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Decay happens: the role of active forgetting in memory

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Although the biological bases of forgetting remain obscure, the consensus among cognitive psychologists emphasizes interference processes, rejecting decay in accounting for memory loss. In contrast to this view, recent advances in understanding the neurobiology of long-term memory maintenance lead us to propose that a brain-wide well-regulated decay process, occurring mostly during sleep, systematically removes selected memories. Down-regulation of this decay process can increase the life expectancy of a memory and may eventually prevent its loss. Memory interference usually occurs during certain active processing phases, such as encoding and retrieval, and will be stronger in brain areas with minimal sensory integration and less pattern separation. In areas with efficient pattern separation, such as the hippocampus, interference-driven forgetting will be minimal, and, consequently, decay will cause most forgetting.

Current thinking on forgetting

Forgetting of established long-term memory (see Glossary) may indicate that memory is either physically unavailable (that is, memory is lost) or that it is (temporarily) inaccessible. With some exceptions, theories proposed within the domains of experimental and cognitive psychology often emphasize one type of forgetting over the other [1]. Two explanations for actual, non-pathological memory loss have been proposed, one involving decay of aspects of the memory trace, the other involving interference with it.

Current consensus favors the latter of these two explanations for actual memory loss (see Supplementary Material for an abbreviated history of decay theory). It is supposed that interference processes are responsible for much of everyday forgetting and the decay hypothesis has been generally rejected as an explanation for forgetting of long-term memories [1,2]. Interference manifests in two principal ways. First, shortly after initial learning, task-related or task-unrelated mental activity can impair memory, probably by disrupting cellular consolidation processes [3,4]. Second, the expression of established, fully consolidated long-term memory can suffer from interference at the retrieval stage [5]. For example, during retrieval, competing memories may interfere with the recall process. Although it was thought that this type of reproductive or output interference mainly determined whether or not a memory was retrieved [6], recent research on post-retrieval memory plasticity suggests that it could also affect the content of memory [7]. Because retrieval of consolidated memories induces plasticity in the relevant traces, subsequent exposure to new material can then affect the restabilization, or reconsolidation, of the reactivated memory, akin to what can happen after initial learning [8]. This can lead to the incidental incorporation of new material into the reactivated

Glossary

Active forgetting: the idea that, instead of passively disintegrating, memories are actively removed, on the basis of, for example, relevance or recency.
AMPA receptor: an ionotropic glutamate receptor responsible for most excitatory fast neurotransmission in the central nervous system.
Catastrophic interference: neural networks store memories as patterns of activity, such that representations consist of a set of nodes and the weights of their connections. Because neural networks have a finite number of nodes and connections, networks eventually reach saturation and the addition of another activity pattern will disrupt existing memories, leading to catastrophic interference.
Consolidation: cellular (or synaptic) consolidation refers to the processes that stabilize the learning-induced changes in synaptic morphology that represent the biological substrate of memory. Disrupting these processes before completion causes partial or full memory loss. Systems consolidation refers to a reorganization process of the brain systems that support memory, specifically, the hypothesis that some memories that initially require hippocampal involvement no longer do so after some time.
Decay: forgetting due to a gradual loss of the substrate of memory. In his law of disuse, Thorndike posited that, unless regularly used, all memory decays, akin to a muscle that will atrophy if it is not exercised [11]. It has generally been assumed that decay is a passive process.
Episodic memory: memory for what, when, and where. It is a matter of debate whether this form of event memory is uniquely human or not.
Explicit memory: unlike implicit memory, explicit memory is consciously and intentionally retrieved. Explicit memory is either episodic (event memory) or semantic (factual knowledge).
Forgetting: forgetting refers to the absence of expression of previously properly acquired memory in a situation that normally would cause such expression. This can reflect actual memory loss or a failure to retrieve existing memory.
Interference: according to interference accounts of forgetting, mental activity can impact memory by affecting actual memory content or its retrieval. Acquiring a new memory, for example, can retroactively impair existing memory, or existing memory can proactively impair memory acquisition.
Reconsolidation: use (retrieval or reactivation) can induce a transient state of heightened plasticity in long-term memories that resembles the unstable state of new, not yet consolidated memories. In this state, reactivated memories are malleable and can be modified and modulated.
Rapid eye movement (REM) sleep: a sleep state characterized by saccadic eye movements typically occurring in rapid bursts, low to absent muscle tone, and EEG activity consisting mainly of theta and beta waves.
Slow-wave sleep (SWS): also called deep sleep, a sleep state characterized by little to no rapid eye movement and EEG activity consisting mainly of slow, large delta waves.
Long-term potentiation: a long-lasting increase in synaptic potentiation (or synaptic strength) that can be induced with high-frequency (tetanic) stimulation pulses or correlated firing of the post-synaptic and pre-synaptic neuron.
Long-term depression: a long-lasting decrease in synaptic potentiation. In the hippocampus, it can be induced with low-frequency stimulation.

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memory [9] or can in some circumstances decrease memory retention [10].

Able to explain many experimental results, interference theories have pushed aside alternative accounts of forgetting. It was once widely assumed that, unless periodically recalled, long-term memory may 'simply' vanish and fade away over time due to some unspecified biological process [11]. It has long been known that the converse is true: regular use supports long-term memory maintenance. The recently well-documented beneficial effects of testing on retention [12] show that the act of recall promotes long-term memory preservation. It should be noted that frequent recall can also distort and impair memories, with the timing of recall after learning determining whether memory distortions or improvements will occur [13]. Memory in animals also benefits from repeated use [14]. When tested two days after learning to fear a certain spatial context, rats will express fear only towards the training context, but not towards other contexts. Three weeks after training, however, rats fear familiar and novel contexts alike. This change in memory for what place to fear can be prevented by reactivating the fear memory, that is, by re-exposing rats briefly to the training context several times during the three weeks between training and memory test. Rats reminded in this way will fear the spatial context in which training was carried out more so than they fear other contexts, whereas rats that have not been regularly re-exposed to the training context will fear the trained as well as other contexts equally [14]. However, these demonstrations of the effects of use provide only indirect support for the original notion of forgetting by decay and can be interpreted as supporting interference theory. It has not been easy to provide direct evidence of memory loss through disuse.

Notwithstanding the success of interference-based theories to describe the factors that promote forgetting, the truth is that we do not know why or how the brain actually forgets [15]. Our goal in this article is to discuss this age-old debate in the context of recent findings in the study of memory at both the cellular and systems levels, and to put forward a neurobiologically-based framework for memory and forgetting. Recent advances in the study of the cellular/molecular underpinnings of long-term memory persistence, to be discussed in detail below, suggest memory decay as a major forgetting process. They allow us to assign organized memory removal a central role in the everyday forgetting of consolidated memories and in memory organization.

It is generally assumed that forgetting is more a vice (i.e., dysfunction) than a virtue (i.e., constitutive process); however, the idea that forgetting might be beneficial for memory has been frequently expressed [3,4,16–19] and Jorge Luis Borges illustrated its essential role for the human experience in his short story about Funes [20]. As Funes could not forget anything, he could not live a normal life because a sea of unimportant details swamped every moment of awareness. We agree that, without constitutive forgetting, efficient memory would not be possible in the first place.

