Making memories last: the synaptic tagging and capture hypothesis

Roger L. Redondo[*‡] *and Richard G. M. Morris*[*]

Abstract | The synaptic tagging and capture hypothesis of protein synthesis-dependent long-term potentiation asserts that the induction of synaptic potentiation creates only the potential for a lasting change in synaptic efficacy, but not the commitment to such a change. Other neural activity, before or after induction, can also determine whether persistent change occurs. Recent findings, leading us to revise the original hypothesis, indicate that the induction of a local, synapse-specific 'tagged' state and the expression of long-term potentiation are dissociable. Additional observations suggest that there are major differences in the mechanisms of functional and structural plasticity. These advances call for a revised theory that incorporates the specific molecular and structural processes involved. Addressing the physiological relevance of previous *in vitro* findings, new behavioural studies have experimentally translated the hypothesis to learning and the consolidation of newly formed memories.

Engram
The concept, first introduced in the nineteenth century, to define the physical entity in the brain that stores information over time and later enables memories to be expressed.

Memory encoding
The physiological process by which patterns of neural activity result in the creation (that is, encoding) of a state somewhere in the brain that can be characterized as an engram.

*Laboratory for Cognitive Neuroscience, Centre for Cognitive and Neural Systems, The University of Edinburgh, 1 George Square, Edinburgh EH8 9JZ, UK.
‡Present address: Picower Institute for Learning and Memory, Massachusetts Institute of Technology (MIT), 43 Vassar Street, Cambridge, Massachusetts, 02139, USA.
Correspondence to R.G.M.M.
e-mail:
R.G.M.Morris@ed.ac.uk
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Memories are made as we go about our daily life: what event has happened, with whom, where and when. Most memories fade, whereas others last. What determines whether we remember or not? A longstanding theory is that the physical substrate of 'engrams' or 'traces' for long-term memory (LTM) is an alteration in the efficacy of synapses within relevant neural networks[1–4]. Different types of learning (declarative, spatial, emotional, procedural and so on) are mediated by distinct brain networks. Some of these networks involve a distributed associative storage system in which specific memory traces are not stored within individual neurons, still less at a single synaptic location, but are distributed in an overlapping manner across multiple neurons and synapses[5].

There are many determinants of the persistence of such engrams. However, a common thread is that memory encoding and initial storage are followed by a 'consolidation' process that, if activated, enables traces to become stabilized, although not necessarily immutable[6–9]. There are both cellular and systems components of memory consolidation, and of the memory-updating process called 'reconsolidation'[7,8]. The systems component involves dynamic interactions between, for example, network activation of hippocampal and neocortical neurons in the creation or updating of lasting engrams. The neurobiological mechanisms underlying the determinants of systems consolidation (which include the passage of time[10,11] and prior knowledge[12]) are gradually being revealed[13]. The cellular component concerns the more immediate determinants of synaptic strength and persistence that are triggered within individual neurons in the minutes and hours after memory encoding. The synaptic tagging and capture (STC) hypothesis, of which we here provide a major revision, focuses mainly on the cellular component of consolidation.

Various predictions derive from this dual framework, one of which is that the temporal persistence of synaptic potentiation (or depression) must be crucial for the persistence of memory[14]. Excitatory, glutamatergic synapses in the hippocampus play a key part in learning and memory, and their activation triggers diverse intracellular signal transduction cascades and somatic and dendritic protein synthesis. Collectively, these processes alter synapses biophysically and structurally, stabilizing a new (possibly temporary) level of synaptic strength. The stabilization process enables synapses to retain their strength for long periods despite continual turnover of their constituent proteins.

There is good evidence for this way of thinking about the consolidation of synaptically mediated memory, but we argue below that it overlooks a key aspect of memory processing. Specifically, stabilization also depends upon the recent history of neuronal activity and immediate future activity, both of which can be independent of neural activity that occurs during or is triggered by encoding itself. This extension of the time window that

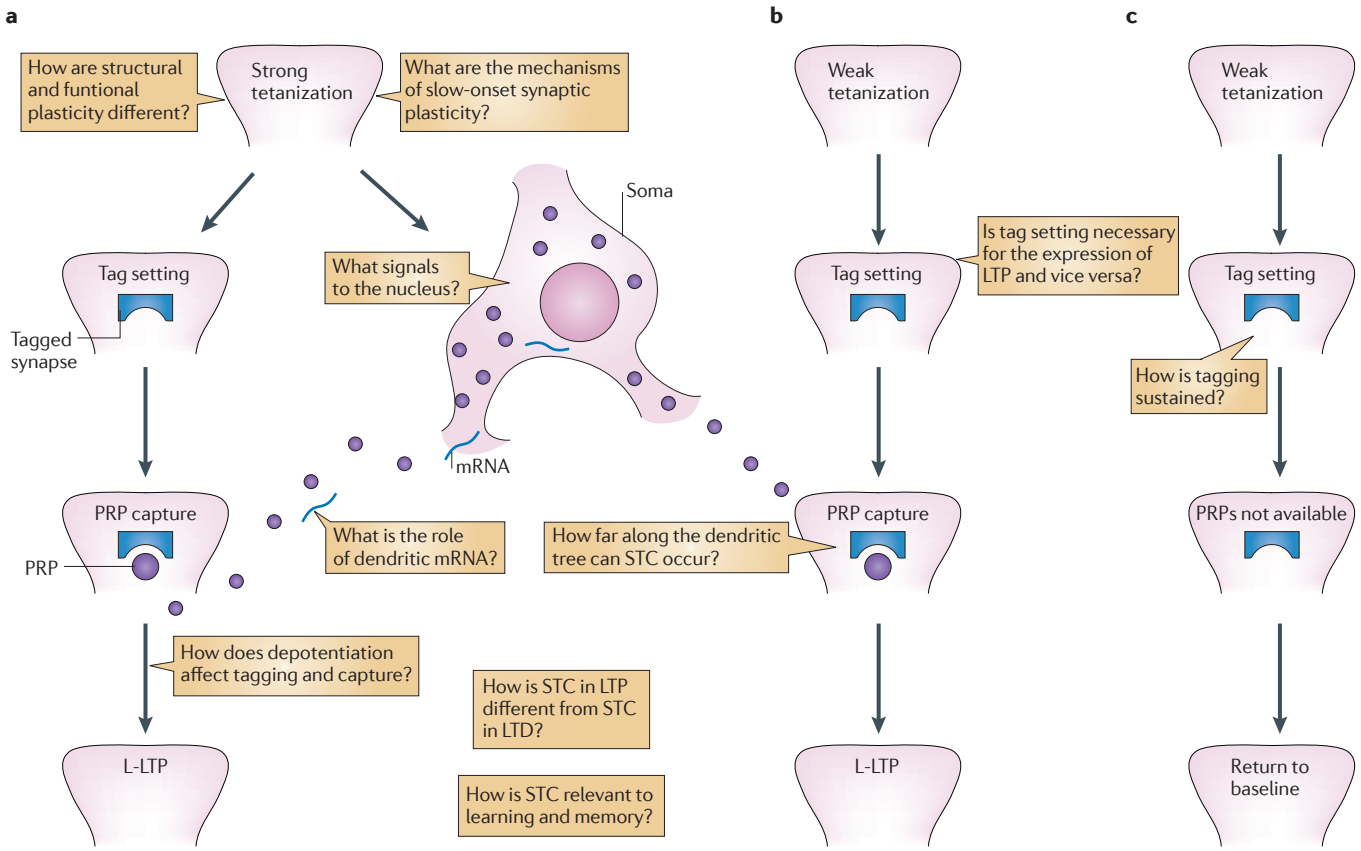


Figure 1 | **The synaptic tagging and capture (STC) hypothesis and its challenges. a** | As originally proposed, the strong tetanization of one synaptic pathway leads to two dissociable events: local tag setting and the synthesis of diffusible plasticity-related proteins (PRPs). The PRPs are then captured by tagged synapses, and this is necessary for the maintenance of late-long-term potentiation (L-LTP). **b** | A weakly stimulated set of synapses that has access to the PRPs will also succeed in maintaining L-LTP. **c** | Without the availability of PRPs, the receptive state (tagging) of the synapses will fade and L-LTP will not be sustained. Challenges to the basic model are highlighted. LTD, long-term depression.

determines memory consolidation — both backwards and forwards — enables the synthesis and distribution of plasticity-related proteins that is induced by other activity to be captured by so called 'synaptic tags' that are set at the time of memory encoding. Synaptic tags, described in detail below, are local molecular changes at synapses that mark synaptic plasticity as having occurred. From a computational perspective, the concept provides a new way of thinking about synaptic potentiation in which the various 'states' of a synapse reflect both the current level of synaptic strength and the potential of the synapse for lasting changes in strength[15,16].

