a mechanism that could support the selectivity of generalization for events in proximity to strong events, they do not detail the processes that 'select' recent information for preservation. According to behavioral tagging models, release of DA helps to trigger the synthesis of PRPs that stabilize weak learning experiences in long-term memory [39]. It is unclear, however, how the widespread release of these neuromodulators across most of the brain would selectively benefit some recent memories but not others. In

both human and rodent studies, weak synaptic tags are presumably set for many sensory inputs encountered before a stronger and arousing learning event, suggesting that arousal should benefit memory consolidation indiscriminately. This raises the crucial question of how arousal-related neuromodulation can selectively and retroactively benefit memory consolidation.

We propose that strong learning triggers local neuromodulatory processes that constrain tag-and-capture to specific neural pathways (Figure 2). This idea is well aligned with the 'glutamate amplifies noradrenergic effects' (GANE) model, which posits that arousal-induced release of NE from the LC interacts with local neural activity to enhance processing and memory of salient information [54]. The GANE model predicts that NE effects on neural excitation differ depending on the local levels of brain activity and adrenoreceptor subtype activation. Under arousal, widespread NE release typically inhibits weak patterns of neural activity by engaging high-affinity α2-adrenoreceptors. By contrast, NE exerts the opposite effect on areas with strong activity, where elevated levels of local glutamate spill over into the extracellular space and engage lower-affinity β-adrenoreceptors