In our view, decay-driven forgetting is a direct consequence of a memory system that engages in promiscuous encoding. The benefit of such promiscuity is access to a lot of information, so that 'choices' about what to keep and what to delete can be made off-line, mostly during certain sleep phases. The cost is the need for a dedicated forgetting mechanism that removes unwanted information. We propose decay as an active, well-regulated process, in contrast to the standard notion of decay as a passive process akin to radioactive decay. In our view, a well-regulated, dedicated process that systematically removes memories not only is more efficient, but can also be better controlled (up- or down-regulated), depending on specific demands and metaplastic constraints, which allows for greater flexibility and adaptability of the memory system.

The circuit architecture of a given brain system, in particular the nature of its pattern separation capacities (i.e., the degree to which neural representations overlap, with orthogonal patterns being maximally separated) will determine whether interference or decay presents as the predominant forgetting mechanism. In systems with efficient pattern separation, such as the hippocampus, interference will be low or even absent. In systems with little pattern separation, encoding of new traces will necessarily cause interference. We propose that during certain sleep phases, such as slow-wave sleep or rapid eye movement (REM) sleep, when interference by new learning is not a factor, decay happens in all brain systems. In brain areas that exhibit low interference at all times, such as the hippocampus, decay will be the primary mechanism to prevent extensive interference, that is, a state of system failure induced by pattern overload.

Forgetting in multiple memory systems: hippocampus and neocortex

In agreement with most current views (for a review, see [21]), we suppose that what are generally referred to as explicit memories initially consist of two components: content representations largely dependent on neocortical networks and a spatial-contextual representation dependent on the hippocampus that indirectly links, and serves to index, the dispersed neocortical representations. The list- or story-learning tasks usually employed to study forgetting (predominantly interference) in humans are examples of such explicit, episodic memories.

At the heart of our approach is the notion that the circuit architecture of the hippocampus diminishes interference between hippocampal memory traces [22]. Together with CA3, the dentate gyrus allows for orthogonalization of representations, or activity patterns, even in light of very similar inputs as, for example, in the case of highly similar spatial environments [23]. It seems that, in the dentate gyrus specifically, young adult-born granule cells promote pattern separation [24]. Taken together, these mechanisms reduce the overlap of representations in CA1 and CA3 [25]. This being the case, interference cannot account for most non-pathological forms of forgetting of hippocampal memory (Figure. 1a). Instead, we propose that forgetting of the hippocampal component of explicit memory takes the form of loss, or reversal, of learning-induced changes in synaptic potentiation [26], the biological substrate of the decay process envisioned by Thorndike in 1913 [11].

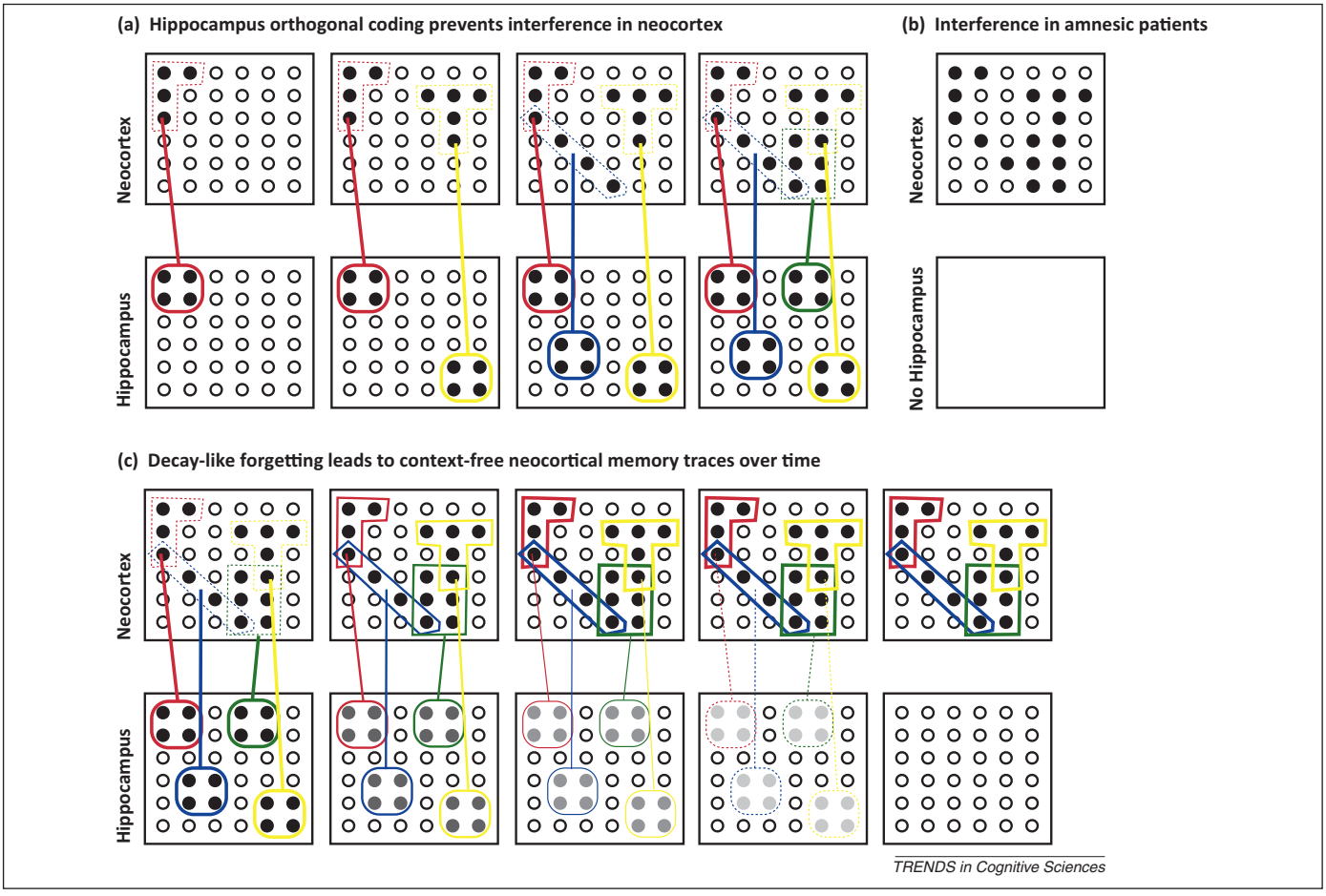

Figure 1. Systems effects of decay-like forgetting in hippocampus. We assume that most memories have hippocampal and extra-hippocampal components. **(a)** The effects of the successive encoding of four memory representations. In the hippocampus, because of efficient pattern separation, even similar inputs will result in non-overlapping representations. This is not the case for most neocortical networks, where the risk of interference by new learning is therefore high. The hippocampal representations, linking to extra-hippocampal memory components, thus allow for reinstantiation of the original pattern despite overlapping extra-hippocampal representations. **(b)** The same input leads to inseparable patterns in neocortical areas when the hippocampal component is missing, as in amnesic patients. **(c)** Once memories are encoded, they are subject to constitutive decay-like forgetting. We show here an example of memory traces that survive this type of forgetting. After encoding, cellular consolidation processes stabilize neocortical memories (this can take from minutes to some hours). During sleep, hippocampal replay reactivates these new memories, which can strengthen extra-hippocampal traces. At the same time, decay-like processes begin to remove hippocampal memories (either during the same or a different sleep phase). Once decay processes remove the hippocampal component, only neocortical components remain, provided that they had been sufficiently strengthened. These memories are thus no longer bound to a spatial-contextual representation hosted by the hippocampus.