In this Review, we outline the conceptual framework of the STC hypothesis, discuss experimental challenges to the original hypothesis and introduce a revised theory. We also consider new behavioural studies that have explored the relevance of the STC hypothesis to learning and the consolidation of newly formed memories. This new, overarching framework considers memory formation as an ongoing process influenced by its past, present and future. This unique approach allows a broader and fuller understanding of the likely molecular underpinnings of the engram.

The core concepts of the STC hypothesis

A core concept of the STC hypothesis[17,18] is that memory encoding creates the potential for LTM but is noncommital with respect to whether persistent memory will actually occur (FIG. 1). For experimental neuroscientists — be they physiologists doing brain slice work on long-term potentiation (LTP) or behavioural scientists studying learning in laboratory animals — it is natural to think of 'memory formation' in one's chosen model as a discrete set of interacting events triggered at a particular moment in time. Thus, strong tetanization, given in the form of a train of high-frequency pulses, increases the amplitude of excitatory postsynaptic potentials (EPSPs) before our eyes; similarly, an animal makes a choice in a behavioural learning task, receives reward or punishment for doing so, and shows changes in its behaviour that reflect such learning.

Reality is otherwise, with memorable events happening before and after others such that, in daily life as opposed to the laboratory, streams of neural activity are being processed continuously. The memorability of an apparently isolated episode is likely to be concurrently affected by what has happened, or will happen soon. By contrast, if memory consolidation mechanisms were

automatically triggered by stimulus events and determined solely by the characteristics of the stimuli (such as their strength or repetition[19]), the declarative and procedural memory systems of the brain would be simultaneously handling numerous consolidation cascades at varying stages of their time course. Given that there can be thousands of synapses on individual cells (for example, in the hippocampus), neurons would have to simultaneously support different points of these cascades for different items of stored information. Thus, determining the fate of successive memories only at the time of encoding would be extremely complicated. Neurons cannot work this way, and we propose that something conceptually important is missing from such models of cellular consolidation.

The STC hypothesis, which has evolved since its original formulation[18,20,21], asserts that the persistence of synaptic potentiation (and depression) involves a set of interacting mechanisms that can be, but do not have to be, triggered at a single moment in time. The experimental foundation was the observation, in two-pathway LTP experiments, that it is possible to induce protein synthesis-dependent LTP during the inhibition of protein synthesis[17]. LTP was proposed to consist of the following steps (FIG. 1): first, the expression of synaptic potentiation with the setting of a local synaptic tag; second, the synthesis and distribution of plasticity-related proteins (PRPs); third, the capture of these proteins by tagged synapses; and forth, the ultimate stabilization of synaptic strength. If the prior activity history of the neuron has upregulated the availability of PRPs in a particular dendritic compartment, these will be captured by local synaptic tags and so ensure the stabilization of the synaptic component of a new memory trace soon after it is encoded. Conversely, if neural activity, which induces PRP synthesis, does not happen until some time after potentiation and tag setting, stabilization of the otherwise temporary synaptic potentiation will occur at this later time, with the temporal duration of the tag being the main determinant of whether stabilization occurs at all.

Thus, according to the STC hypothesis, the time course of cellular consolidation is a malleable entity that varies as a function of what the neural network has been doing or may do in the near future. This theoretical framework is conceptually distinct from those that include a 'grace period' or 'window of time' after encoding when consolidation can be interrupted[22,23]. By contrast, we propose that heterosynaptic events that occur before or after encoding can determine the fate of memory traces. Recent computational models of STC that comprise the four steps of LTP described above can explain the induction of protein synthesis-dependent late-LTP (L-LTP) on a weakly tetanized pathway, and have been used to make novel predictions about the statistical variability of EPSPs after LTP induction[15,16].

Limitations of the existing STC model. Although the basic STC framework has stood the test of time, limitations of the original hypothesis[18] have emerged. The first two mechanisms in the process of LTP — synaptic potentiation and tag setting — were assumed to be triggered simultaneously, and tag decay and the decline of potentiation to baseline were thought to follow an identical time course. New findings, discussed below, question this assumption. Other limitations of the original hypothesis include that it addresses the determinants of L-LTP but not of late-long-term depression (L-LTD). Cross-capture experiments point to the existence of a common pool of PRPs that is made available after the induction of persistent forms of LTP and LTD from which all tagged synapses can benefit regardless of the direction of their synaptic change[24].

Another limitation of the hypothesis rests on the mistaken assertion that the synthesis of PRPs occurs solely in the soma, but there is now good evidence for dendritic synthesis[25–27] as well as the targeting of mRNAs to dendritic branches or compartments[28,29]. PRPs that have been implicated in learning and plasticity include activity-regulated cytoskeleton-associated protein (ARC), Homer1a and the AMPAR (α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate receptor) subunit GluR1[30,31]. As there are intricate regulatory mechanisms capable of repressing mRNA translation until they reach appropriate (that is, tagged) synapses[32], a revised STC hypothesis needs to include dendritic mRNAs as diffusible plasticity-related molecules, in addition to proteins. The acronym PRP should perhaps stand for 'plasticity-related products' (used as such hereafter) of transcription.

The dendritic control of mRNA translation addresses the problem of protein diffusion, targeting and capture by compartmentalizing these processes into specific regions of an individual neuron. However, the need for local PRP capture at synapses re-appears once mRNAs are translated. In addition, the original STC hypothesis provided little detail about the likely molecular mechanisms by which synaptic tags capture PRPs. It was speculated that tag setting itself may be mediated by the phosphorylation state of a synapse-associated molecule (such as calcium–calmodulin-dependent kinase 2 (CaMKII)) or could require a structural change (such as variation in the diameter of the neck of the dendritic spine), but the molecular basis was unknown. When synaptic tagging was discovered in 1997, little was known about candidate PRPs (including dendritic mRNAs) and the possibility of intersynaptic competition for PRPs was not considered[33]. Some suggestions were made about the likely signal transduction processes catalysing the synthesis of PRPs, particularly the synergistic action of neuromodulatory transmitters such as dopamine, but this was not definitively stated.

Recent challenges to the STC hypothesis

Although the core concepts remain intact, new findings present intriguing limitations of and thus challenges to the original STC hypothesis, as discussed below.

Tag setting and initial expression of LTP are separate and dissociable. New findings suggest that the induction of early-LTP (E-LTP) and the setting of synaptic tags can be independent (FIG. 2). Novel electrophysiological protocols

Two-pathway LTP experiment
An experiment that studies two independent sets of synapses that converge onto the same cell.

Cross-capture experiment
A two-pathway experiment in which a weak, early-long-term potentiation (E-LTP)-inducing protocol delivered to one pathway is rescued into late-LTP (L-LTP) if a strong, L-LTD-inducing protocol is delivered to the other pathway at around the same time. The phenomenon is reciprocal, as rescue of E-LTD into L-LTD occurs when another pathway experiences a strong, L-LTP-inducing protocol.

(see BOX 1 for the analytical logic of 'strong and weak' protocols on independent pathways) have enabled tests of the specificity of certain molecular actions underlying both processes. For example, reversible pharmacological interference with the actin network[34] and the autophosphorylation of CaMKII[35] blocks tag setting in pathways that still express E-LTP. The drugs used in those experiments not only have no effect on PRP availability, but they also leave the functional expression of E-LTP unaffected. That is, E-LTP can coexist with a state in which a synaptic tag has not been set or has been blocked. The crucial evidence is that, in the presence of low-dose KN-93, which selectively inhibits CaMKII[35] (FIG. 2b), or latrunculin, which selectively inhibits actin[34], E-LTP following a strong tetanus fails to stabilize into L-LTP even though PRPs are available (see also BOX 1 for explanation of these 'tag-blocker' experiments). This implies that these drugs have blocked tag setting while allowing E-LTP expression. Questions that a revised STC theory must therefore address include: how is this dissociation between tagging and LTP expression realised at the molecular level? And what are the implications of this dissociation for memory consolidation?