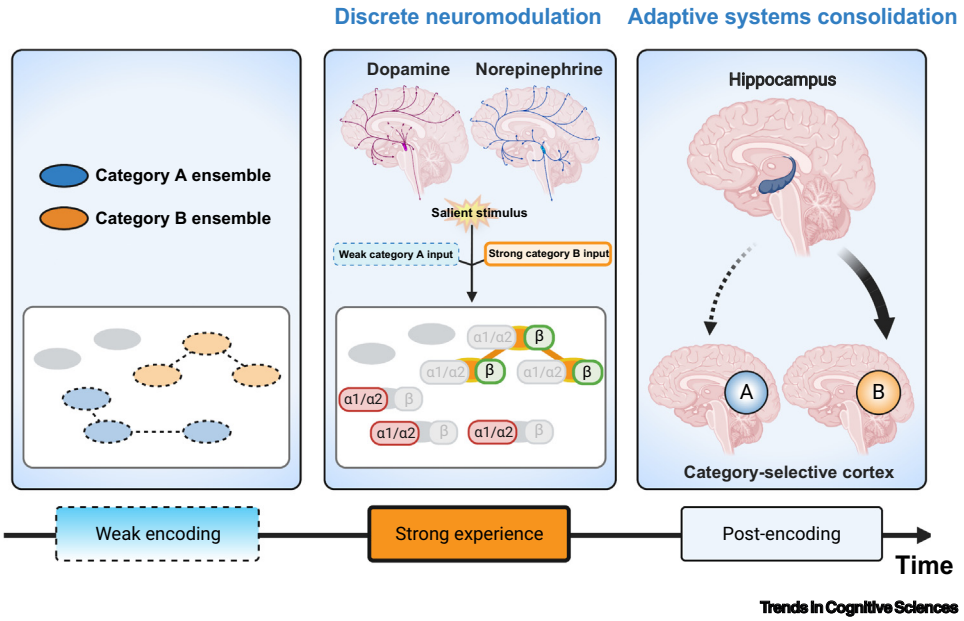

Figure 2. Proposed neural mechanisms by which salient events retroactively augment weak memory. (Left panel) Weak encoding of unique information (categories A and B) sets transient learning tags in separate neural ensembles. (Middle panel) Building on the 'glutamate amplifies noradrenergic effects' (GANE) model, release of norepinephrine (NE) may exert different effects on regions transmitting high (category B) and low (category A) priority inputs by engaging the facilitating and inhibitory effects of different adrenoreceptors, respectively. NE release may suppress weak sensory inputs to the category A ensemble and weaken synaptic plasticity by engaging the inhibitory effects of high-affinity α2- and α1-adrenoreceptors, respectively. Coincident release of NE with strong sensory inputs to the category B ensemble triggers a positive glutamate–NE feedback loop, or 'hotspot', that upregulates local excitation and NE concentration. This self-strengthening feedback loop generates sufficient NE levels to engage low-affinity β-adrenoreceptors (green boxes) that enhance neural activity and synaptic plasticity in the category B ensemble. Building on synaptic tag-and-capture, β-adrenoreceptor activation triggers the production of the plasticity-related proteins (PRPs) to stabilize recently established learning tags. The opposing effects of NE on strong and weak patterns of brain activity thereby amplifies the effects of priority in memory consolidation. A salient event also triggers the dopaminergic system to synthesize release of PRPs to enhance consolidation in those same high-priority pathways. (Right panel) Memory selection processes may continue to occur 'offline' after the strong experience. According to this adaptive systems-consolidation perspective, strong experiences bias post-encoding hippocampal communication towards sensory cortical regions representing a now-significant category of information. This shift in hippocampal processes privileges selective consolidation of distantly encountered information that overlaps with the significant event. Together, these online and offline processes help to explain how the brain adaptively prioritizes and preserves mundane memories that acquire significance in the future.

Box 2. Implications for education and memory remediation

There is an important precedent for incorporating knowledge from animal research to inform education interventions and policy [77] as well as to inspire novel interventions for memory disorders or decline. The concept of behavioral tagging is somewhat unique in the realm of a possible translational neuroscience application to improve educational performance. For starters, the proof of principle has already been tested in school children in Argentina with positive – although narrowly aimed – results [61,62]. The concept of behavioral tagging is also well aligned with the goal of rescuing suboptimal learning of information that is otherwise prone to forgetting, and should not be misunderstood as a panacea to boost learning performance across the board. Instead, the judicious and well-timed use of novelty exposure can be targeted to benefit situations in which material is learned at an insufficient level or is a challenge to remember, especially for particular populations [63].

Further, evidence that tag-and-capture facilitates the generalization of information related to salient events in long-term memory is perfectly suited to the types of memory representations that are most important for positive educational outcomes. Namely, education interventions may be more effective when they target more conceptual/semantic forms of knowledge rather than individual episodic facts. Crucially, multiple theories suggest that conceptual knowledge formation emerges from extracting statistical regularities from related events [69]. In this way, the enhancement of more mundane episodes that are related to salient events would provide a guiding principle for supporting conceptual knowledge formation.

that facilitate LTP. Thus, under arousal, LC activity promotes a few 'hotspots' of neuronal excitation in the context of widespread suppression, thereby selectively enhancing highly active and prioritized mental representations while also suppressing more mundane or distracting representations.

Although GANE is primarily an account of how NE amplifies perceptual and encoding selectivity, it may also explain how recent memories can be enhanced if they overlap with a strong learning event. A core feature of the GANE model is that the mnemonic benefits of β-adrenoreceptor activation are limited to the most active neural pathways during encoding. Importantly, however, activation of β-adrenoreceptors also plays a central role in promoting behavioral tagging processes that enhance the consolidation of recently encoded memories. Thus, the selective engagement of these adrenoreceptors during strong learning provides a common mechanism for prioritizing overlapping past and present memory representations with high priority. The GANE model also raises

Box 3. Rescuing otherwise forgettable memories in the aging brain

Unlike other influential frameworks of emotional memory, behavioral tagging is a model for improving weak learning. Consequently, strong learning may not produce a noticeable impact on learning that was already sufficient to induce memory consolidation. For this reason, behavioral tagging will not (necessarily) further enhance learning that was already above threshold for consolidation. This is important in appreciating the limits to adapting strategies based on behavioral tagging as adjuncts for learning and memory in populations who exhibit weaker learning in the first place.

In this regard, older adults stand to benefit from these types of interventions, given hallmark declines in episodic memory in late adulthood [78]. Although research on behavioral tagging in normal aging is sparse, there is reason to believe that this process is compromised in older adults due to changes in the ingredients necessary to strengthen weak memories [79]. Aging is characterized by a profound decrease in NMDAR function, suggesting that molecular tags set by an initial learning experience are weaker and/or less ubiquitous than in younger adults [80]. This possibility is supported by empirical work showing that neural plasticity and synaptic tag-and-capture mechanisms in CA1 are impaired in aged rodents [80,81].