We assume that explicit memories always include both a hippocampal and neocortical component, even when memory tasks can in principle be performed without the involvement of the hippocampus. In plastic memory phases, typically termed cellular consolidation and reconsolidation, this hippocampal trace can be modulated, that is, strengthened or weakened, thus increasing or decreasing the speed of its decay. In many, perhaps most, cases of everyday memory, the hippocampal spatial-contextual trace decays rather quickly, that is, within days and weeks, whereas the dispersed neocortical traces can persist, despite the loss of the hippocampal representation of the context initially linking these contents and their neocortical traces.

The regions that represent the varied contents of an everyday memory are dispersed across the neocortex and are only sparsely linked, if at all. This fact creates a problem for the associative learning of arbitrary multimodal associations, which form the basis of episodic or episodic-like memories. This problem led to the suggestion that the hippocampus serves as a hub that links dispersed neocortical representations, allowing for arbitrary associations and, hence, for the formation of episodic memories [27,28]. Given the nature of neocortical coding, the laying down of new neocortical representations can interfere with existing representations, which may result in what has been referred to as catastrophic interference [29,30]. Absent the powerful pattern separation mechanism instantiated in hippocampal circuits, neocortical circuitry suffers from a relative inability to separate one memory from another – which can manifest as memory loss on the behavioral level.

By contrast, the pattern separation properties of the dentate gyrus [24,25] greatly minimize the probability of interference between memories in the hippocampus, even closely related ones [23]. Because the sensory/perceptual content of memory is represented in neocortical structures from the outset, namely, during encoding [31], one way to minimize confusion between similar memories in neocortex is by linking the contents of a specific episodic memory to its unique spatio-temporal context. These contextual memory representations serve as indices that point directly and indirectly to discrete synaptic subpopulations in neocortical areas. Thus, although the neocortex likely

represents memories using overlapping neuronal populations, discrete subsets that represent specific memory contents can be activated by virtue of the hippocampal contextual index, that is, the hippocampal projections to these neurons (Figure 1a). The hippocampal contribution is, therefore, critical for the protection of recently acquired memories, which are presumed to be relatively weak and especially prone to disruption by interference caused by new learning [32]. It is important to bear in mind, of course, that there are multiple synapses separating the hippocampal contextual representation from the highly specific sensory-perceptual details that define a specific episode, and that the indexing process must work its way through many levels.

We assume that the more 'perceptual' (and less 'conceptual') the representations a brain area supports, the stronger the retroactive interference caused by the encoding of new memory traces. That is, in early sensory processing areas, interference will be more pronounced than in areas further along the visual processing stream. For example, recently formed memories will suffer extensive interference from new visual encoding in V1, whereas in perirhinal cortex interference levels will be moderate to low, and in hippocampus interference will be low or generally absent. As sensory signals become more integrated, the risk of interference from new input diminishes because the recruited neuronal subpopulations overlap less and less. This means that perceptual details should be more readily lost and that, as a consequence, forgetting processes are intimately involved in the development of 'schemas', or 'concepts', or 'abstract' knowledge.

Our proposal resembles in some respects the hierarchical-representational perspective on memory organization [33]. Briefly, this view assumes that visual representations are distributed along the visual processing stream, in that early (in humans, posterior) regions, such as V1, represent concrete object features, whereas later (in humans, anterior) regions, such as perirhinal cortex, represent the conjunctions of these. Feature conjunction representations reduce interference probability because they bind together a relatively unique set of distributed representations that together constitute the representation of an object. Rats with perirhinal lesions often present with deficits in object recognition, which are exacerbated by visual experience during the retention interval. Similar to findings with amnesic patients [34], such deficits can be overcome if visual stimulation is reduced in the time between learning and memory testing [35].

Over time, neocortical representations may, with the help of the hippocampus, become sparser and more efficient, the network contents becoming better integrated into existing memory ensembles by adjusting and optimizing synaptic potentiations, probably by virtue of offline hippocampal reactivations (during certain sleep phases or periods of quiet wakefulness). In a sense, this hippocampus-mediated pattern optimization is similar to the idea that the hippocampus functions as a 'teacher' that permits the neocortex to gradually integrate new memories into existing representations, but the proposed mechanisms differ significantly [29]. Once these new representations have been integrated into existing network representations, the hippocampus is no longer essential to retrieval of some aspects of a memory. Although expression of the memory would still benefit from a hippocampal contribution, in that this would, for example, allow situation-specific retrieval, expression in a generic sense might be possible without it (hence the limited effect of hippocampal lesions on expression of gist-like older memories, which occurs in a context-generalized fashion).

Like others, we propose that during learning the hippocampus indirectly provides a kind of pattern separation for potentially overlapping neocortical memory representations (Figure 1a), thereby reducing the probability that interference will impair these not-yet-consolidated new memory patterns [36]. This account finds some support in the finding that less forgetting of existing memories is observed when during learning of new, similar material, these old memories are reactivated, as indicated by hippocampal activity patterns associated with these memories [37]. Indirect support for this assumption comes from studies showing that interference can be reduced in rats when the first and the second list of items are encoded in different spatial contexts [38]. Strong support, however, comes from recent findings on the role of adult neurogenesis in rodents. The dentate gyrus supports continuous neurogenesis in the adult brain [39]. Suppression of neurogenesis in the dentate gyrus impairs spatial learning [40], and the removal of newly generated dentate gyrus neurons disrupts established hippocampus-dependent memories, but has no impact on memories that do not require the hippocampus [41]. Increasing evidence links dentate gyrus neurogenesis to pattern separation [22,42]. In accord with the notion that pattern separation mediated by the dentate gyrus reduces interference, suppression of neurogenesis promotes interference in a hippocampus-dependent olfactory discrimination task [43].

Our proposal accounts for the oft-reported observation that amnesic patients, who suffer from compromised medial-temporal and hippocampal function, present with extensive interference [44]. Instead of viewing this increased interference as the cause of amnesia, we view it as an indirect consequence of the inability to separate overlapping neocortical ensembles (Figure 1a, b). Research in recent years has convincingly demonstrated that memory retention in amnesic patients can be dramatically enhanced when periods of rest and reduced sensory stimulation follow memory encoding; when similar material is learned or when other activity follows memory encoding, amnesic patients forget (and much more so than healthy control subjects). Amnesic patients forget word lists or prose text within minutes after learning, but if learning is followed by up to one hour of inactivity or rest, forgetting is greatly reduced [34,45], and memory acquired in this manner can then even persist for at least a week [4]. These findings strongly suggest that in brains with damaged or compromised hippocampal function interference from new learning can cause extensive forgetting during wake, or active states, possibly by disrupting memory consolidation processes. Importantly, this type of interference mainly affects memories in plastic states, such as those after encoding (consolidation) and after retrieval (reconsolidation). If these memories are allowed to consolidate without

interference, they can last as long as they would in healthy individuals.

