

# Synaptic tagging during memory allocation

Thomas Rogerson, Denise J. Cai, Adam Frank, Yoshitake Sano, Justin Shobe, Manuel F. Lopez-Aranda and Alcino J. Silva

**Abstract** | There is now compelling evidence that the allocation of memory to specific neurons (neuronal allocation) and synapses (synaptic allocation) in a neurocircuit is not random and that instead specific mechanisms, such as increases in neuronal excitability and synaptic tagging and capture, determine the exact sites where memories are stored. We propose an integrated view of these processes, such that neuronal allocation, synaptic tagging and capture, spine clustering and metaplasticity reflect related aspects of memory allocation mechanisms. Importantly, the properties of these mechanisms suggest a set of rules that profoundly affect how memories are stored and recalled.

The molecular and cellular mechanisms underlying the acquisition, consolidation, reconsolidation, extinction and recall of memory have attracted a great deal of attention<sup>1–7</sup>. By comparison, little is known about memory allocation<sup>8</sup>, the process that determines which specific neurons and synapses in a neural network will store a given memory. We propose that memory allocation is a phase of memory formation that encompasses those processes that determine the exact sites where memories are stored and that has specific interactions with other more traditional phases of memory, including acquisition and consolidation (see below). The significance of having mechanisms that determine the allocation of information to particular neurons and synapses within a neural network is theoretically crucial for the efficient storage and recall of that information. Inefficient allocation of information leads to suboptimal use of storage space, whether hard disks or synaptic sites are involved. For example, theoretical studies suggest that there is a balance between the stability and size of a memory representation and the maximum amount of information that can be stored: larger representations can be more stable, but storage space could be wasted; small representations save storage space, but memories are more easily disrupted<sup>9–12</sup>.

By directing related information to overlapping populations of neurons, memory allocation mechanisms could link these memories, place them within a common context, save storage space and perhaps alter memory strength and stability<sup>8</sup>. Memory allocation mechanisms may also organize the storage of information into component elements that encode features that are shared

across related experiences, thereby linking the storage of these experiences<sup>13,14</sup>. Thus, memory allocation includes mechanisms that ‘file’ and ‘cross-reference’ information in brain circuits.

This Review presents research detailing the mechanisms of memory allocation at both the synaptic (synaptic allocation) and neuronal (neuronal allocation) scale. More importantly, it attempts to integrate these previously separate areas of memory research into a unified view of how brain circuits regulate which neurons and synapses are committed to storing a given memory. Hopefully, this will facilitate the development of hypotheses, experiments and theories that elucidate why specific neurons and synapses are committed to storing a given memory as opposed to other neurons and synapses that receive similar input.

## Neuronal allocation

Neuronal allocation is a newly discovered phenomenon of memory formation that accounts for how specific neurons in a network, and not others that receive similar input, are committed to storing a specific memory. For example, previous studies have shown that changes in neuronal excitability that are triggered by the transcription factor cyclic AMP-responsive element-binding protein (CREB) modulate the probability that a given neuron will be involved in storing a specific memory. We propose that neuronal allocation mechanisms work closely with synaptic allocation mechanisms (that is, synaptic tagging and capture, spine clustering, and so on) that determine how information is parcelled to specific synapses. Although neuronal and synaptic allocation mechanisms

Departments of  
Neurobiology, Psychiatry &  
Biobehavioral Sciences, and  
Psychology, Integrative  
Center for Learning and  
Memory, Brain Research  
Institute, University of  
California, Los Angeles,  
California 90095–1761, USA.  
Correspondence to A.J.S.  
e-mail:

[silvaa@mednet.ucla.edu](mailto:silvaa@mednet.ucla.edu)  
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most probably work seamlessly during memory formation, their distinction is useful for designing, interpreting and describing allocation studies.

**Molecular and cellular studies of neuronal allocation.** Most studies of neuronal allocation to date used the amygdala as a model circuit. For example, previous studies suggested that changes in neuronal excitability triggered by CREB modulate the probability that a given lateral amygdala neuron will be involved in memory<sup>15,16</sup>. As many of the memory mechanisms studied to date are conserved across different brain regions, it is possible that the mechanisms of memory allocation found in the amygdala will also be present throughout the brain.

The amygdala has a key role in the modulation and storage of fear memories<sup>17</sup>. Circuits in the lateral amygdala are thought to store the association between the conditioned stimulus (for example, a tone) and the unconditioned stimulus (for example, a footshock) in fear conditioning<sup>17</sup>. More than 70% of all lateral amygdala neurons receive information regarding the auditory conditioned stimulus<sup>18</sup> or the unconditioned stimulus<sup>19</sup>. However, only a smaller subset of these neurons goes on to encode the memory<sup>20</sup>. Accordingly, only a subset of lateral amygdala neurons undergoes plasticity after auditory fear conditioning. Studies of modified AMPA receptors that can electrophysiologically tag synapses that are involved in learning indicated that only one-third of recorded amygdala neurons showed synaptic changes after fear conditioning<sup>21</sup>. Other studies confirm that only a fraction of lateral amygdala neurons actually encode memory for auditory fear conditioning<sup>22</sup>. This suggests that specific mechanisms govern the allocation of fear memories to specific neurons in the amygdala, with further studies suggesting that CREB plays an important part in this process<sup>8</sup>.

Initial memory allocation studies used viral vectors to demonstrate that changing the levels of CREB within a specific subpopulation of lateral amygdala neurons could affect the probability of these neurons being recruited into an auditory fear memory: increasing the levels of CREB within a subset of lateral amygdala neurons increases the probability that these neurons are involved in fear conditioning, whereas decreasing the levels of this transcription factor has the opposite effect<sup>15,16,23</sup>.