Depotentiation and re-setting of the synaptic tag. A second challenge to the original STC hypothesis is that activity-dependent functional depotentiation (that is, reversal of E-LTP) can occur with or without the re-setting (that is, inactivation) of synaptic tags. It has long been known that low-frequency stimulation (LFS) can depotentiate E-LTP[36–39]. One type of LFS — 250 pulses at 1 Hz — will not only depotentiate LTP, but will also interfere with the tag[39,40] — that is, the tag-resetting process. However, the time window for this tag-resetting effect of LFS is restricted to less than 10 min after the initial induction of E-LTP. LFS applied later is still able to depotentiate LTP, but only temporarily without, we think, affecting the tag. The key evidence (FIG. 2c) is that when, in a two-pathway experiment, LFS is delivered 10 min or more after weak tetanization, LTP can

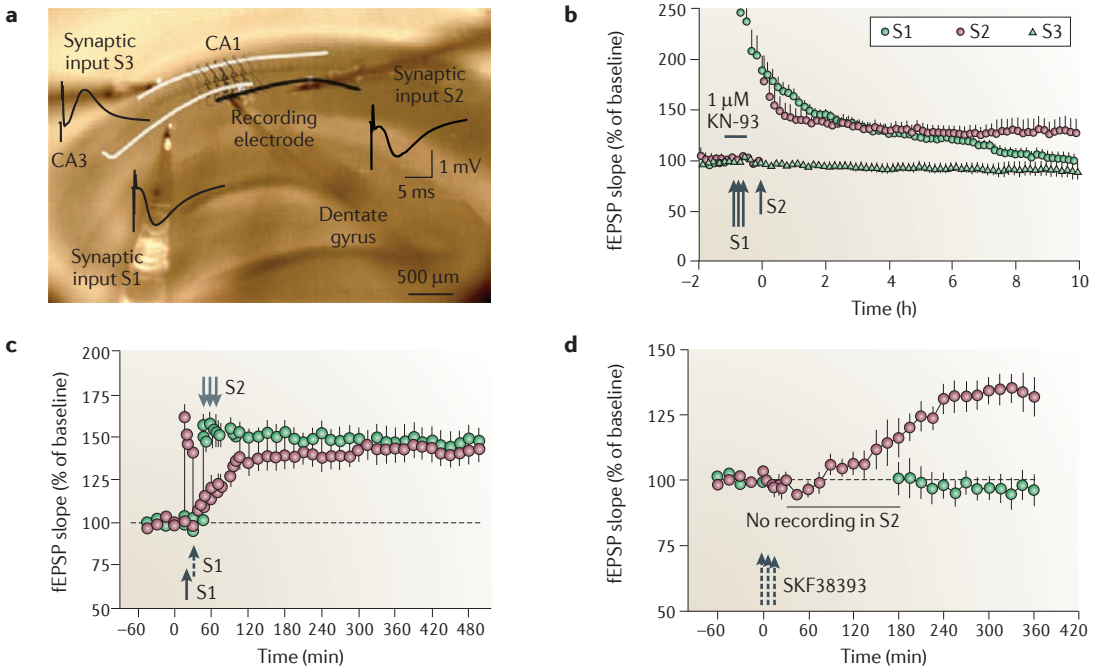


Figure 2 | **The dissociation of LTP expression and synaptic tagging. a** | A slice preparation from our laboratory with superimposed labels depicting the positioning of the electrodes. **b** | Application of the calcium–calmodulin-dependent kinase 2 inhibitor KN-93 fails to stabilize the potentiation induced by strong tetanization (three arrows) in pathway S1, but does not block the potentiation expressed in the weakly stimulated (single arrow) pathway S2 after drug washout, which is normally insufficient to induce late-long-term potentiation (L-LTP). Such 'strong before weak' experiments reveal the specific effect of KN-93 in blocking tagging, and also show that tagging can be blocked while allowing early-LTP to be expressed (pathway S1). **c** | Low-frequency stimulation (LFS; dashed arrow) depotentiates pathway S1 but its synapses gradually repotentiate if an independent but convergent pathway (S2) receives strong tetanization. Because repotentiation requires the heterosynaptic stimulation of S2 (not shown), LFS to S1 10 min after potentiation is sufficient to depotentiate the functional expression of LTP but does not prevent the capture of plasticity-related products (PRPs). However, the tag can be reset by LFS when delivered within 5 min of strong stimulation (not shown). **d** | Three applications of the dopamine D1/D5 receptor agonist SKF38393 can chemically induce slow-onset LTP specifically on synapses that are activated by test stimulation (pink circles) but not those that are silent (green circles). This could be accounted for by the interplay between PRPs induced after D1/D5 activation and the synapse-specific events (tagging) induced by NMDA (*N*-methyl-D-aspartate) receptor-dependent calcium influx. fEPSP, field excitatory postsynaptic potential. Part **b** is reproduced, with permission, from REF. 35 © 2010 Society for Neuroscience. Part **c** is reproduced, with permission, from REF. 40 © 2004 Elsevier. Part **d** is reproduced, with permission, from REF. 41 © 2007 Elsevier.

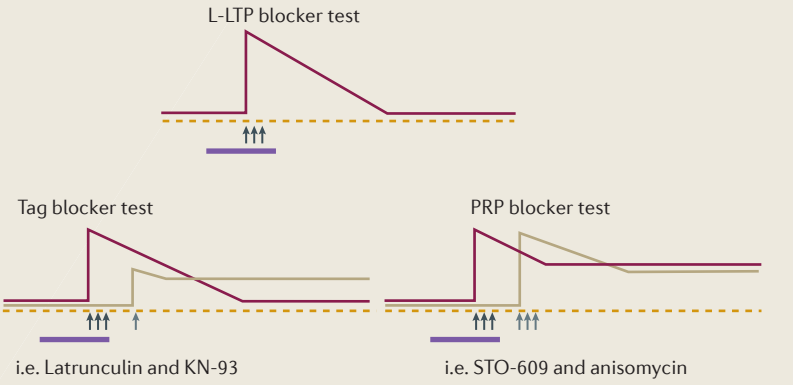
Box 1 | **Assigning roles to molecules**

The response of independent but convergent pathways (that is, different synapses onto the same cell) to strong or weak tetanization can be used to discover the role of particular molecules in synaptic tagging and capture. The approach involves a series of logical steps:

Step 1. Find a reversible inhibitor of late-long-term potentiation (L-LTP) (see the figure, top). Application of such a drug (indicated by the purple bar) during strong tetanization (shown by dark arrows) blocks L-LTP, as indicated by the schematic representation of normalized field excitatory postsynaptic potential slope. Several drugs can block L-LTP, but this raises the question of the mechanism of action: are these drugs acting on a tag-specific mechanism, are they specific to plasticity-related proteins (PRPs), or general blockers of PRPs and tags?

Step 2. The tag-blocker test (see the figure, bottom left). An analytical protocol can be used to determine one possible mechanism responsible for the block of L-LTP by the drug identified in step 1. The key result is the fate of subsequent weak tetanization (light arrow) at an independent but convergent set of synapses after the drug present at the time of strong tetanization has been washed out. If the weak pathway is capable of maintaining L-LTP, the drug is a candidate tag-specific blocker. The synapses tagged by the weak stimulation have captured PRPs that were synthesized in response to the strong stimulation during application of the drug. These tag–PRP interactions on the weakly tetanized pathway stabilize L-LTP even though the strongly tetanized pathway fails to show L-LTP. This test can also be run with the weak tetanus delivered before application of the drug and the strong tetanus[34,35].