A role for decay in everyday forgetting

The findings from these studies with amnesic patients also show that new learning of similar material or interpolated activity does not cause complete amnesia in healthy control subjects, and, depending on the material, forgetting due to interference may even be minimal. For example, in one study [34], retention of a word list dropped from 41% immediately after learning to 19% when new learning was followed by ten minutes of exacting cognitive tasks. When memory for a story was tested, however, one hour of potentially interfering activity only led to a drop from 62% to 50%, whereas retention after one hour without interfering activity was 57%. Interference thus does not always cause meaningful loss for recently acquired memories and it may not be the main factor that causes forgetting in fully consolidated memories [34].

In everyday life, mental activity follows almost all learning, including encoding of similar memories, yet many memories are retained at the end of the day and some even survive for a lifetime. Some memories will be compromised during the day as a consequence of interference caused by new memory encoding or, more generally speaking, stimulus processing, which somehow impairs ongoing cellular consolidation. It remains to be determined, however, how the consolidated remains of the day may be lost, especially for memories that stay dormant or are rarely used, such that they do not enter retrieval-induced states of plasticity, during which they would be vulnerable again to interference processes.

We propose that for many consolidated memories decay-like processes, rather than interference, lead to the active removal of their neurobiological substrate. What is lost in the hippocampus likely includes the spatial-contextual component (Figure 1c), which itself seems to serve as the memory trace that permits the retrieval of memory contents stored elsewhere [46]. Decay-like forgetting in the hippocampus may remove the cues necessary to retrieve extra-hippocampal content. Because this component of a memory also protects the extra-hippocampal content component from interference (Figure 1a), its removal will render extra-hippocampal memory representations more vulnerable to disruption by new learning. In this way, decay of traces in the hippocampus can indirectly promote interference in neocortical sites. As studies with amnesic patients have demonstrated, interference by mental activity exerts its strongest influence on subsequent retention only if it occurs shortly after encoding [4]. Thus, once a memory is consolidated, this type of interference may not be effective in permanently removing it should it turn out to be irrelevant. The type of memory decay described in our proposal provides a mechanism that can remove obsolete consolidated memory traces in many brain areas; in the hippocampus it seems to be the main forgetting mechanism.

We suppose that such decay is an integral feature of memory systems, providing a solution to an adaptive problem that the brain must solve. Often organisms cannot immediately determine the lasting importance of an arbitrary conjunction of events. Prior experience, and thus available knowledge, may guide attention, but frequently an organism cannot know *a priori* whether a long-lasting memory should be formed, and if so, which aspects of an event should be encoded and which aspects ignored. The ability to quickly acquire as much information as possible is highly adaptive, increasing the probability of having captured knowledge that might prove important later. Since significance often becomes evident only after the fact, preserving as much detailed information as possible is important. Having stored this information, some form of post-hoc significance/relevance signaling, such as stress or other emotional reactions, can then lead to the selective strengthening of some of the recently acquired memoires [47]. A good example of the dynamics displayed by such a system is memory for the preceding day's lunch. Most likely, this memory will still be available the following day. However, a week later, or even just a few days later, it will have faded out. Nonetheless, should malaise set in few hours after dinner, memory for what had been eaten might be available longer, and, in the case of severe aversive reactions, this memory may persist for years or even a lifetime, and often in great episodic detail.

Increases in the levels of certain stimulants, such as epinephrine and glucocorticoids, accompany these emotional reactions, which can enhance memory retention, and it has been shown that these substances modulate cellular consolidation processes in several brain regions, such as the hippocampus and amygdala [48]. Affecting expression of AMPA receptors and thereby synaptic potentiation, this modulation can regulate synaptic strength [49]. These post-acquisition modulatory signals can also regulate metaplasticity, affecting the extent to which synapses will undergo plastic alterations, such as increases or reductions of synaptic strength, in the future [50]. Similar regulatory processes can also follow memory use, as has been demonstrated in several studies on the reconsolidation effect [8]. This kind of promiscuous memory formation, left unchecked, would saturate the system fairly quickly, compromising memory function. Automated forgetting in the form of potentiation reduction would be a simple yet efficient method to remove mnemonic waste in a system in which interference cannot effectively and systematically eliminate memories deemed less relevant. Those memories that were strengthened after formation will better withstand the forces of forgetting (i.e., decay, as well as interference), and thus, eventually, only those memories will remain. In addition, metaplastic modulations can render memories less likely to lose potentiation by promoting processes that increase potentiation relatively more than processes that decrease it [51].

It seems that the best time for this form of well-organized memory removal of consolidated memories is during sleep, when the brain is not engaged in the encoding of new memories. The notion that systematic forgetting is an important function of sleep is not new. It has been proposed that reverse learning occurs during REM sleep in order to remove unnecessary memories acquired during the day [17]. According to the homeostatic synaptic scaling account of sleep [18], synaptic potentiation (stemming from daytime learning) is down-regulated brain-wide during slow-wave sleep. This rescaling process, which is supposed to

reduce overall energy requirements, preserves relative synaptic weight differences and may eventually lead to forgetting because downscaling may effectively silence, or even remove, synapses that are already weakly potentiated.

The suggestion that forgetting occurs during sleep does not run counter to the many demonstrations of memory enhancing effects of sleep [52]. First, these beneficial mnemonic effects could reflect the selective protection of retained memories against the effects of systematic forgetting, whereas other, unprotected, memories are lost. This view finds some support in recent studies that indirectly suggest the occurrence of forgetting in sleep. Two studies have shown that sleep can strengthen certain, relevant memories, whereas no such benefits are observed for memories deemed irrelevant [53,54]. A study in human infants provides stronger evidence, showing that a nap promotes rule generalization in artificial language learning [55]. This finding suggests that contextual elements were forgotten during sleep, permitting abstraction. Second, it is possible that different sleep phases will selectively promote specific types of plasticity. This idea finds some support in recent findings which suggest that synaptic downscaling occurs preferentially in REM sleep [56], whereas selective synaptic potentiation characterizes slow-wave sleep instead [57]. Thus, the numerous demonstrations of the beneficial effects of sleep on memory retention in species as diverse as honeybees [58], rats [59], and humans [60] may reflect the net benefit of processes that eliminate memories and processes that strengthen them. Memory-specific plasticity parameters, set by the type of post-acquisition signaling discussed above, determine how much decay and how much strengthening will take place during certain sleep phases.