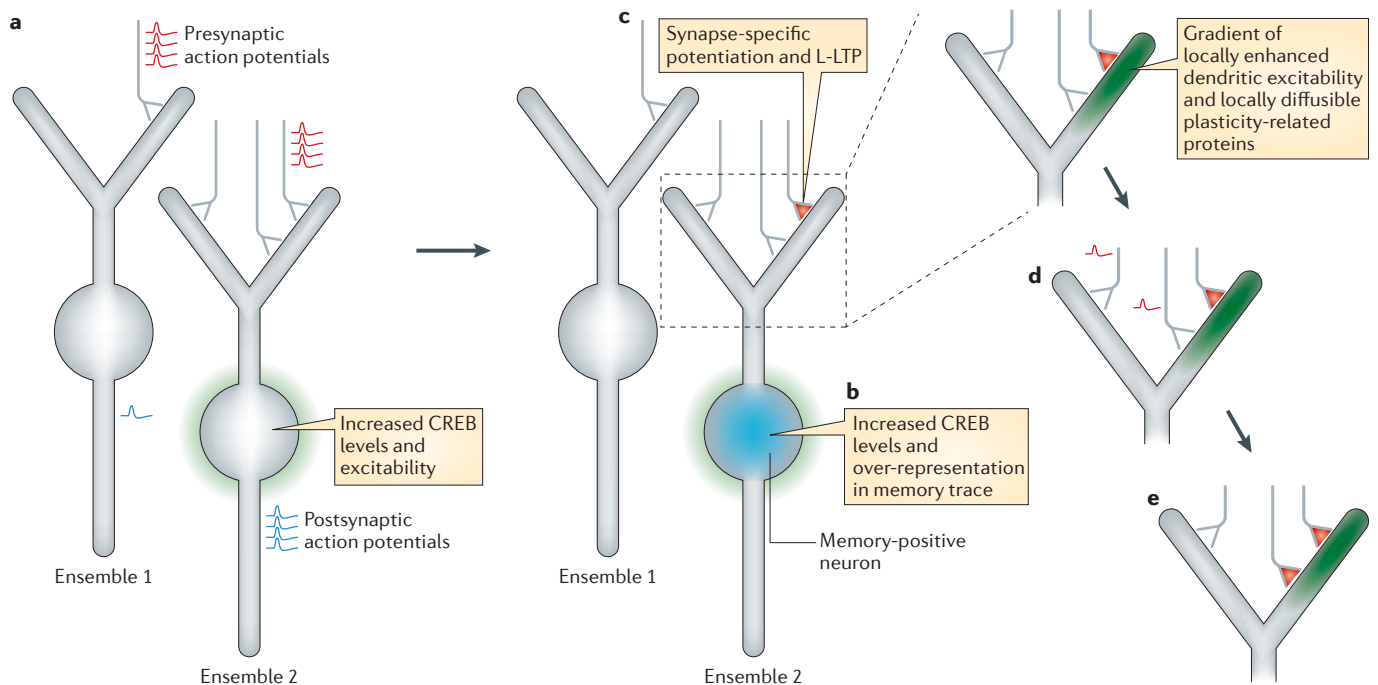
Three main strategies were used to demonstrate the role of CREB in neuronal allocation. First, studies using immediate-early genes as markers for a memory trace showed that lateral amygdala neurons with higher levels of virus-encoded CREB were approximately three times more likely to be recruited to the auditory fear memory trace than their neighbouring neurons. A number of control experiments showed that if learning was blocked, the memory trace was no longer biased to the neurons with higher CREB levels<sup>15</sup>, showing that learning is needed for biasing immediate-early gene expression to the cells with high CREB levels. In addition, manipulations that interfered with CREB functioning in specific lateral amygdala neurons decreased the probability of these neurons being recruited to the memory trace<sup>15</sup>.

Second, strategies that either inactivated<sup>16</sup> or deleted<sup>23</sup> the lateral amygdala neurons that expressed virus-encoded CREB also suggested that the memory was disproportionately represented in these neurons. For example, inactivation of lateral amygdala neurons expressing virus-encoded CREB with the allostatin system<sup>24</sup> triggered temporary amnesia for auditory fear conditioning, whereas inactivating a similar number of neurons with normal levels of CREB did not<sup>16</sup>. Related results were also obtained with conditioned taste aversion, another form of memory that involves amygdala circuits<sup>16,25</sup>.

Last, electrophysiological studies showed that after training in auditory fear conditioning, the lateral amygdala neurons transfected with the virus-encoded CREB showed greater synaptic strength than non-transfected neurons, a result that is consistent with the idea that memory is encoded in these neurons as increases in synaptic strength<sup>16</sup>. Importantly, additional results supported the hypothesis that CREB modulates neuronal allocation by controlling neuronal excitability<sup>16</sup>: neurons with higher CREB levels are more excitable and therefore more likely to fire in response to sensory input, more likely to be involved in synaptic changes underlying memory and thus are more likely to be over-represented in the memory trace (FIG. 1).

As mentioned, findings from other brain regions have generally paralleled those from memory allocation studies in the amygdala. Studies in the cortex have suggested that the population of neurons encoding a given memory is a subset of the population that was initially activated during learning<sup>26</sup>. The barrel cortex receives somatosensory information from facial whiskers, and therefore it has been used to study cortical plasticity during fear conditioning in which whisker stimulation is paired with a footshock<sup>27</sup>. Whisker stimulation has also been used for a whisker-signalled trace eyeblink-conditioning task; in this case, repeatedly pairing whisker stimulation with a mild periorbital shock<sup>28</sup> (or air puff<sup>29</sup>; see below), following a stimulus-free trace interval, triggered trace conditioning in mice. These results were extended by recent work using two-photon *in vivo* calcium imaging that showed that pairing whisker stimulation with a footshock led to a decrease in the number of neurons in the barrel cortex that responded to whisker stimulation<sup>29</sup>, suggesting refinement of the memory trace. Importantly, similar findings were also obtained in rabbits with the whisker-signalled trace eyeblink-conditioning approach<sup>30</sup>, suggesting that there are processes that determine which neurons in the barrel cortex are involved in conditioning responses. We propose that these processes are not random and that instead there are mechanisms that determine not only which cells respond initially but also shape the sparser and possibly more efficient memory trace.