Other evidence suggests that the capturing process is also compromised with age. Across species, age-related declines in the noradrenergic and dopaminergic systems are prevalent [82], suggesting that the synthesis of PRPs is also impaired [80]. In addition, exposure to novelty – which presumably triggers LC and/or VTA activation – following weak appetitive delayed-matching-to-place learning enhances memory persistence in young but not middle-aged rats [83]. Existing evidence thereby implicates deficits in both the setting and subsequent capture of weak learning tags in age-related memory decline.

Despite these alterations in neural processes that promote behavioral tagging, there are some indications that weak memories can still be rescued by proximal novel events in older age. For example, re-exposing middle-aged rodents to an initial weak learning environment improves long-term memory [83]. Thus, although behavioral tagging may weaken with age, it can be rescued through memory reactivation and reconsolidation. Paralleling these behavioral interventions that strengthen (re)encoding processes, enhancing the excitability of CA1 neurons in older mice can also rescue deficits in neural coallocation mechanisms that are thought to complement synaptic tag-and-capture mechanisms [84]. Together these findings suggest that, in older adults, encoding processes must be strengthened to create a memory trace that can benefit from a nearby strong event.

the intriguing possibility that weak learning tags that do not subsequently overlap with a salient event will become further suppressed due to the differing effects of α-adrenoreceptors on weak patterns of brain activity. Indeed, *in vitro* evidence suggests that, although β-adrenoreceptor activation facilitates long-term synaptic potentiation, α-adrenoreceptor activation instead drives long-term synaptic depression [75]. Taken together, although many sensory inputs acquire weak learning tags, the subsequent release of NE during salient or emotional moments may help to prevent irrelevant tags from being captured and ensure that only the most behaviorally relevant memory traces survive.

Although the GANE model is centered on NE-related mechanisms, the discrete, or phasic, DA release during a salient stimulus is also well suited to promote the selective preservation of motivationally relevant memories. Supporting this idea, one recent fMRI study in humans adapted the two-phase category threat-conditioning protocol to examine the neural mechanisms that support retroactive memory effects [73]. The results revealed a prominent role of VTA/SN engagement in predicting selective retroactive memory benefits. Thus, together with the GANE model, these empirical data capture temporally discrete mechanisms of memory modulation whereby arousal-induced DA and NE signaling must coincide with activity driven by a strong sensory input. This neuromodulatory framework represents a crucial extension of behavioral tagging models, because it helps to account for the selective memory benefits that have been observed in humans [65–67], and it helps to explain how corelease of DA and NE can constrain the memory preservation process to regions processing important information.

Concluding remarks

It is a longstanding axiom in psychological research that personally meaningful and motivationally relevant experiences are prioritized in long-term memory. We have reviewed emerging models for

Box 4. Implications for affective disorders

Integrative models of tag-and-capture can be leveraged to support memory generalization. Although these mechanisms likely evolved to support adaptive behavior, aberrations in key nodes of these neural circuits can underlie psychiatric disorders. For instance, overengagement of NE and DA systems driving tag-and-capture could contribute to memory disturbances in the context of post-traumatic stress disorder (PTSD). In PTSD, a host of details associated with a negative emotional memory can later serve as reminders, triggering physiological arousal, avoidance, and other related symptoms. A unique feature of intense memories associated with a trauma is that the intrusive memories are often composed of details from the moments leading up to the traumatic event [85]. Behavioral tagging offers a possible mechanism that contributes to both this persistent intrusive cueing and characteristic overgeneralization in PTSD. Ehlers and colleagues [85,86] sought to understand what aspects of a trauma are re-experienced, and found that many intrusive memories consisted of brief sensory details experienced before fully realizing the danger. These types of otherwise mundane sensory cues act as types of warning signals, which conforms to conditioning-based models of PTSD. Conditioning models have been applied to understanding PTSD because cues present at the time of the trauma take on properties characteristic of conditioned stimuli that trigger behavioral responses through association with the worst details of the trauma (i.e., the unconditioned stimulus) [87,88]. That these intrusive details are at least peripherally related to the nature of the trauma itself aligns with the selective nature of memory preservation described in the human studies mentioned previously. One can thus imagine that hyperactivity of NE systems in the context of trauma could cause a generalized enhancement in memory for temporally proximal details that are construed as warning signals of trauma.