Possible molecular pathways of decay-like forgetting

Recent studies on long-term memory maintenance support the notion that hippocampal traces can decay over time. These studies established the constitutively active, atypical protein kinase C isoform M-zeta (PKMζ) as both necessary and sufficient for maintaining long-term potentiation and for sustaining long-term memory in various tasks and brain regions [61]. PKMζ is synthesized upon induction of LTP or during formation of memory [62]. After translation, PKMζ is phosphorylated and then stays constitutively active [63]. Transiently inhibiting PKMζ activity impairs and often abolishes fully established memories [64], even those that are several months old [65]. On the other hand, overexpression of the kinase can enhance weak long-term memories [66].

Two of these studies on the role of PKMζ in long-term memory maintenance are of particular importance for our proposal regarding forgetting by decay. In these, rats acquired non-reinforced long-term object location memory, which is known to depend on the hippocampus [67,68]. The first study established that maintaining long-term memory of object location requires continuous activity of PKMζ, at both recent (1 day) and more remote (6 days) time points. Despite dependency on PKMζ, however, object location memory is lost sometime between 7 and 35 days after training [69]. The second study asked how PKMζ maintains these object location memories and showed that it does so by regulating the trafficking of GluA2-containing AMPA receptors in the dorsal hippocampus [70]. These data support the conclusion that PKMζ prevents the internalization of these receptors. In that paper, it was also shown that, for auditory fear conditioning, the strength of the freezing response correlates linearly with the amount of GluA2-AMPARs in post-synaptic densities in the basolateral nucleus of the amygdala. The smaller the amount of GluA2-AMPARs in these post-synaptic densities, the less memory was expressed. Taken together, these two studies suggest that the loss of object location memory observed between 7 and 35 days after acquisition likely reflects the loss of GluA2-containing AMPA receptors in the relevant synapses in the dorsal hippocampus. This loss of the substrate that supports memory over time is reminiscent of the idea articulated in Thorndike's law of disuse – that synaptic connections weaken over time when memory is not exercised [11].

Recent findings demonstrating preserved LTP and long-term memory formation in developmental, as well as inducible, PKMζ knockout mice [71,72] seem to question whether PKMζ is essential for long-term memory maintenance, as we claim here. These findings are quite interesting, as they likely provide evidence for evolutionarily conserved compensatory mechanisms [73], similar to what has been observed in mutant mice in which αCaMKII autophosphorylation was deficient [74]. Although αCaMKII autophosphorylation is necessary in wild type animals to form memories, mutant mice were able to compensate by using different mechanisms. In the case of PKMζ, another atypical PKC isoform, PKCι/λ, can functionally compensate when PKMζ is absent [75,76]. This is not surprising, as the nucleotide sequences of the full-length isoforms, such as PKCζ and PKCι/λ, are almost identical: both have the same pseudosubstrate sequence, such that ZIP, the peptide used in many studies to inhibit PKMζ, also inhibits PKCι/λ [77]. Proteolysis can transform activated PKC isoforms into constitutively active PKM forms [78]. In addition, like PKMζ, PKCι/λ is also activated during LTP [79]. Thus, we suggest that, in the absence of PKMζ, PKCι/λ may assume the essential functional roles of PKMζ, such as maintaining memory by regulating GluA2-dependent AMPA receptor trafficking.

There are several possible mechanisms that naturally implement decay [80,81], although it remains to be seen which of these in fact occur. We mention here only two of these. First, it is known that learning can lead to synthesis of PKMζ within minutes after the event [82]. Memory reactivation or strengthening (by post-acquisition modulations) could maintain PKMζ upregulation, thereby sustaining the AMPA receptors critical to the maintenance of the memory. If the memory is not reactivated or strengthened, no new PKMζ would be supplied, and when existing PKMζ is degraded, internalization of GluA2-containing AMPA receptors will set in, leading to the loss of potentiation and thus memory. Second, reductions of synaptic strength in the form of LTD and depotentation require GluN2b-containing NMDA receptors [83]. A signal to internalize GluA2-containing AMPA receptors might thus come in the form of an LTD-like stimulus from GluN2B-containing NMDA receptors. LTD leads to degradation of PKMζ [84], and PKMζ loss leads to the loss of memory. In order to

activate NMDA receptors, action potentials are not necessary [85]. Glutamate is released in small amounts even during basal states and, when it binds to NMDA receptors, a small amount of calcium can enter the cell. For this type of calcium channeling, the magnesium block does not need to be removed from the receptor [86]. This calcium influx might resemble an LTD- or depotentiation-like signal, leading to the internalization of GluA2-containing AMPA receptors. The finding that blocking NMDA receptors during a five-day retention interval prevents forgetting of spatial memory in rats [87] lends support to this account of the role of NMDA receptors in forgetting. Owing to the role of the NMDA receptor in learning and memory formation, this result has been interpreted as supportive of interference-based accounts of forgetting [16] because blocking NMDA receptors during the retention interval likely blocks new learning. However, because the drugs used in this study (CPP and AP5) block all NMDA receptors, irrespective of subtype composition, it is also possible that memory was preserved because inactivating GluN2b-NMDA receptors reduced LTD or depotentiation, which prevented memory decay.

Other mechanisms that implement decay are certainly possible [81] and most likely several will be involved; we mention these two to illustrate some possible ways the form of decay we propose here could emerge. We assume, however, that decay-like forgetting will depend on actively regulating GluA2-AMPAR contents at post-synaptic sites and that the NMDA receptor will play a metaplastic role in determining the degree to which memories will be subject to decay. Such regulation is necessary, as those memories deemed significant will need to be protected from the constant force of forgetting. This might include, for example, memories accompanied by strong emotional reactions, novelty signals, or memories that reflect recurring events. GluN2b-containing NMDARs may be involved in these regulatory mechanisms, having been linked in previous research to metaplastic processes. For example, they are necessary to induce reconsolidation after retrieval [88]. More importantly, it seems that strong memories, that is, memories that are not quickly forgotten, are characterized by reduced GluN2b-NMDAR expression [89,90]. It is thus possible that resistance to forgetting could be inversely related to the presence of GluN2b-NMDAR at postsynaptic sites. This suggestion is similar to the notion that the ratio of GluN2A- to GluN2b-containing NMDA receptors determines the direction of synaptic plasticity [91] – a stronger GluN2b than GluN2A expression thus favors LTD over LTP processes and vice versa.

Our proposal views forgetting of consolidated long-term memory as an active process that systematically removes learning-induced changes in synaptic potentiation over time. Recent data from *Drosophila melanogaster* provide strong support for these suggestions [92]. Here, olfactory memory requires the dDa1 dopamine receptor in the mushroom body. Surprisingly, another type of dopamine receptor, DAMB, is necessary for forgetting. In mutant flies that did not express the DAMB receptor, forgetting of labile

Box 1. Predictions

In our model of forgetting, the hippocampal component of most memories is ultimately lost, such that long-term human memories will generally be of a semantic rather than an episodic nature (Figure 1c). This episodic-to-semantic shift over time is very similar, if not identical, to the context generalization phenomenon, that is, the tendency to express behavior that once was specific to the learning context in other contexts over time. In animals, such generalization is often studied using contextual fear conditioning, as briefly alluded to above. Approximately 10-15 days after learning, animals that shortly after training only feared the training context now fear any context remotely resembling the original one. According to our model, this generalization results from forgetting of the hippocampal contextual component of the memory, such that only elemental stimuli represented outside the hippocampus remain to trigger the fear response, and these elemental stimuli (e.g., the metal grid on the floor, the shape of the box, etc.) are common to many contexts. Along with others [93], we thus predict that such generalization would not be observed when the hippocampal trace is artificially maintained during the retention interval by interfering with normal decay processes.