The results reviewed above strongly support the role of CREB in neuronal memory allocation and suggest that similar mechanisms may also be present in other brain regions. Accordingly, there is indirect evidence that CREB is involved in regulating neuronal allocation in the hippocampus. First, transduction of CA1 neurons with virus-encoded CREB before training in



**Figure 1 | Integrating neuronal and synaptic allocation.** **a** | Neurons with increased cyclic AMP-responsive element-binding protein (CREB) levels (green ‘halo’ in ensemble 2) are more excitable and therefore more likely to fire postsynaptic action potentials in response to presynaptic action potentials and are more likely to be involved in synaptic changes underlying memory. **b** | Thus, these neurons are more likely to be over-represented in the memory trace (‘memory-positive’ neuron). **c** | Synapse-specific potentiation results in the local diffusion of plasticity-related proteins (for example, RAS and RHOA) from an activated synapse and a local enhancement in excitability. **d** | This increased excitability promotes plasticity in nearby synapses for a brief period of time. **e** | This results in clustering of potentiated synapses in close proximity to previously activated synapses. L-LTP, late long-term potentiation.

the Morris water maze<sup>31</sup> or in contextual conditioning<sup>32</sup> enhances these hippocampus-dependent memories. In these experiments, the virus only transduced approximately 25% of neurons in CA1 (REF. 32), resulting in a subset of neurons expressing increased levels of CREB; these neurons probably recruited a higher proportion of the memory trace in order for the memory to be strengthened by CREB. Importantly, viral transduction had to occur before training for the behavioural enhancement, as post-training injection of virus-encoded CREB without any other manipulation did not alter memory performance<sup>31</sup>. This is consistent with the idea that the enhancement observed was cell-specific and due to recruitment of the memory trace by high levels of CREB in a subset of neurons as opposed to some other effect of CREB.

As in the amygdala, there is evidence that an increase in excitability may also affect memory allocation in the hippocampus. For example, transgenic mice expressing a constitutively active form of CREB showed reduced afterhyperpolarization currents in hippocampal CA1 pyramidal neurons that led to increased excitability and reduced thresholds for long-term potentiation (LTP)<sup>33</sup>. Whole-cell recordings in behaving rats showed that hippocampal CA1 neurons that were recruited into encoding a given place (place cells) showed lower spike thresholds. In addition, these place cells showed peaked versus flat subthreshold membrane potentials that were sensitive to an animal’s location<sup>34</sup>. Interestingly, this

increase in excitability seemed to precede place-cell formation during spatial exploration<sup>34</sup>, as if prior events set the stage for the allocation of place information to a subset of neurons in the hippocampus. Furthermore, increasing excitability by depolarizing the somatic membrane potential of a silent neuron (that is, a neuron that previously did not fire to a spatially tuned location) during spatial exploration led to the emergence of a spatially tuned place cell<sup>35</sup>. CREB also seems to regulate neuronal excitability in other structures that are required for memory, in which it may again affect neuronal allocation<sup>36</sup>.

The aforementioned hypothesis stating that prior events determine which place cells will encode a given environment is supported by additional evidence from studies of a phenomenon termed ‘preplay’ (REF. 37). Preplay is complementary to the better-known phenomenon of replay, the recapitulation of place-cell sequences experienced during previous spatial explorations (usually while the animal is in quiet rest or sleep). Preplay takes place before (not after) exploration of novel environments. Remarkably, the preplay studies suggested that not only are there mechanisms that allocate which specific hippocampal place cells will encode a given place but that these neuronal allocation mechanisms may also determine the sequence in which these future place cells are activated during spatial exploration. It is conceivable that spontaneous firing events that occur before actual spatial

exploration engage neurons with the highest excitability more often than they engage neurons with comparatively lower excitability, thus leading to the statistical regularities reflected in preplay. Consequently, during preplay, and then spatial exploration, neurons with the lowest spike thresholds would on average be recruited first, followed by others with the next higher spike thresholds, and so on. This process would attach spatial attributes to a sequence of place cells with the highest excitability. From the perspective of memory allocation, these studies provide another piece of evidence that memory allocation is not random and that instead there are mechanisms that determine, ahead of time, which neurons may be involved in a given memory.

Studies in the piriform cortex also support the idea that increases in excitability have a crucial role in determining the neuronal ensemble encoding a given memory<sup>38</sup>. The stimulation of a random subpopulation of piriform cortex neurons by activation of channelrhodopsin 2, paired with either an aversive or an appetitive stimulus, is sufficient to allocate the storage of that information to these activated neurons. This suggests that in the piriform cortex, as in the amygdala and perhaps the hippocampus, increasing the probability that a neuron will fire during learning (in this case, by activation of channelrhodopsin 2) is sufficient to bias the allocation of both appetitive and aversive memories to specific subpopulations of neurons.