Step 3. The PRP blocker test (see the figure, bottom right). A different analytical protocol ('strong before strong') reveals that a drug that blocks L-LTP in a single-pathway study may be doing so by limiting PRPs. The key result in a two-pathway study is the outcome of the potentiation that is induced in the presence of the L-LTP blocker. If this pathway shows L-LTP, the drug is a likely to be a PRP-specific inhibitor. This is because synaptic tags that were created during application of the drug captured the PRPs that were synthesized in response to the later strong tetanization of the other pathway[17,35].



be re-induced and maintained as L-LTP on the initially depotentiated synaptic pathway if a second and independent synaptic pathway is strongly tetanized[39]. The STC interpretation of this finding is that PRPs associated with strong tetanization of the second pathway are captured by the depotentiated pathway, which is possible because the tags have not been reset by the late-arriving LFS. A revised STC theory must take into account this apparent independence of the neural mechanisms underlying tag resetting and depotentiation, and address questions such as: how can synapses re-potentiate that have reverted to baseline levels of strength after LFS?

Slow-onset synaptic potentiation. Most forms of LTP, including spike timing-dependent plasticity, are characterized by a fast change in EPSP magnitude. By contrast, for slow-onset potentiation there is no change in EPSP at the time of induction but a gradual increase in synaptic strength over time. An important example of such an effect is that, following application of the dopamine receptor D1/D5 agonist SKF38393, LFS is sufficient to induce slow-onset potentiation over the course of 1–2 h[41] (FIG. 2d). Other molecules are also capable of inducing slow-onset LTP, including brain-derived neurotrophic factor (BDNF), carbachol and forskolin[41–45]. Slow-onset LTP is also seen following place cell activity replay[46], in which patterns of activity of two place cells recorded during exploration of an environment are used as inputs for *in vitro* experiments in spike timing-dependent plasticity.

The observation of slow-onset LTP represents a further challenge to the original STC hypothesis, which assumes that tag setting and E-LTP must occur together. Slow-onset potentiation might suggest that there are forms of L-LTP that do not require synaptic tags or, alternatively, that tags can be set by mechanisms that are separate from those underlying the immediate expression of E-LTP.

The relevance of STC to memory — interactions between cellular and systems consolidation. The major focus of research on the determinants of LTP has been on the underlying molecular mechanisms. However, the STC hypothesis asserts its relevance to real memory and not just to physiological models of memory formation. Accordingly, a different kind of challenge to the hypothesis concerns the need for behavioural experiments that directly test the heterosynaptic concept that lies at the heart of the STC idea. Can other neural events, happening before or after memory encoding, directly affect the persistence of memory? And do they do so in a manner predicted by the STC hypothesis? This challenge differs from the others in not necessarily requiring a revision of the original hypothesis, but it is one that has only recently been addressed. We return to the relevant data below (see the section 'Implications for learning and memory').

Structural versus functional plasticity

A revised STC hypothesis can account for these challenges but, before introducing it, we consider experiments tangential to studies of L-LTP that concern an emerging distinction between functional and structural plasticity. Recent findings suggest this distinction might provide insight into the mechanisms underlying synaptic tagging and those involved in synaptic potentiation.

The expression of E-LTP can be dissociated from structural changes at dendritic spines. A growing body of evidence from cell biology, electron microscopy and live confocal imaging studies points to a distinction between the initial functional expression of a change in synaptic strength and the structural remodelling of the cytoskeleton at the synapse[47–49]. Although these changes commonly occur at the same time, they are mechanistically distinct and can occur independently[23,50,51] (FIG. 3A).

Thus, the expression of E-LTP is mediated in part by the synaptic incorporation of additional AMPARs[52,53], representing a key postsynaptic change. In addition, as

Place cell
A neuron that exhibits a high rate of firing when an animal is at a specific location in an environment.

the vesicle-associated protein synaptophysin pairs new AMPAR clusters with presynaptic vesicle release sites[54], there can also be an increase in quantal content (that is, an increase in neurotransmitter release), reflecting a presynaptic change[55]. These functional changes can occur in the absence of a structural change to the dendritic spine[56,57]. However, as shown in studies of both LTP[49] and LTD[58], structural remodelling of dendritic spines can also take place in parallel with, or even in the absence of, changes in AMPAR trafficking. This spine remodelling serves an important purpose, as discussed below, but will not necessarily persist unless a functional change also occurs[56]. Furthermore, neither the functional nor the structural changes will persist without the supply and incorporation of new PRPs.

Cytoskeletal reconfiguration depends on actin and CaMKII. Recent reports describe structural changes of the dendritic spine associated with different pools of F-actin and G-actin. Isoforms of CaMKII have been proposed to have multiple roles in regulating the actin cytoskeleton, depending on the pool of actin on which they are acting[50,59]. For example, CaMKIIβ could act on a pool of actin to mediate spine expansion[51,60–62]. This polymerization of F-actin has been visualized via live imaging within single dendritic spines[61,63,64] (FIG. 3B). The structural remodelling of the spine[65] therefore seems a necessary[34,35] but not sufficient precursor for the expression of L-LTP. This spine enlargement is accompanied by an expanded synaptic cleft and an increase in presynaptic terminal release sites[66,67].

CaMKII and cytoskeletal reconfiguration are necessary for synaptic tagging but not for E-LTP. Even though CaMKII mediates multiple aspects of structural plasticity, inhibiting this kinase with KN-62 and