This approach can be extended to other memory phenomena. For example, conditioned responses, such as fear to a tone acquired during auditory fear conditioning, can be extinguished by repeatedly presenting the conditioned stimulus alone (i.e., presenting the tone without the reinforcer). As a consequence of this extinction training, the conditioned stimulus no longer elicits the conditioned response. However, the conditioned response can return some days after the extinction training. It remains unclear what processes mediate this spontaneous recovery, but one possibility is that the extinction memory could be lost over time through the action of decay-like forgetting processes as outlined above. Because extinction training does not literally erase the conditioning memory it inhibits [94], the conditioned response would return when the extinction event is forgotten. Consequently, spontaneous recovery could be prevented by artificially maintaining the extinction memory. This possibility remains to be tested.

If this type of forgetting represents a well-regulated feature of the brain, then perhaps it could play a part in certain pathologies. One obvious candidate would be Alzheimer's disease (AD). Whereas later stages of AD are characterized not only by devastating memory loss but also by the inability to form new memories, in earlier stages of the disease memories can still be formed, even though they are rather quickly forgotten. Accelerated forgetting has also been found in a mouse model of AD [95]. Such findings are generally seen as indicating impaired memory consolidation processes, but it is possible that deregulated forgetting plays a role, as well. Findings showing that beta-amyloid promotes removal of postsynaptic AMPA receptors by engaging pathways involved in long-term depression [96] suggest that forgetting processes as described above may be involved in AD pathology. If forgetting is indeed a well-regulated process, and deregulated forgetting plays a part in AD, then the pathways involving forgetting may offer novel pharmacological targets for clinical interventions to alleviate some symptoms of the disease.

Our model assumes that hippocampal circuit architecture prevents interference by virtue of pattern separation. Several lines of evidence suggest that pattern separation is largely a function of the dentate gyrus. The dentate gyrus is one of the two currently identified areas in which neurogenesis occurs in the adult brain [97]. As others before us, we propose that neurogenesis is involved in pattern separation and thus predict that the rate of neurogenesis in the dentate gyrus will be inversely correlated with the degree of interference in the hippocampus [98–100]. Thus, the less neurogenesis, the more new learning will interfere with memory traces in the hippocampus. We further predict that reduction of neurogenesis will lead to interference in both hippocampus-dependent and hippocampus-independent tasks, based on our assumption that the hippocampus provides pattern separation for extra-hippocampal areas.

Box 2. Questions for future research

- What distinguishes strong, long-lasting consolidated memories from weak, short-lasting consolidated memories on the molecular and the systems levels? Are strong memories distinguished by down-regulation of the molecular pathways involved in decay?
- Is decay of the same speed in all brain areas?
- Does suppression of sleep decelerate decay-dependent forgetting, as predicted by our model?
- Do forgetting and memory consolidation occur during different sleep phases or could both processes occur at the same time?
- Does suppression of decay in the hippocampus lead to eventual catastrophic interference?

long-term memories was absent; stronger memories required additional activation of the dopaminergic pathway. In *Drosophila*, forgetting appears to be an organized process that depends on activation of a specific pathway that removes long-term memories. Although it remains to be demonstrated to what extent these processes found in an invertebrate organism translate to mammalian brains, it is worth noting (i) that the same receptor class involved in learning is also involved in forgetting, which is similar to the role we propose for the NMDA receptor, and (ii) that the mushroom body, at least functionally, has many similarities to the mammalian hippocampus.

Concluding remarks

In this article, we have suggested that decay-like forgetting is a well-organized neuronal process that systematically removes memories from the hippocampus over time, perhaps preferentially during sleep. This type of forgetting is essential to maintain overall system functionality. Because most of the memories automatically formed during the day are irrelevant, such forgetting will ensure that most of these unwanted and unneeded memories are removed. Understanding decay-like forgetting as a normal and regulated component of memory offers alternative, simpler, and testable explanations for several memory phenomena, and perhaps even contributes to a better understanding of some disorders, such as Alzheimer's Disease (Box 1). Recent advances in discovering the molecular mechanisms involved in long-term memory maintenance will provide efficient tools to study these predictions (see also Box 2).

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tics.2013.01.001.

References

1 Roediger, H.L., III *et al.* (2010) Forgetting: preliminary considerations. In *Forgetting* (Della Salla, S., ed.), pp. 1–22, Psychology Press
2 Neath, I. and Brown, G.D.A. (2012) Arguments against memory trace decay: a SIMPLE account of Baddeley and Scott. *Front. Psychol.* 3, 35
3 Wixted, J.T. (2005) A theory about why we forget what we once knew. *Curr. Dir. Psychol. Sci.* 14, 6–9
4 Dewar, M. *et al.* (2012) Brief wakeful resting boosts new memories over the long term. *Psychol. Sci.* 23, 955–960
5 Skaggs, E.B. (1933) A discussion on the temporal point of interpolation and degree of retroactive inhibition. *J. Comp. Psychol.* 16, 411–414
6 Dewar, M.T. *et al.* (2007) Forgetting due to retroactive interference: a fusion of Müller and Pilzecker's (1900) early insights into everyday forgetting and recent research on anterograde amnesia. *Cortex* 43, 616–634
7 Hardt, O. *et al.* (2010) A bridge over troubled water: reconsolidation as a link between cognitive and neuroscientific memory research traditions. *Annu. Rev. Psychol.* 61, 141–167
8 Nader, K. and Hardt, O. (2009) A single standard for memory: the case for reconsolidation. *Nat. Rev. Neurosci.* 10, 224–234
9 Hupbach, A. *et al.* (2007) Reconsolidation of episodic memories: a subtle reminder triggers integration of new information. *Learn. Mem.* 14, 47–53
10 Walker, M.P. *et al.* (2003) Dissociable stages of human memory consolidation and reconsolidation. *Nature* 425, 616–620
11 Thorndike, E.L. (1913) *Educational Psychology*, Teachers College, Columbia University
12 Roediger, H.L.H. and Karpicke, J.D.J. (2006) Test-enhanced learning: taking memory tests improves long-term retention. *Psychol. Sci.* 17, 249–255
13 Wheeler, M.A. and Roediger, H.L. (1992) Disparate effects of repeated testing: Reconciling Ballard's (1913) and Bartlett's (1932) results. *Psychol. Sci.* 3, 240–245
14 de Oliveira Alvares, L. *et al.* (2011) Periodically reactivated context memory retains its precision and dependence on the hippocampus. *Hippocampus* 22, 1092–1095
15 Wixted, J.T. (2004) The psychology and neuroscience of forgetting. *Annu. Rev. Psychol.* 55, 235–269
16 Rosenzweig, E.S. *et al.* (2002) Making room for new memories. *Nat. Neurosci.* 5, 6–8
17 Crick, F. and Mitchison, G. (1983) The function of dream sleep. *Nature* 304, 111–114
18 Tononi, G. and Cirelli, C. (2003) Sleep and synaptic homeostasis: a hypothesis. *Brain Res. Bull.* 62, 143–150
19 James, W. (1892) *Textbook of Psychology*, Macmillan
20 Borges, J.L. (1998) *Collected Fictions*, Penguin
21 Nadel, L. and Hardt, O. (2011) Update on memory systems and processes. *Neuropsychopharmacology* 36, 251–273
22 Yassa, M.A. and Stark, C.E.L. (2011) Pattern separation in the hippocampus. *Trends Neurosci.* 34, 515–525
23 Leutgeb, J.K. *et al.* (2007) Pattern separation in the dentate gyrus and CA3 of the hippocampus. *Science* 315, 961–966
24 Nakashiba, T. *et al.* (2012) Young dentate granule cells mediate pattern separation, whereas old granule cells facilitate pattern completion. *Cell* 149, 188–201
25 McHugh, T.J. *et al.* (2007) Dentate gyrus NMDA receptors mediate rapid pattern separation in the hippocampal network. *Science* 317, 94–99
26 Tsumoto, T. (1993) Long-term depression in cerebral cortex: a possible substrate of 'forgetting' that should not be forgotten. *Neurosci. Res.* 16, 263–270
27 Marr, D. (1971) Simple memory: a theory for archicortex. *Philos. Trans. R. Soc. Lond. B: Biol. Sci.* 262, 23–81
28 Teyler, T.J. and Rudy, J.W. (2007) The hippocampal indexing theory and episodic memory: Updating the index. *Hippocampus* 17, 1158–1169
29 McClelland, J.L. *et al.* (1995) Why there are complementary learning systems in the hippocampus and neocortex: insights from the successes and failures of connectionist models of learning and memory. *Psychol. Rev.* 102, 419–457
30 McCloskey, M. and Cohen, N.J. (1989) Catastrophic interference in connectionist networks: the sequential learning problem. In *The Psychology of Learning and Motivation* (Bower, G.H., ed.), pp. 109–165, Academic Press
31 Danker, J.F. and Anderson, J.R. (2010) The ghosts of brain states past: Remembering reactivates the brain regions engaged during encoding. *Psychol. Bull.* 136, 87–102