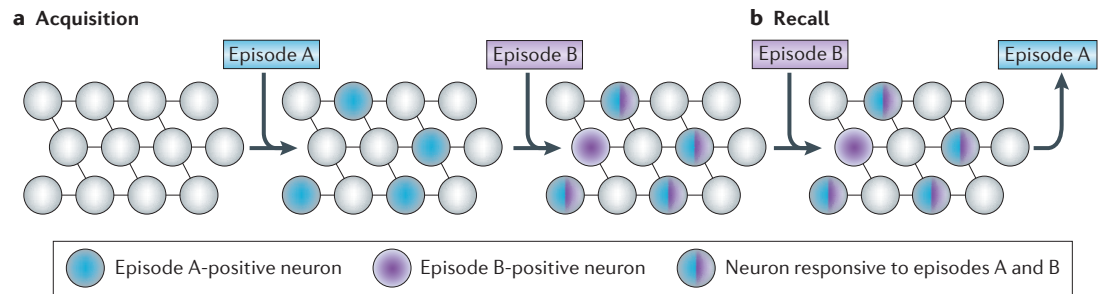
The aforementioned studies, in the amygdala, hippocampus and piriform cortex, all suggest that increased neuronal excitability has a profound role in memory allocation. Owing to this convergent evidence, it is highly likely that increased neuronal excitability is a determinant of memory allocation. Beyond CREB, there are many other mechanisms that modulate neuronal excitability in specific neurons of a circuit. It is very likely that some or many of these mechanisms may also affect neuronal allocation. The hypothesis proposed here is that the mechanisms involved in the consolidation of one memory may also trigger changes in the excitability of the neurons engaged in storing that memory, so that for a time they are more likely to be involved in the storage of subsequent memories. Any mechanism that affects excitability within these parameters could very well affect the probability that a given neuron responds and stores stimuli that trigger memory formation. Considering the fundamental evolutionary importance of recalling the right set of memories at a critical time, we suspect that there are many mechanisms of memory allocation, including multiple strategies to shape the excitability of neurons after memory formation. Indeed, abnormalities in mechanisms that affect neuronal excitability are thought to contribute to a range of cognitive disorders<sup>39</sup>.

Nevertheless, it is important to note that there are other strategies (in addition to increases in neuronal excitability) that determine which neurons are involved in storing a given memory. For example, extensive elegant experiments in the sensory and motor cortices have shown that the very neurons and networks that are active in processing motor and sensory information are the ones that are engaged in storing pertinent related information<sup>40–42</sup>.

**A key function of memory allocation mechanisms.** One of the proposed roles of memory allocation is to link memories that are formed within a defined temporal window<sup>8</sup>. The idea is that the first memory-creating event activates CREB in a subpopulation of neurons; this activation leads to an increase in excitability in these neurons that then biases the storage of memory for a second event to many of the same neurons that stored the first event. Because of the overlap between the memory traces for the two events, recall of one event may also lead to the recall of the other. The result would be the coordinated storage and retrieval of related memories (FIG. 2). Although this hypothesis has not been directly tested, the evidence reviewed next is consistent with its predictions.

Recent studies that used transgenic mice that express DREADDs (designer receptors exclusively activated by designer drugs) addressed the important question of how the brain could link two separate memories<sup>43</sup>. The artificial ligand clozapine-*N*-oxide (CNO) binds to transgenic DREADD and triggers strong depolarization and spiking. In these studies, DREADD was expressed under the control of the activity-dependent *Fos* promoter and the tetracycline-inducible system, so that DREADD could be expressed in an inducible and activity-dependent manner. The results showed that in a novel environment (context A), these transgenic mice expressed DREADDs from the *Fos* promoter in activated neurons. Later, this ensemble of neurons expressing DREADDs was reactivated by CNO while the mice were fear conditioned in a different context (context B). To recall the memory for context B, both populations of neurons (the DREADD-expressing neurons activated in context A and those neurons activated during exposure to context B) needed to be simultaneously activated. The results suggested that the transgenic mice formed a memory representation that integrated or linked contexts A and B. It is likely that CNO-driven activation of the representation of context A biased the allocation of the memory for context B to many of the same neurons that stored context A, thus closely integrating the memories for both contexts. A subsequent study<sup>44</sup>, which specifically manipulated the dentate gyrus using channelrhodopsin 2, further substantiated the claims of Garner *et al.*<sup>43</sup>. Together, these findings suggest that memory allocation mechanisms could be one of the reasons why recalling one memory while encoding another can result in the linking or integration of the two memories<sup>45</sup>.

In addition to increases in neuronal excitability as a mechanism for memory integration, findings from a study using calcium imaging and electrophysiological stimulation in rat hippocampal slices suggest that synaptic plasticity could contribute to possible post-training shifts in neuronal allocation<sup>46</sup>. The results indicated that initially distinct neuronal ensembles (that is, possibly representing distinct memories) can become more similar after co-activation of these two neuronal ensembles using stimulation protocols that are designed to trigger synaptic plasticity. The authors stimulated a set of hippocampal Schaffer collateral inputs and visualized the activated CA1 pyramidal neurons using calcium imaging.



**Figure 2 | Coordinated storage and retrieval of temporally related memories.** **a** | During acquisition, neurons in a neural circuit (grey circles) are recruited into encoding episode A (blue). This increases their excitability so that shortly thereafter, they are also very likely to be involved in encoding episode B (purple). **b** | With time, the increase in excitability wanes and sequent episodes are no longer stored in the same neurons. A consequence of this pattern of storage is that recall of episode B will also result in the recall of episode A (and vice versa), whereas recall of subsequent episodes will be unaffected. Figure is adapted, with permission, from REF. 8 © (2009) American Association for the Advancement of Science.

This was then repeated for a distinct set of Schaffer collateral inputs. Using stimuli that were expected to produce synaptic plasticity, the authors paired stimulation of the two Schaffer collateral inputs and found that the overlap between the ensembles of activated CA1 pyramidal neurons increased significantly. This suggests a mechanism for neuronal allocation in which the neuronal ensembles encoding two distinct memory traces can change and become linked (that is, there is greater overlap in the neurons engaged by each memory) owing to their coordinated activation (that is, possibly recall) in the hippocampus.