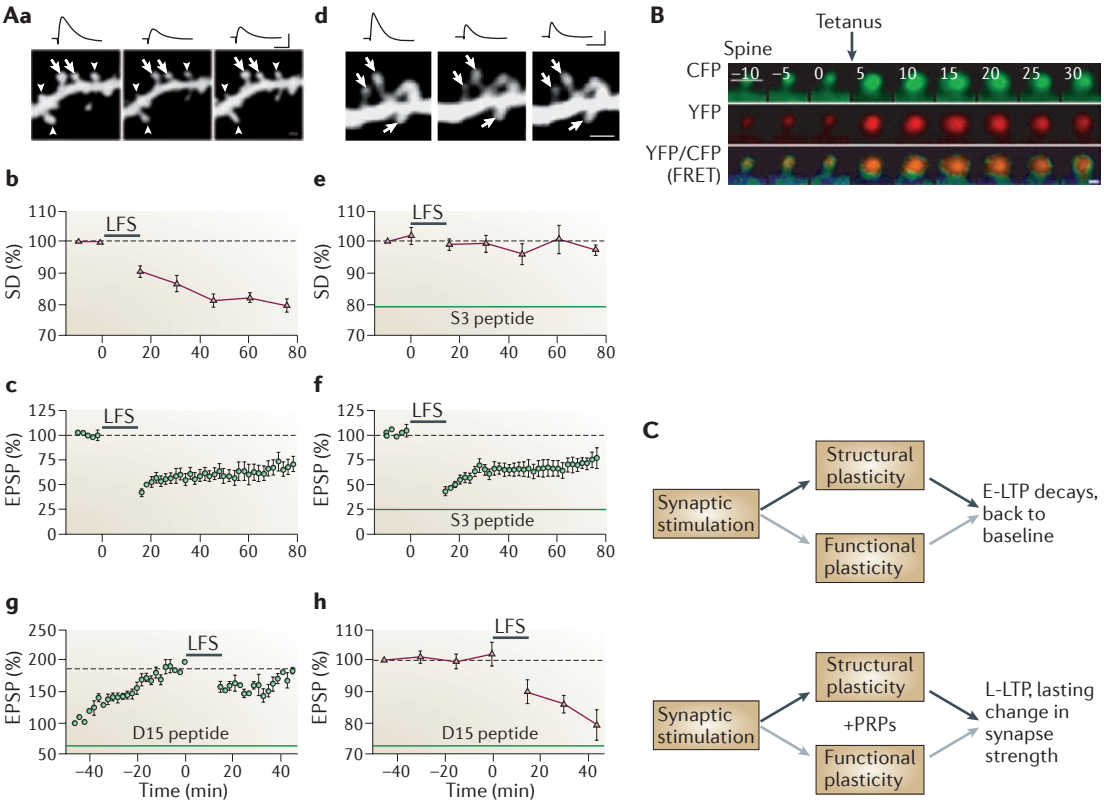


Figure 3 | **A distinction between structural and functional plasticity. A** | Using confocal imaging, the functional expression of long-term depression (LTD) is shown to be independent from spine shrinkage. Whereas spine shrinkage (**Aa**,**b**) and LTD (**Ac**) occur concomitantly in response to low-frequency stimulation (LFS), the inhibition of spine shrinkage by activation of cofilin using S3 peptide (**Ad**,**e**) still allows for the expression of LTD (**Af**). Conversely, preventing endocytosis of receptors by application of D15 peptide blocks LTD expression (**Ag**), while spine shrinkage remains unaffected (**Ah**). **B** | Using fluorescence resonance energy transfer and the tagging of actin monomers with either cyan fluorescence protein (CFP) or yellow fluorescence protein (YFP), the ratio of CFP bound to YFP (that is, the signal specific for actin filaments but not for globular actin) is observed to increase after tetanization. This reconfiguration of the actin cytoskeleton is sustained for at least 30 min. The induction of LTP elevates the level of F-actin relative to that of G-actin, while the spine expands structurally. **C** | The requirements of a revised synaptic tag and capture model. The induction of LTP leads to two independent but convergent processes — structural and functional plasticity. Both require the arrival of new plasticity-related proteins (PRPs) to be sustainable and are temporary in their absence (top) but become lasting if they arrive and are captured (bottom). E-LTP, early-LTP; EPSP, excitatory postsynaptic potential; L-LTP, late-LTP; SD, spine diameter. Part **A** is reproduced, with permission, from REF. 58 © 2007 Society for Neuroscience. Part **B** is reproduced, with permission, from REF. 63 © 2004 Macmillan Publishers. All rights reserved.

KN-93 allows the expression of E-LTP while still blocking tagging[35,68]. For example, when strong tetanization occurs in the presence of a low concentration of KN-93 that specifically blocks CaMKII autophosphorylation, E-LTP is induced and expressed but it decays to baseline over several hours[35] (FIG. 2b). CaMKII is necessary for the functional expression of LTP, as revealed by studies using CaMKII-knockout mice and pharmacological inactivation of CaMKII catalytic activity[35,69,70]. However, the use of KN compounds has identified a level of inhibition of CaMKII that is sufficient to block tagging while still allowing the expression of E-LTP. Similarly, a low concentration of latrunculin (which blocks actin polymerization) does not block E-LTP[34]. When either drug is used during tetanization in tag-blocker experiments (BOX 1), they do not prevent L-LTP from being induced on the weakly tetanized pathway once these drugs have been washed out. We argue that this happens because these drugs have no effect on either the early functional plasticity or on the synthesis and distribution of PRPs.

Taken together, the data discussed so far in this section suggest that structural plasticity is crucial for tag setting and depends on cytoskeletal reconfiguration and CaMKII activity, and that its disruption can have an effect on tag setting without interfering with the expression of E-LTP.

Structural plasticity alone is insufficient for L-LTP. The question then arises of how protein synthesis-independent structural plasticity can be rendered persistent. It now seems that there is a surprising interaction between the early functional and structural aspects of plasticity such that the addition of AMPARs is one of the requirements for maintaining structural changes[56]. The other requirement is that this increase in AMPARs at the postsynaptic density (PSD) must be sustained in the face of trafficking and protein turnover — which depends on the supply of PRPs. Many molecules may be implicated in sustaining the elevated levels of AMPARs in the PSD of potentiated synapses; one of them is protein kinase Mζ (PKMζ)[71,72], a PRP the activity of which is known to be necessary for LTP and memory maintenance[73,74]. Unless this and other PRPs reach the expanded (that is, tagged) synapse, L-LTP will not be sustained.

To summarize, these data point to the independence and interdependence of structural and functional plasticity. The induction of E-LTP triggers two separate processes — one associated with increasing the functional strength of the synapse, the other with altering the structure of the synapse. When these occur alone, only a transitory change in synaptic strength is observed. However, when accompanied by the delivery of PRPs, a more lasting increase in synaptic strength occurs. These are the essential prerequisites of a revised STC hypothesis (FIGS 3C,4,5).

A revised STC hypothesis

We are now in a position to outline a revised STC hypothesis (FIG. 4; see Supplementary information S1 (movie) and Supplementary information S2 (movie)). The main revision is the distinction between the mechanisms underlying synaptic tagging and those responsible for the expression of plasticity (potentiation and depression), which is consistent with the observed dissociations between structural and functional plasticity. The synaptic tagging process probably requires an alteration of dendritic spine architecture that is both permissive and necessary for the remodelling of the PSD. This remodelling is essential for the stabilization of LTP. The functional expression of E-LTP requires structural and functional changes that are short-lasting unless stabilizing PRPs arrive. The postsynaptic capture of PRPs allows for the subsequent stabilization of the change in spine structure, which enables maintenance of the functional change in efficacy.

In our revised STC hypothesis, we follow Lisman and Raghavachari[75] in asserting that there is an initial increase in the number of AMPARs inserted into the available PSD slots of existing dendritic spines (FIG. 4b). However, over time, post- and presynaptic changes reflect both the time course of E-LTP and the steps towards induction of L-LTP. In both cases, there is a complementary increase in the number of release sites that appose the new AMPARs (FIG. 4c). In the case of E-LTP, the number of release sites and AMPARs gradually decay back to baseline levels (FIG. 4d,e). By contrast, for L-LTP, the supply of PRPs (FIG. 4f) anchors the additional AMPARs via new PSD slots, which are matched by a sustained and complementary increase in release sites (FIG. 4g,h).

Tagging is a state of the synapse, not of a single molecule. The identity of the tag has until now been considered likely to be a single or at most a few molecules[76]. One of the key revisions of the STC hypothesis is that tagging should instead be seen as a temporary structural state of the synapse that probably involves a large number of proteins and their interactions (BOX 2). Based on the current knowledge of molecular interactions, tagging should be considered a permissive 'unlocking' process (FIG. 5b) without which the novel synthesis and supply of PRPs is incapable of stabilizing plasticity (FIG. 5c–e). That is, tagging is not a single molecule or the phosphorylated state of that molecule, nor is capture of PRPs likely to be the interaction of just one protein with another. This general model applies equally to LTD and LTP, but some molecules required for tagging are specific to the direction of the synaptic change (that is, CaMKII for potentiation, and calcineurin for depression[48]).

The lifetime of the tag. The prolonged but temporary activity of particular kinases may account for the limited lifespan of the tagged state — approximately 90 min as revealed by 'weak before strong' brain slice protocols[77]. For LTP, an autophosphorylated form of CaMKII remains active in the PSD even after the calcium concentration returns to baseline levels[78,79]. Autophosphorylated CaMKII moves into the PSD[80], closer to many of its targets, where it becomes less accessible to inhibitory phosphatases[81–84]. However, CaMKII bound to the PSD will still be inactivated and released

PSD slot
A group of proteins in the postsynaptic density (PSD) that is capable of binding AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole) receptors.