32 Dudai, Y. (2004) The neurobiology of consolidations, or, how stable is the engram? *Annu. Rev. Psychol.* 55, 51–86
33 Saksida, L.M. and Bussey, T.J. (2010) The representational-hierarchical view of amnesia: translation from animal to human. *Neuropsychologia* 48, 2370–2384
34 Cowan, N. *et al.* (2004) Verbal recall in amnesiacs under conditions of diminished retroactive interference. *Brain* 127, 825–834
35 McTighe, S.M. *et al.* (2010) Paradoxical false memory for objects after brain damage. *Science* 330, 1408–1410
36 Becker, S. and Wojtowicz, J.M. (2007) A model of hippocampal neurogenesis in memory and mood disorders. *Trends Cogn. Sci.* 11, 70–76
37 Kuhl, B.A. *et al.* (2010) Resistance to forgetting associated with hippocampus-mediated reactivation during new learning. *Nat. Neurosci.* 13, 501–506
38 Butterly, D.A. *et al.* (2012) Hippocampal context processing is critical for interference free recall of odor memories in rats. *Hippocampus* 22, 906–913
39 Lledo, P-M. *et al.* (2006) Adult neurogenesis and functional plasticity in neuronal circuits. *Nat. Rev. Neurosci.* 7, 179–193
40 Zhang, C-L. *et al.* (2008) A role for adult TLX-positive neural stem cells in learning and behaviour. *Nature* 451, 1004–1007
41 Arruda-Carvalho, M. *et al.* (2011) Posttraining ablation of adult-generated neurons degrades previously acquired memories. *J. Neurosci.* 31, 15113–15127
42 Sahay, A. *et al.* (2011) Increasing adult hippocampal neurogenesis is sufficient to improve pattern separation. *Nature* 472, 466–470
43 Luu, P. *et al.* (2012) The role of adult hippocampal neurogenesis in reducing interference. *Behav. Neurosci.* 126, 381–391
44 Warrington, E.K. and Weiskrantz, L. (1978) Further analysis of the prior learning effect in amnesic patients. *Neuropsychologia* 16, 169–177
45 Dewar, M. *et al.* (2009) Delaying interference enhances memory consolidation in amnesic patients. *Neuropsychology* 23, 627–634
46 Hardt, O. *et al.* (2009) Storage or retrieval deficit: the yin and yang of amnesia. *Learn. Mem.* 16, 224–230
47 Roozendaal, B. and McGaugh, J.L. (2011) Memory modulation. *Behav. Neurosci.* 125, 797–824
48 McGaugh, J.L. and Roozendaal, B. (2009) Drug enhancement of memory consolidation: historical perspective and neurobiological implications. *Psychopharmacology* 202, 3–14
49 Krugers, H.J. *et al.* (2010) Stress hormones and AMPA receptor trafficking in synaptic plasticity and memory. *Nat. Rev. Neurosci.* 11, 675–681
50 Kim, J.J. and Yoon, K.S. (1998) Stress: metaplastic effects in the hippocampus. *Trends Neurosci.* 21, 505–509
51 Pérez-Otaño, I. and Ehlers, M.D. (2005) Homeostatic plasticity and NMDA receptor trafficking. *Trends Neurosci.* 28, 229–238
52 Diekelmann, S. and Born, J. (2010) The memory function of sleep. *Nat. Rev. Neurosci.* 11, 114–126
53 Rauchs, G. *et al.* (2011) Sleep contributes to the strengthening of some memories over others, depending on hippocampal activity at learning. *J. Neurosci.* 31, 2563–2568
54 Wilhelm, I. *et al.* (2011) Sleep selectively enhances memory expected to be of future relevance. *J. Neurosci.* 31, 1563–1569
55 Gómez, R.L. *et al.* (2006) Naps promote abstraction in language-learning infants. *Psychol. Sci.* 17, 670–674
56 Grosmark, A.D.A. *et al.* (2012) REM sleep reorganizes hippocampal excitability. *Neuron* 75, 1001–1007
57 Chauvette, S.S. *et al.* (2012) Sleep oscillations in the thalamocortical system induce long-term neuronal plasticity. *Neuron* 75, 1105–1113
58 Beyaert, L. *et al.* (2012) Honeybees consolidate navigation memory during sleep. *J. Exp. Biol.* 215, 3981–3988
59 Inostroza, M. *et al.* (2013) Sleep-dependency of episodic-like memory consolidation in rats. *Behav. Brain Res.* 237, 15–22
60 Axmacher, N. *et al.* (2008) Ripples in the medial temporal lobe are relevant for human memory consolidation. *Brain* 131, 1806–1817
61 Sacktor, T.C. (2011) How does PKMζ maintain long-term memory? *Nat. Rev. Neurosci.* 12, 9–15
62 Ling, D.S.F. *et al.* (2002) Protein kinase Mζ is necessary and sufficient for LTP maintenance. *Nat. Neurosci.* 5, 295–296
63 Yao, Y. *et al.* (2013) Matching biochemical and functional efficacies confirm ZIP as a potent competitive inhibitor of PKMζ in neurons. *Neuropharmacology* 64, 37–44
64 Serrano, P. *et al.* (2008) PKMζ maintains spatial, instrumental, and classically conditioned long-term memories. *PLoS Biol.* 6, e318
65 Shema, R. *et al.* (2009) Boundary conditions for the maintenance of memory by PKM in neocortex. *Learn. Mem.* 16, 122–128
66 Shema, R. *et al.* (2011) Enhancement of consolidated long-term memory by overexpression of protein kinase Mzeta in the neocortex. *Science* 331, 1207–1210
67 Hawk, J.D. *et al.* (2011) Post-training intrahippocampal inhibition of class I histone deacetylases enhances long-term object-location memory. *Learn. Mem.* 18, 367–370
68 Roozendaal, B. *et al.* (2010) Membrane-associated glucocorticoid activity is necessary for modulation of long-term memory via chromatin modification. *J. Neurosci.* 30, 5037–5046
69 Hardt, O. *et al.* (2010) PKMzeta maintains 1-day- and 6-day-old long-term object location but not object identity memory in dorsal hippocampus. *Hippocampus* 20, 691–695
70 Migues, P.V. *et al.* (2010) PKMzeta maintains memories by regulating GluR2-dependent AMPA receptor trafficking. *Nature* 13, 630–634
71 Volk, L.J. *et al.* (2013) PKM-ζ is not required for hippocampal synaptic plasticity, learning and memory. *Nature* 493, 420–423
72 Lee, A.M. *et al.* (2013) Prkcz null mice show normal learning and memory. *Nature* 493, 416–419
73 Frankland, P.W. and Josselyn, S.A. (2013) Neuroscience: Memory and the single molecule. *Nature* 493, 312–313
74 Radwanska, K. *et al.* (2011) Mechanism for long-term memory formation when synaptic strengthening is impaired. *Proc. Natl. Acad. Sci. U.S.A.* 108, 18471–18475
75 Kishikawa, M. *et al.* (2008) aPKC enables development of zonula adherens by antagonizing centripetal contraction of the circumferential actomyosin cables. *J. Cell Sci.* 121, 2481–2492
76 Rodriguez, E.M. *et al.* (2009) Atypical protein kinase C activity is required for extracellular matrix degradation and invasion by Src-transformed cells. *J. Cell. Physiol.* 221, 171–182
77 Sacktor, T.C. (2012) Memory maintenance by PKMζ - an evolutionary perspective. *Mol. Brain* 5, 31
78 Inoue, M. *et al.* (1977) Studies on a cyclic nucleotide-independent protein kinase and its proenzyme in mammalian tissues. II. Proenzyme and its activation by calcium-dependent protease from rat brain. *J. Biol. Chem.* 252, 7610–7616
79 Kelly, M.T. *et al.* (2007) Regulation of protein kinase Mzeta synthesis by multiple kinases in long-term potentiation. *J. Neurosci.* 27, 3439–3444
80 Silva, A.J. and Josselyn, S.A. (2002) The molecules of forgetfulness. *Nature* 418, 929–930
81 Genoux, D.D. *et al.* (2002) Protein phosphatase 1 is a molecular constraint on learning and memory. *Nature* 418, 970–975
82 Osten, P. *et al.* (1996) Protein synthesis-dependent formation of protein kinase Mzeta in long-term potentiation. *J. Neurosci.* 16, 2444–2451
83 Dalton, G.L. *et al.* (2012) NMDA GluN2A and GluN2B receptors play separate roles in the induction of LTP and LTD in the amygdala and in the acquisition and extinction of conditioned fear. *Neuropharmacology* 62, 797–806
84 Hrabetova, S. and Sacktor, T.C. (2001) Transient translocation of conventional protein kinase C isoforms and persistent downregulation of atypical protein kinase Mzeta in long-term depression. *Brain Res. Mol. Brain Res.* 95, 146–152
85 Espinosa, F. and Kavalali, E.T. (2008) NMDA Receptor Activation by Spontaneous Glutamatergic Neurotransmission. *J. Neurophysiol.* 101, 2290–2296
86 Lüscher, C. and Malenka, R.C. (2012) NMDA Receptor-Dependent Long-Term Potentiation and Long-Term Depression (LTP/LTD). *Cold Spring Harb. Perspect. Biol.* 4, http://dx.doi.org/10.1101/cshperspect.a005710
87 Villarreal, D.M. *et al.* (2002) NMDA receptor antagonists sustain LTP and spatial memory: active processes mediate LTP decay. *Nat. Neurosci.* 5, 48–52
88 Lee, J.L.C. and Everitt, B.J. (2008) Appetitive memory reconsolidation depends upon NMDA receptor-mediated neurotransmission. *Neurobiol. Learn. Mem.* 90, 147–154
89 Zinebi, F. *et al.* (2003) NMDA currents and receptor protein are downregulated in the amygdala during maintenance of fear memory. *J. Neurosci.* 23, 10283–10291