The examples from the amygdala, hippocampus and cortex described above demonstrate that there are allocation mechanisms that determine which neurons store a given memory in a neurocircuit. As we previously proposed, these mechanisms may function to link memories and modulate their storage and retrieval<sup>8</sup>. Next, we summarize the evidence for synaptic allocation mechanisms. Although neuronal and synaptic allocation mechanisms have a different history and have been studied separately, we propose that they are seamlessly integrated during memory formation.

### Synaptic allocation

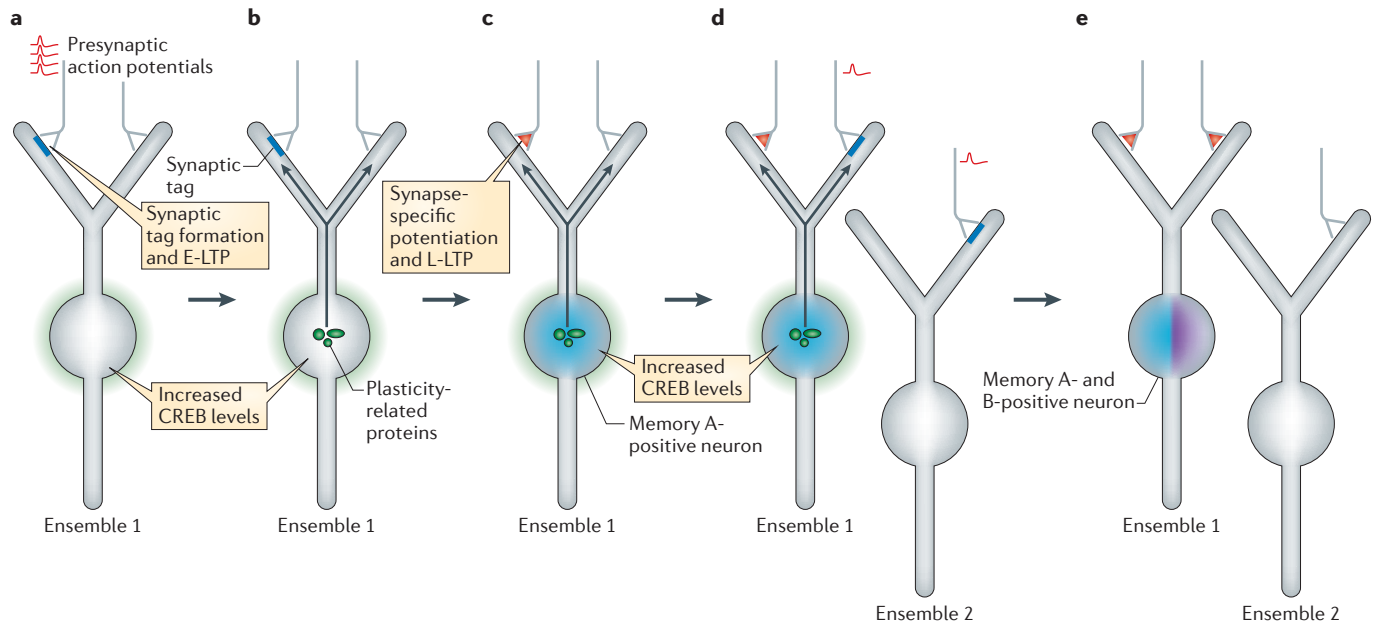
Synaptic allocation encompasses any mechanism that governs how specific synapses come to store a given memory. Inherent in the idea of synaptic allocation is the concept that multiple synapses could be activated by a given set of inputs, but specific mechanisms determine which synapses actually go on to encode the memory. For example, there is evidence that synapses do not always respond identically to a given stimulation pattern<sup>47</sup> and that a synapse's history of activation can affect its responses, a phenomenon referred to as metaplasticity<sup>48,49</sup>. In addition, there is also extensive evidence that the stable potentiation of a given set of synapses can, under certain circumstances, affect how other synapses in the same neuron respond to plasticity-inducing stimuli, a phenomenon that reflects mechanisms of synaptic tagging and capture<sup>50,51</sup>. All of these mechanisms may shape how synapses are recruited to encode a given

memory, how memories become linked in neurocircuits and whether they will be remembered. It is important to note that there is a natural relation between synaptic and neuronal allocation and that these two processes work seamlessly during memory encoding and storage: for example, the excitability of a cell, which determines neuronal allocation, is also a key determinant of whether any given synapse will undergo plasticity during encoding. Higher excitability increases, whereas lower excitability decreases, the probability of synaptic plasticity occurring at any one engaged spine. Nevertheless, there are useful distinctions between these two processes, and this section focuses specifically on synaptic allocation mechanisms.

### Molecular and cellular studies of synaptic allocation.

Synaptic tagging and capture mechanisms provide a compelling example of memory allocation at the synaptic scale. The idea of synaptic tagging was developed to explain how input specificity is achieved during LTP<sup>50,51</sup>. A mechanism was needed to account for the fact that many plasticity-related proteins (PRPs), which are essential for the maintenance of LTP and long-term memory, are generated in the cell body, but only specific synapses<sup>52,53</sup> are potentiated. The synaptic tagging and capture hypothesis proposes that the synapses activated during LTP induction become tagged in a protein synthesis-independent manner. These tagged synapses then capture PRPs, which are needed for the maintenance of LTP and, by extrapolation, long-term memory<sup>50,51</sup> (FIG. 3).