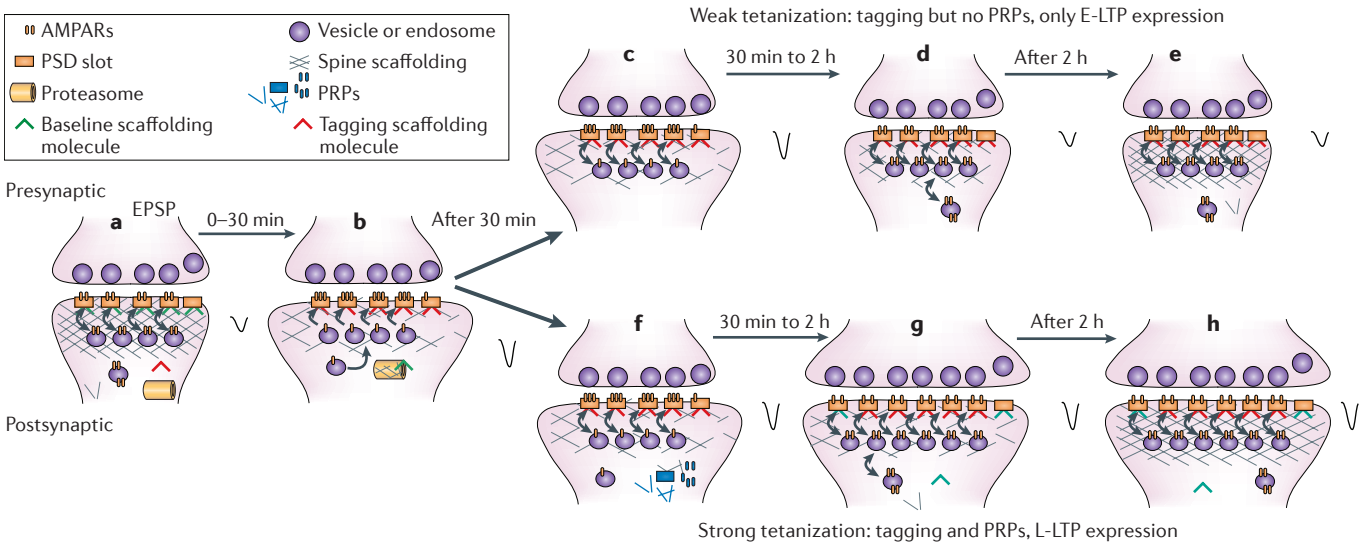


Figure 4 | **The revised STC hypothesis — molecular events associated with induction of E-LTP and L-LTP. a** | The basal state of a prototypical glutamatergic synapse with presynaptic vesicles apposed to postsynaptic density (PSD) slots containing AMPARs (α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate receptors) that are anchored to the dynamic but stable actin cytoskeleton by scaffolding molecules. There is continuous turnover of the AMPARs, as depicted by the double-headed arrow. Typical field excitatory postsynaptic potential traces are inset. **b** | The induction of early-long-term potentiation (E-LTP) triggers the faster incorporation of AMPARs from perisynaptic pools into existing slots that are paired with presynaptic vesicles, as well as the disruption and expansion of the cytoskeleton by the proteasome, and also kinases (not shown). In this way, baseline scaffolding molecules are replaced by tagging scaffolding molecules from a limited pool that is always available in the dendritic spine. These molecules (shown in red) support tagging but require new plasticity-related products (PRPs) to sustain synaptic plasticity. **c** | If weak tetanization is used to induce LTP in **b**, the spine remains in an expanded, yet tagged, state. **d** | Without the arrival of PRPs, E-LTP decays as the rates of endo- and exocytosis of receptors return the number of AMPARs available to the synapse to baseline levels. **e** | Additionally, the decay in kinase activity forces the synapse to revert to an untagged and unreceptive state. **f**,**g** | If PRPs are made available to a synapse in the tagged state, following strong tetanization in **b** or other heterosynaptic neural activity, they will be captured to sustain the increase in synaptic strength even after receptor turnover rates return to baseline levels (**g**). The number of AMPARs per slot is comparable to that in part **a**, but the overall number of slots has increased. **h** | The structurally expanded and functionally potentiated synapse assumes a new steady state with increased pre- and postsynaptic components, leading to the expression of late-LTP (L-LTP). STC, synaptic tagging and capture.

from the PSD by the action of phosphatases (mainly protein phosphatase 1 (PP1))[85]. A tagged synapse that has received PRPs will stabilize its new structural conformation before the tagging state fades and so maintain its change in synaptic efficacy.

Arrival and capture of PRPs is essential for stabilization. Capture of PRPs is the first step in the stabilization of both the functional and structural alterations to a dendritic spine (FIG. 4g). The molecular identity of all the PRPs is unknown, but includes GluR1, Homer1a, PKMζ and ARC. According to our model, additional PSD slots (or scaffolding molecules) are inserted into an enlarging PSD, and there are complementary changes on the presynaptic side of the cleft[75]. The number of AMPARs per slot returns to the original level but against this background of a greater number of PSD slots. AMPAR trafficking into and out of these slots continues in a dynamic fashion, creating a new and sustained state of potentiation that is characterized as L-LTP. Without these PRPs, the altered structural 'scaffold' will gradually revert to an untagged (that is, locked) state as the activity of kinases responsible for synaptic tagging fades. PRPs cannot be added to the PSD if they arrive after the untagging of the spine, and therefore synapses exhibiting E-LTP fail to capture new PRPs arriving more than 90 minutes after the induction of LTP[77].

The final state. The end result of the remodelling of spine structure is an increase (L-LTP) or decrease (L-LTD) in the number of slots available for AMPARs (FIG. 4h), and a corresponding presynaptic change in vesicle release sites[75,86]. AMPARs are endocytosed to and exocytosed from these slots in the dynamic steady state, similarly to the trafficking of glutamate to vesicular release sites. In the case of LTP, there is the further possibility of division of the PSD[67] and the expansion or multiplication of the spine with both pre- and postsynaptic modifications[87].

The explanatory power of the revised STC hypothesis. With the revised STC hypothesis in mind, we can briefly re-examine some of the challenges to the original STC hypothesis.

The first challenge concerned the apparent dissociation between synaptic tagging and E-LTP expression[35,68] (FIG. 2b). This is now explained in terms of the mechanistic distinction between structural and functional plasticity, with the role of CaMKII autophosphorylation central to

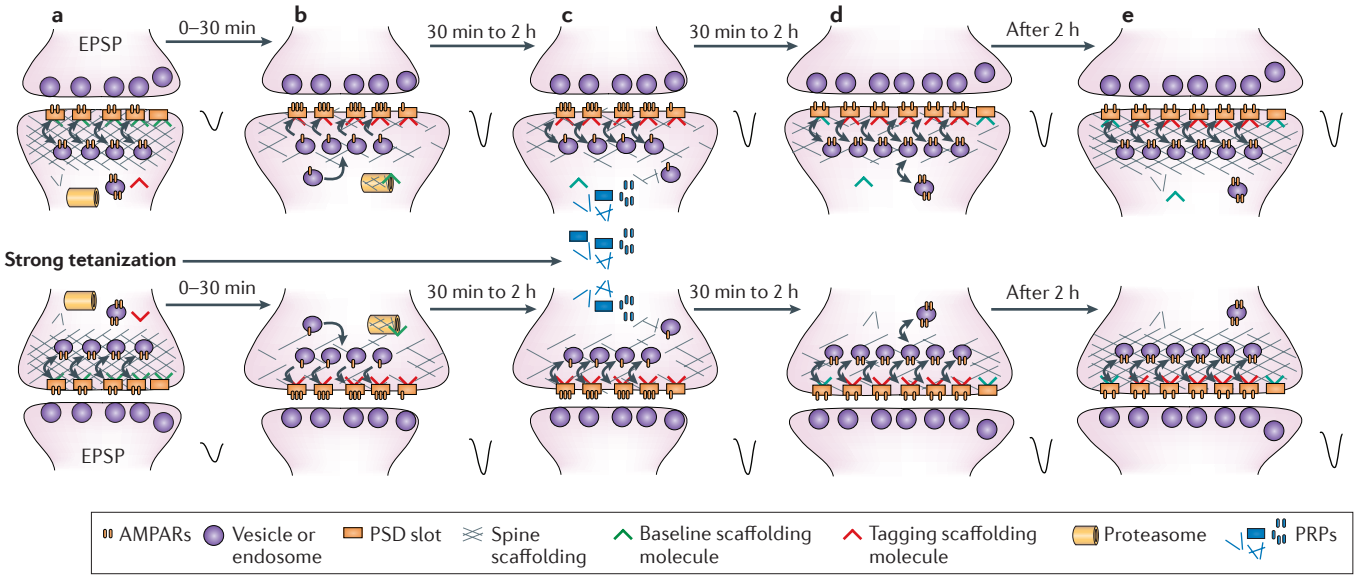


Figure 5 | **Synaptic tagging and capture. a,b** | Two synapses of the same neuron start in the same basal state and receive plasticity-inducing stimuli of low intensity (top) and high intensity (bottom) that will trigger both functional and structural plasticity. **c** | The synaptic tagging and capture hypothesis explains the observed rescue of early-long-term potentiation (E-LTP) into late-LTP (L-LTP) at the weakly stimulated synapse by the ability of the synapse to make use of plasticity-related products (PRPs) that are synthesized in response to the strong tetanus and transported cell-wide in a nonspecific manner. **d** | Thus, both the strongly and weakly tetanized synapses 'capture' PRPs from a common pool, and scaffolding molecules are added that crosslink with the actin cytoskeleton. AMPARs (α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate receptors) are also inserted in new postsynaptic density (PSD) slots, which both induce and stabilize pre- and postsynaptic changes. **e** | The stable potentiated state assumed by both synapses is ready again for additional plasticity. Typical field excitatory postsynaptic potential traces are inset.

enlarging the actin cytoskeleton[61,63] (see Supplementary information S3 (figure) and Supplementary information S4 (movie)).