90 Wang, S-H. *et al.* (2009) Cellular and systems mechanisms of memory strength as a constraint on auditory fear reconsolidation. *Nat. Neurosci.* 12, 905–912
91 Yashiro, K. and Philpot, B.D. (2008) Regulation of NMDA receptor subunit expression and its implications for LTD, LTP, and metaplasticity. *Neuropharmacology* 55, 1081–1094
92 Berry, J.A.J. *et al.* (2012) Dopamine is required for learning and forgetting in Drosophila. *Neuron* 74, 530–542
93 Biedenkapp, J.C. and Rudy, J.W. (2007) Context preexposure prevents forgetting of a contextual fear memory: Implication for regional changes in brain activation patterns associated with recent and remote memory tests. *Learn. Mem.* 14, 200–203
94 Bouton, M.E. *et al.* (2006) Contextual and temporal modulation of extinction: behavioral and biological mechanisms. *Biol. Psychiatry* 60, 352–360
95 Daumas, S. *et al.* (2008) Faster forgetting contributes to impaired spatial memory in the PDAPP mouse: deficit in memory retrieval associated with increased sensitivity to interference? *Learn. Mem.* 15, 625–632
96 Hsieh, H. *et al.* (2006) AMPAR removal underlies aβ-induced synaptic depression and dendritic spine loss. *Neuron* 52, 831–843
97 Zhao, C. *et al.* (2008) Mechanisms and functional implications of adult neurogenesis. *Cell* 132, 645–660
98 Winocur, G. *et al.* (2012) Adult hippocampal neurogenesis and memory interference. *Behav. Brain Res.* 227, 464–469
99 Appleby, P.A. and Wiskott, L. (2009) Additive neurogenesis as a strategy for avoiding interference in a sparsely-coding dentate gyrus. *Network* 20, 137–161
100 Becker, S. (2005) A computational principle for hippocampal learning and neurogenesis. *Hippocampus* 15, 722–738