The initial experimental evidence<sup>54</sup> in support of the synaptic tagging and capture hypothesis came from a series of elegant *in vitro* electrophysiological studies in which two stimulating electrodes (S1 and S2) were placed in independent pathways that innervate the same population of rodent hippocampal CA1 neurons. In agreement with previous experiments demonstrating the specificity of LTP<sup>52,53</sup>, repeated strong tetanization of the S1 pathway could elicit lasting protein synthesis-dependent LTP (late LTP (L-LTP)) in the S1 but not S2 pathway. Surprisingly, after induction of L-LTP in the S1 pathway, repeated tetanization of the S2 pathway was able to induce L-LTP even in the presence of protein synthesis



**Figure 3 | Synaptic tagging and capture.** **a** | The synaptic tagging and capture hypothesis proposes that the synapses activated during early long-term potentiation (E-LTP) induction (as depicted by the presence of presynaptic action potentials) become tagged in a protein synthesis-independent manner that involves calcium/calmodulin-dependent protein kinase II (CaMKII) and actin (not shown). **b** | These tagged synapses then capture plasticity-related proteins (PRPs) downstream of the CaMKII–CaMKIV–cyclic AMP-responsive element-binding protein (CREB) pathway, which is needed for the maintenance of LTP and, by extrapolation, long-term memory linked to ensemble 1. **c** | The formation of the strong memory A (indicated by turquoise shading) induces late LTP (L-LTP) in a subset of synapses in neuronal ensemble 1 (depicted as a single neuron for clarity) but not in neuronal ensemble 2 (not shown). For at least 1 hour after strong training, neuronal ensemble 1 is able to share plasticity-related proteins that can convert a weak memory into a strong one ('synapse-specific potentiation'). **d** | An arriving action potential (memory B) at the top right synapse of ensembles 1 and 2 sets a new synaptic tag. **e** | Subsequently, the weak memory B (depicted in part **d**) is able to elicit L-LTP in neuronal ensemble 1 (owing to the presence of plasticity-related proteins) but not in neuronal ensemble 2. Ensemble 1 therefore becomes positive for memory A and memory B (indicated by dual blue and purple shading). This is an example of how synaptic tagging and capture can determine which neurons (not just synapses) would encode a given memory.

inhibitors. Perhaps the proteins needed for the maintenance of L-LTP, which were synthesized during the repeated tetanization of the S1 pathway, could be shared by synapses tagged during S2 tetanization and therefore support L-LTP in this second pathway. Accordingly, a weak tetanization of the S2 pathway, which could only elicit a transient potentiation (early LTP (E-LTP)), if preceded 1 hour earlier by L-LTP induction in the S1 pathway, was capable of inducing L-LTP in the S2 pathway<sup>54</sup>. Perhaps, E-LTP was sufficient to tag the S2 set of synapses that were then capable of capturing the proteins needed for the maintenance of L-LTP that was generated by repeated tetanization of the S1 pathway.

Later studies<sup>55</sup> using similar techniques confirmed that the subthreshold E-LTP-inducing tetanization could precede the repeated L-LTP tetanization by up to 1 hour and still be converted to L-LTP. This suggested that the tag set during E-LTP can be maintained for up to 1 hour. Remarkably, long-term depression (LTD) also seems to be capable of taking advantage of this synaptic tagging and capture mechanism<sup>56</sup>: short-lived LTD in one set of synapses can be converted into long-lasting or late LTD by L-LTP at another set of synapses of the same neurons.

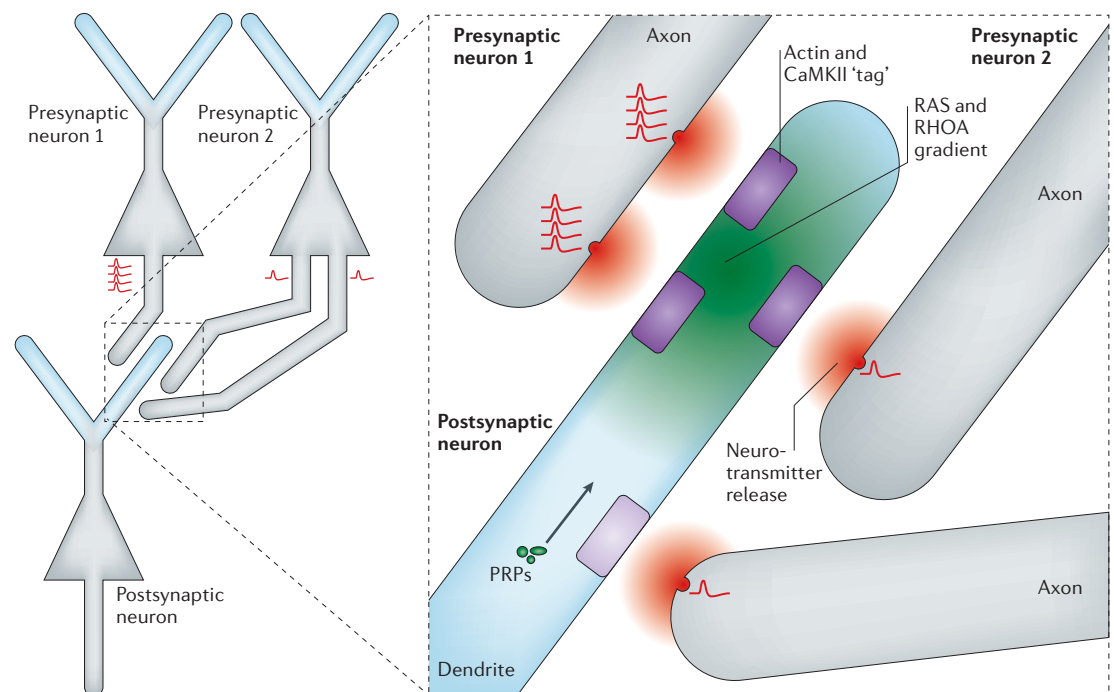
Converging evidence for the synaptic tagging and capture hypothesis came from pioneering studies conducted on cultured *Aplysia* spp. neurons<sup>57</sup>. These studies used a neuronal culture system in which a single *Aplysia* spp. sensory neuron makes synaptic connections with two physically separate motor neurons. In this elegant co-culture system, five pulses of serotonin adjacent to the synapses between the sensory and the motor neurons trigger long-term facilitation (LTF; the *Aplysia* spp. equivalent of L-LTP) of synaptic transmission, whereas a single pulse of serotonin only generates short-term facilitation (STF; the *Aplysia* spp. equivalent of E-LTP). In agreement with the synaptic tagging findings in rodents, STF induced in a set of synapses of the sensory neuron can be converted into LTF by inducing LTF in another set of synapses of the same sensory neuron. Presumably, STF generates tags that can then be used to capture PRPs generated by LTF in other synapses of the same sensory neuron. Subsequent studies established that the temporal properties of the tag were similar to those of the tag in the rodent hippocampus and that synaptic tagging and capture required protein kinase A activity and CREB function<sup>58</sup>.