The second challenge concerned the differential time course of activity-dependent depotentiation and of tag resetting. LFS engages phosphatases that block both the expression of LTP and the structural reconfiguration of the dendritic spine[57,88]. The ability of LFS to depotentiate E-LTP and cause tag resetting requires the actions of PP1 and is associated with a reduced activity of protein kinase A[89,90], with depotentiation mediated by AMPAR dephosphorylation[91] and tag resetting through inhibition of CaMKII[81]. If the actions of the LFS-driven phosphatases arrive after 10 min, the synapse will already be tagged (structural plasticity), with CaMKII having moved closer to the PSD[84] and away from some phosphatases[81]. This will keep the synapse tagged even in the absence of functional expression of LTP. If new PRPs become available, this tagged synapse can still incorporate and use them (FIG. 2c), leading to re-expression of LTP[39]. It is interesting that CaMKII inhibition disrupts short-term memory only when done within 10 min of encoding in the mouse forebrain[92], consistent with this revised hypothesis (see Supplementary information S3 (figure)).

The third challenge to the original STC hypothesis is slow-onset plasticity. The revised hypothesis accounts for this in a similar vein. BDNF, for example, triggers L-LTP in the hippocampus but does so in a delayed form that does not require NMDA (*N*-methyl-D-aspartate) receptor activation[45]. BDNF application to hippocampal slices upregulates gene transcription and translation[93], which is probably mediated by extracellular signal-regulated kinase (ERK) and other kinases[94], resulting in the upregulation of immediate early genes encoding transcription factors and PRPs. In addition, BDNF promotes cytoskeletal changes in the hippocampus by expanding the actin cytoskeleton and capturing postsynaptic density protein 95 (PDS95) into the PSD[95–97]. It also induces dendritogenesis through local calcium influx. This effect is blocked by KN-93, suggesting a BDNF-dependent activation of CAMKs[98]. The effect of these two actions — PRP synthesis and cytoskeletal changes — support the necessary role of BDNF in L-LTP[99]. The actions on the cytoskeleton expand the scaffold that holds together the synapse and the PSD, effectively tagging all synapses and making room for new PRPs (see Supplementary information S3 (figure) and Supplementary information S5 (movie)). This revised STC hypothesis explains why this BDNF-dependent tagging can be independent of the immediate expression of LTP[100]. That is, the hypothesis explains slow-onset plasticity as an interaction between tag setting and the gradual incorporation of PRPs (see also FIG. 2d).

Immediate early genes
Genes whose expression is upregulated transiently but quickly in response to a specific stimulus, such as memory encoding.

Implications for learning and memory

In addition to the challenges that have led to this revision of the molecular mechanisms of STC, there is the further challenge of its relevance to learning and memory.

First, STC — so far only shown *in vitro* — must also occur *in vivo*. This is clearly an essential prerequisite of its functional relevance in learning. Surprisingly, this key evidence is still not definitively established despite efforts in several laboratories. Findings so far are supportive but indirect, such as that imposing unexpected novelty (exploratory behaviour) after prior LTP induction can augment the persistence of LTP and/or LTD *in vivo*[101]. Similarly, other behavioural experiences that might be expected to upregulate the availability of PRPs, such as providing a water reward to a thirsty rat, also have the effect of increasing the persistence of previously induced LTP[102]. These findings do not directly demonstrate that weakly induced LTP *in vivo* can be converted into persistent L-LTP following the associated induction of protein synthesis-dependent L-LTP on a separate pathway. The experiment is more challenging than in brain slices *in vitro* because it is not easy to guarantee that two independent pathways converge on a common pool of neurons using only stereotaxic techniques *in vivo*. In connection with such studies, it would be valuable to establish whether LTP *in vivo* entails a functional expression that includes a change in AMPAR trafficking, as has shown for amygdala-dependent learning[103].

Second, given that novelty exploration is known to upregulate numerous plasticity related genes (such as early growth response 1 (also known as *ZIF268*) and *ARC*[104]), the STC hypothesis predicts that unexpected novelty exploration around the time of memory encoding should augment the persistence of a separate behavioural memory. Accordingly, memory would be mediated by synaptic potentiation with associated structural tagging, enabling the synapse to sequester the novelty-associated PRPs that are upregulated independently at a different time.

This prediction about the behavioural impact of novelty was first upheld in rats in an inhibitory avoidance paradigm involving the delivery of an aversive shock to rats when in a test box[105]. The strength of the aversive shock reinforcement was reduced to produce only a transitory LTM of the inhibition of approach to the test box. When a novel experience was arranged to follow this single trial of learning in a different group of rats, the memory of the inhibitory response lasted longer on average. In addition, the 'rescue' of LTM was symmetrical — novelty could precede or follow the inhibitory training. Novelty failed to induce LTM if the exploratory experience occurred when either the dopamine receptor D1/D5 antagonist SCH23390 or the protein synthesis

Box 2 | **Molecules with a necessary role in tagging**

In addition to the role of Ca^{2+}–calmodulin-dependent kinase 2 (CaMKII), there are other mechanisms by which synaptic stimulation can lead to a tagged state. Interfering with any of them can also block tagging:

Protein degradation. Protein degradation by the proteasome is another necessary step in the unravelling of the scaffolding of the dendritic spine and the postsynaptic density (PSD)[115], without which the maintenance of long-term potentiation (LTP) is impossible[116–119]. For example, inhibition of the proteasome enhances the expression of early-LTP (E-LTP) while impairing the maintenance of late-LTP (L-LTP)[119]. This is another example of the dissociation between the expression of LTP from synaptic tagging and plasticity-related protein synthesis. Interestingly, the autophosphorylation of CaMKII engages another structural function, by bringing the proteasome closer to the PSD and thereby enhancing proteasomal activity[120]. Evidence that the proteasome plays a part in synaptic tagging has recently been reported[113].

Scaffolding molecules. Some proteins change their motility after NMDAR (*N*-methyl-D-aspartate receptor) activation[121]. Among them, Homer1a is trafficked into the spine[122] on its way towards the PSD. Homer1a and other scaffolding molecules link the expanded PSD with support structures such as the endoplasmic reticulum (ER)[123]. Homer1a binds to metabotropic glutamate receptors[124] and to postsynaptic density protein 95 complexes through SH3 and multiple ankyrin repeat domain (SHANK) proteins[125]. Homer1a also links this PSD machinery to ryanodine and inositol-1,4,5-trisphosphate receptors in the ER[126] whereas SHANK proteins recruit Homer1 a into the PSD[127]. At about the same time, spine-associated Rap–GTPase-activating protein (SPAR; also known as SIPA1) reorganizes the actin cytoskeleton linking F-actin to NMDARs[128]. Interfering with the actions of these and other scaffolding molecules could prevent the synapse from reaching a tagged state.

Extracellular, glial and presynaptic processes. The temporary breakdown of the physical attachment between pre- and postsynaptic membranes, as well as that of glial cells, may be necessary for the setting of the tag. For example, neuropsin degrades the extracellular matrix, cleaves the neural cell adhesion molecule L1 and has been implicated in E-LTP and tagging[129–131]. All this should allow pre- and postsynaptic membranes and glial cells to break their close contact with one another and unlock the synapse for further changes. When such a process is inhibited, as with the use of matrix metalloproteinase blockers, L-LTP but not E-LTP is blocked after tetanic stimulation, as is chemically induced LTP[132]. These molecules and processes may also be necessary for tagging.