These same mechanisms that may underlie the enhancement of PTSD-related symptoms could also be leveraged to treat PTSD. The most widely used evidence-based treatment for many types of affective disorders, including PTSD, is exposure therapy based on Pavlovian extinction. There is clinically relevant evidence that novelty exposure after suboptimal extinction learning can strengthen long-term extinction memory retrieval, such that rats that undergo weak contextual fear-extinction training express less freezing at future tests if they are exposed to a novel open field before or after extinction training within a critical time-window [33,34,40,89,90]. This in principle provides a potentially straightforward way to augment exposure therapy by incorporating novel experiences in the minutes preceding or following a treatment session, which is aligned with behavioral tagging. However, it is possible that tonic hyperarousal symptoms could interfere with the phasic NE responses possibly involved in behavioral tagging effects, thus rendering novelty exposure less effective in affective disorders marked by hyperarousal. There is to date a lack of basic research translating these fear-extinction findings from rodents to humans. We envisage that work translating behavioral tagging to preclinical research in humans will be arriving soon.

Outstanding questions

What is the precise duration of the 'penumbra' generated by strong events? Is the time-window symmetrical for events encoded before and after? Is the duration of the time-window affected by different types of salient events, as well as by different forms of memory supported by different brain regions and different neurotransmitter systems?

Could neurostimulation (e.g., transcranial magnetic stimulation, focused ultrasound) take the place of a strong learning event to retroactively enhance weak memories in humans?

Does enhancement of memory consolidation via temporal proximity to a salient event require the hippocampus, or is it a general mechanism of long-term memory across multiple neural regions? Animal neurobiological investigations on tag-and-capture outside the hippocampal system are so far extremely limited.

How might behavioral tagging mechanisms function differently in older adults, given significant alterations in neurobiological processes that support learning and memory (e.g., catecholamines and glutamate)?

What features of a strong learning event (e.g., context, conceptual overlap, causal relationship) determine whether a recently encoded weak memory will be rescued?

How can findings from behavioral tagging be incorporated as an adjunct to improve outcomes in educational settings? Would 'common' novelty be sufficient to repeatedly bolster suboptimal learning? Do these effects require 'distinct' novel events (unrelated to prior experience) which could be a challenge to sustain over the long term, especially in a classroom environment.

How precise or accurate are episodic memories that have been enhanced via temporal proximity to a strong event? Although research in humans suggests that subjects remember information encoded in the penumbra of a strong event, is there a loss of memory accuracy for peripheral details? Is the precision of memory affected by whether the strong learning event is negatively or positively valenced?

explaining the process of organizing mundane events in memory that only gain significance by virtue of temporal proximity to these more powerful experiences. There is increasing evidence in support of a tag-and-capture model, across rodents and humans, to explain how events at the time of encoding do not necessarily determine the long-term fate of a memory. Much work will be necessary, however, to determine the boundary conditions involved in behavioral tagging effects, and what conditions promote reliable retroactive enhancements in memory (see Outstanding questions). Crucial questions also remain regarding the underlying neurobiology of memory enhancements via temporal proximity to a strong event, including the discrete, complementary, or synergistic roles of DA and NE released in the hippocampus from the VTA or LC [13]. Advances in understanding the underlying neurobiology will be important for better cross-species translation. Further neurobiological and behavioral experimentation is strongly warranted because it may provide easily adaptable and straightforward applications to improve educational performance (Box 2) and enhance the effects of clinical treatment for a host of mental health disorders (Boxes 3 and 4). At a much broader level, understanding how specific experiences are selected for long-term memory consolidation provides essential insights into the adaptive nature of our memory systems.

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Declaration of interests

The authors declare no conflicts of interest.

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