Recently, pharmacological studies further explored the molecular underpinnings of synaptic tagging<sup>59,60</sup>. These studies suggested that calcium/calmodulin-dependent protein kinase II (CaMKII) and actin remodelling are important for setting the tag and that the CaMKII–CaMKIV–CREB pathway is important for the synthesis of the PRPs that are presumably shared between tagged synapses (FIGS 3,4). These proteins could include activity-regulated cytoskeleton-associated protein (ARC), GluR1, HOMER1A and protein kinase M $\zeta$ . Interestingly, low-frequency stimulation in conjunction with the application of dopamine D1 and D5 receptor agonists, brain-derived neurotrophic factor (BDNF) and carbachol can induce L-LTP, suggesting that these molecules may mediate the effects of repeated tetanization and trigger the production of proteins that are needed for the maintenance of L-LTP<sup>61–63</sup>.

**Structural studies of synaptic crosstalk.** Recent studies have also probed synaptic tagging and capture-like phenomena at individual dendritic spines. Findings from these and related studies<sup>64–66</sup> have also revealed other molecules that are likely to be involved in this process. Specifically, two-photon glutamate uncaging and fluorescence lifetime imaging were used to show that induction of LTP at one spine (which is reflected by increases in spine size) can

affect the probability of LTP being induced at a nearby spine in response to subthreshold stimulation<sup>64</sup>. The probability of this synaptic ‘crosstalk’ is inversely related to both distance between spines and time between inducing stimuli. This and another related study<sup>64,65</sup> found that, after LTP induction, calcium-dependent RAS activity increases for ~5 minutes within the activated spine and then diffuses ~10  $\mu\text{m}$  into adjacent spines. This spread of RAS signalling affects the threshold for LTP induction locally, perhaps via its ability to briefly (~1 minute) increase AMPA receptor exocytosis, leading to synaptic strengthening within and around the stimulated spine<sup>64,65</sup>. Furthermore, activated RHOA, a RAS homologue, is able to briefly (~5 minutes) diffuse up to 5  $\mu\text{m}$  from stimulated spines and could also be another mechanism for local synaptic crosstalk<sup>66</sup>.

Further research using two-photon imaging has provided additional functional insights into synaptic tagging and capture-like processes that are localized to neighbouring dendritic spines. These ground-breaking experiments used both imaging and electrophysiological recordings to study synaptic tagging and capture at the level of single spines<sup>67</sup>. The results indicated that E-LTP at one spine can be converted to L-LTP when L-LTP has previously been induced at a nearby spine. LTP was measured as an increase in spine volume using two-photon microscopy and was validated using perforated-patch



**Figure 4 | Molecular mechanisms for synaptic clustering and synaptic tagging and capture.** Neuron 1 is strongly activated (depicted by multiple red action potential traces), which leads to the formation of synaptic tags involving calcium/calmodulin-dependent protein kinase II (CaMKII) and actin in stimulated synapses. Diffusion of RAS and RHOA (indicated by green shading) from the activated synapses promotes plasticity in nearby synapses (~10  $\mu\text{m}$ ) for a brief period of time (<10 minutes). Production of plasticity-related proteins (PRPs) in the postsynaptic neuron is needed for stable synaptic strengthening, and these PRPs are shared by tagged synapses. In response to a single stimulation bout (single red trace), presynaptic neuron 2 fires weakly within 10 minutes, resulting in the formation of synaptic tags. Synapses closer to those that are strongly stimulated in neuron 1 will be more likely to be potentiated, resulting in synaptic clustering.

electrophysiological recordings. The E-LTP-to-L-LTP conversion process is protein synthesis-dependent and, interestingly, temporally asymmetrical<sup>67</sup>.

As mentioned, distance between activated spines is crucial for synaptic crosstalk. The results of Govindarajan *et al.*<sup>67,68</sup> also suggest that there is an inverse relationship between spine participation in synaptic tagging and capture and inter-spine distance, with little to no synaptic tagging and capture if spines are more than 70 µm apart on the same dendritic branch. Furthermore, less synaptic tagging and capture is observed if spines are located on different dendritic branches. Finally, simultaneous induction of L-LTP at two nearby spines causes a reduction in spine growth rate (which is thought to be correlated with synaptic potentiation), suggesting that there is competition for a limited pool of PRPs between nearby synapses<sup>67</sup>. These imaging results add to the original electrophysiological findings concerning synaptic tagging and capture mechanisms. They show that there are not only temporal constraints but also structural constraints that limit synaptic tagging and capture mechanisms. Activity-induced protein synthesis, which is localized to spine neighbourhoods<sup>69,70</sup>, may account for the inverse relationship between distance and the probability that a spine participates in synaptic tagging mechanisms<sup>68</sup>.