Compartmentalized mRNA translation. During a transcription-independent, translation-dependent phase of LTP[29], regulators of mRNA translation that affect activated synapses may take part in the capture of mRNAs[32]. Following the induction of LTP, and downstream of the mitogen-activated protein kinase and mammalian target of rapamycin pathways, the local, synaptic translation of mRNAs is regulated by cytoplasmic polyadenylation element-binding protein[133,134] and eukaryotic elongation factor 1A[135,136]. In this way, cell-wide diffusion of mRNA can be restricted and compartmentalized within dendritic branches[137,138]. This 'capture' of mRNAs — although parallel to CaMKII activation, proteasome activity and extracellular processes — may be equally necessary for the stabilization of a synaptic change and tagging[138,139].

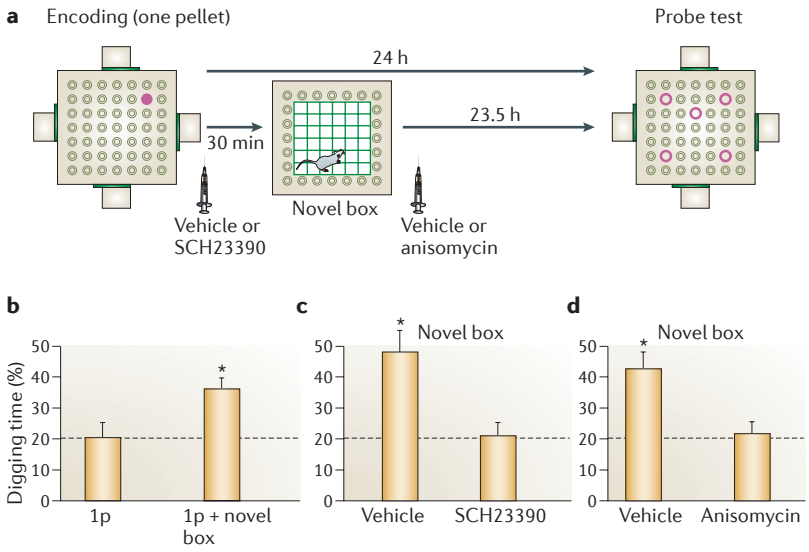


Figure 6 | **Behavioural correlates of synaptic tagging and capture. a** | Rats dug in a single open well (filled pink circle) of an event arena for one food pellet (1p). This was followed by a non-rewarded probe trial with 5 open wells (open pink circles) 24 h later, in which memory for the location of food reward (the 'event') was tested. For the behavioural manipulation, rats explored a novel box for 5 min — which is known to upregulate the synthesis of immediate early genes — 30 min after encoding. **b** | Whereas animals showed no preference for the correct well after 24 h in control trials, the exploration of the novel box enhanced memory persistence. **c**,**d** | Delivery of the dopamine receptor D1/D5 antagonist SCH23390 (**c**) or of the protein synthesis inhibitor anisomycin (**d**) reduces the memory of the event at 24 h. Figure is modified, with permission, from REF. 108 © 2010 National Academy of Sciences.

inhibitor anisomycin was locally micro-infused into the hippocampus. Later work by the same group established the general applicability of this novelty-induced enhancement of LTM to other tasks including object recognition memory and taste conditioning, the latter being mediated by information storage in a cortical network including the insular cortex[106]. Other studies also support an STC account of memory consolidation for taste learning[107].

Our laboratory has taken a similar approach[108], using a within-subjects appetitive paradigm that is more like the 'everyday' memory task of remembering where you have put something. Rats were trained in an 'event arena' (that is, an arena in which events happen) (FIG. 6a) and allowed to encode where food could be found each day (the location changed each day throughout the weeks and months of training). Typically, the animals remembered the daily location well when tested after 30 min but displayed overnight forgetting after 24 h. We also observed that unexpected novelty exploration could convert these rapidly forgotten spatial memories into more lasting traces (FIG. 6b), and that this effect was dependent on hippocampal dopamine receptors D1/D5 and protein synthesis (FIG. 6c,d). A further observation was that increasing the food found during incidental encoding from 1 to 3 pellets caused memory to last longer even without exploration. However, if such memory encoding occurred in the presence of intrahippocampal SCH23390, spatial memory faded rapidly. Prior novelty exploration could 'rescue' the persistence of this otherwise fading spatial memory. These observations were made in the same animals, enabling individual comparisons across conditions, and coupled to parallel and complementary *in vitro* LTP experiments.

Collectively, these observations indicate that a procedure that upregulates PRPs in an apparently nonspecific manner, possibly through novelty activation of the ventral tegmental area and the consequent dopaminergic activation of the hippocampus[109], augments the persistence of a separately encoded memory. This is a unique prediction of the STC framework as it implies that events at the time of memory encoding are not the sole catalysts of the consolidation mechanisms that enable memories to persist; rather, these mechanisms depend on the past and/or future neural activity in the network mediating that form of memory (spatial, taste and so on). This prediction differentiates the STC hypothesis from standard models of memory consolidation[110]. It also offers an intriguing, novel, but still speculative account of the memory of inconsequential events that occur in association with 'flashbulb memories' (such as trivial events around the time of the terrorist attacks of September 11, 2001).

Future directions for the relevance of STC to memory. The development of a revised STC hypothesis offers further predictions in relation to memory that constitute experimental challenges for the future. First, a physiological procedure (LFS) or drug (low-dose KN-93 or lantrunculin) that blocks tagging should enable memory for a short period of time that would then fade. Rescue of LTM by subsequent novelty, as used in behavioural experiments described above, should then fail as no local synaptic tags would have been set to sequester novelty-associated PRPs.

Second, when a weak memory persists into LTM by the encoding of an independent 'strong' memory rather than the use of novelty, it should be possible to use tag-specific blockers to impair the strong memory, whereas the weak memory should persist (behavioural tag blocking).

Third, it should be possible to obtain more direct and definitive evidence of the role of dopamine and other neuromodulators in STC with the use of optogenetics.

Finally, the reactivation of memories renders them vulnerable to the effect of protein synthesis inhibitors[111]. The STC hypothesis, drawing upon the phenomenon of 'competitive maintenance'[33] and findings in contextual fear conditioning[112], proposes that first, synapses encoding the memory engram are routinely tagged when memories are retrieved; and second, sufficient levels of PRPs, available under normal conditions, allow these tagged synapses to stabilize any changes (memory updating), or revert to the stable memory state, leaving the network functionally unchanged; but third, if PRPs are made scarce (that is, by protein synthesis inhibitors), proteasomal degradation of some of the scaffolding molecules to allow synaptic tagging[113] (BOX 2) is not complemented by the arrival of new PRPs. Consequently, the synapse cannot sustain its memory state and the network will

Competitive maintenance
The theory explaining the observation that two pathways already expressing long-term potentiation (LTP) will compete for scarce plasticity-related products when they are further tetanized after a period of protein synthesis inhibition during the maintenance phases of LTP.

lose its engram; fourth, lack of tagging due to proteasome inhibition will protect against the effects of protein synthesis blockers, but also prevent new learning[112,114].

Conclusion

We began by noting that some memories fade whereas others last. We end by pointing out that this is entirely desirable, because a memory system that retained everything would rapidly saturate to a point where information could not be retrieved. If systems consolidation is the set of processes that determine which memory traces last in neocortical networks, cellular consolidation can be thought of as the filter that determines the subset of newly encoded information that may be subject to systems consolidation. The biophysical mechanisms of synaptic tagging and capture — which we now propose as involving dynamic interactions between structural and functional changes at excitatory synapses — provide a biologically elegant way of extending the time course during which the memory system can determine whether lasting memory traces are formed. This time course extends both backwards and forwards in time, as events such as the experience of novelty that upregulate the availability of PRPs may occur before or after other events, the memory traces of which may otherwise be transient. We think that the molecular players and processes identified in this Review are behind the neuronal algorithms that determine the persistence of synaptic and network changes and that are engaged by the multitude of everyday events that characterize animal and human life. A grand challenge for the future of the neuroscience of memory is to better understand the neural circuits and patterns of neural activity that intersect between cellular and systems consolidation.

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Competing interests statement
The authors declare no competing financial interests.

FURTHER INFORMATION
Roger L. Redondo's homepage: http://www.ccns.sbms.mvm.ed.ac.uk/people/postdoc/redondo.html
Richard G. M. Morris's homepage: http://www.ccns.sbms.mvm.ed.ac.uk/people/academic/morris.html

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