**Metaplasticity and synaptic allocation.** One of the key components of the allocation model introduced at the beginning of this Review is that the acquisition and storage of one memory changes a neurocircuit in such a way as to affect the storage and properties of another subsequent memory. Similarly, the synaptic tagging studies described above suggest that one memory can affect the synaptic mechanisms that set the thresholds for storage of a subsequent memory. Analogously, there is extensive evidence that an episode of synaptic plasticity can affect the properties of subsequent synaptic plasticity (for example, whether a synapse becomes potentiated or depressed). Metaplasticity has been coined 'the plasticity of plasticity' and is known to regulate both LTP and LTD<sup>48,49</sup>.

Metaplasticity can integrate bouts of synaptic plasticity that are separated by minutes to days<sup>48,49</sup>. Homosynaptic metaplasticity and heterosynaptic metaplasticity refer to whether the modulation of the subsequent plasticity is at the same or different synapses, respectively. Cellular excitability has been proposed as one of the mechanisms responsible for heterosynaptic metaplasticity<sup>71</sup>. As described above, CREB activation during learning induces changes in cellular excitability, which are implicated in neuronal allocation. It is possible that these changes in excitability also help to mediate other potential memory allocation phenomena, such as heterosynaptic metaplasticity.

Metaplasticity as well as synaptic tagging and capture mechanisms have important implications for memory allocation. They suggest a set of rules that could potentially modulate the interaction between memories allocated to an overlapping neuronal population. The studies that have been described above suggest that the synaptic mechanisms engaged by one memory could change the synaptic rules for storing a subsequent memory, a

finding that has profound implications for memory storage. For example, the synaptic tagging studies reviewed above suggest that, under certain circumstances, a weak memory (capable of triggering only E-LTP), which would otherwise be forgotten, could be strengthened and stabilized by a strong memory (capable of triggering L-LTP), provided that they were encoded within certain time constraints, by synapses of the same neuron. Next, we review a number of studies that demonstrate the behavioural implications of memory allocation mechanisms.

**Behavioural implications of synaptic allocation.** As discussed earlier, the synaptic tagging and capture hypothesis has three critical components with possible behavioural implications: first, a weak synaptic input creates a temporary synaptic tag; second, a strong synaptic input (to the same neuron) triggers the induction of PRPs, which can be shared with tagged synapses of weak inputs; and, third, owing to the shared PRPs, the synapses of the weak input can undergo long-lasting changes and these changes are dopamine- and protein synthesis-dependent. These properties of synaptic tagging can be used to make the following behavioural predictions: first, a strong, long-lasting memory can convert a short-term, weak memory into a stronger, long-term memory; and, second, this conversion from an unstable to a stable memory by another strong memory should be dopamine- and protein synthesis-dependent.

Elegant behavioural experiments have uncovered interactions between memories that exhibit the defining features of the synaptic tagging and capture hypothesis<sup>72</sup>. These experiments in rats showed that a weak inhibitory avoidance memory (that only lasted for a few hours) could be converted into a stronger inhibitory avoidance memory (that lasted for days) if the rats were first exposed to a novel environment (but not to a familiar environment) 1 hour before training. Moreover, this conversion from a weak to a strong memory was both dopamine- and protein synthesis-dependent. The implications of these findings are that weak inhibitory avoidance training tagged a set of synapses encoding this training and that the exposure to the novel environment created PRPs that were shared with the tagged synapses allocated to the weak memory. These shared PRPs then strengthened and stabilized the weak memory for the mild inhibitory avoidance training.

A follow-up study showed that weak memories for spatial object recognition, contextual fear conditioning and conditioned taste aversion (all lasting on the order of a few hours) could also be converted into long-lasting memories (lasting for days) if they were preceded by exposure to a novel experience<sup>73</sup>. In all cases, protein synthesis was required during exposure to the novel environment. Interestingly, human learning and memory studies have shown that providing a novel context can strengthen memory<sup>74</sup>, a result that is consistent with these findings and the predictions of the synaptic tagging and capture hypothesis. The idea is that providing a novel context in these human studies strengthens otherwise weak memories, just as exposure to a novel open field strengthens weak memories in rats.



Parallel behavioural and electrophysiological studies of synaptic tagging have uncovered compelling evidence for this hypothesis<sup>75</sup>. Rats were given one trial per day to find food in different spatial locations and later had to recall that day's spatial location. A weak food reward led to weak encoding of the food's spatial location that was quickly forgotten. However, when followed by novelty exploration 30 minutes later, a weak encoding episode triggered a long-lasting memory for the food's location. Similarly, strong tetanization, analogous to exposure to a novel environment, both induced L-LTP and converted E-LTP to L-LTP on an independent but convergent pathway. Again, these processes required hippocampal dopamine D1 and D5 receptor function and protein synthesis<sup>75</sup>.

Interestingly, behavioural studies, using some of the same tasks used in the experiments above, do not always lead to the predicted memory enhancements. For example, a previous study suggested that exposure to a novel open field 1 hour after inhibitory avoidance training actually impairs the original inhibitory avoidance memory<sup>76</sup>. The impairment was observed for both strong and weak avoidance training. However, there was no impairment with a shorter delay (that is, 5 minutes), a longer delay (that is, 6 hours) or when the open field was familiar. These results suggest that the exact parameters (for example, strength of training, length of intervals, novelty and other characteristics of the open field) of these experiments matter and that we have only started to tap the complexity that regulates the interactions between memory-encoding events.

The studies described above provide imaging and electrophysiological evidence for the idea that synaptic plasticity in one set of synapses alters plasticity in another group of synapses. Next, we review evidence that spine formation is also sensitive to the previous synaptic history of that neuron. In another words, the molecular and physiological changes triggered by a given behavioural training episode seem to affect the rules that control the formation or loss of spines triggered by subsequent behavioural training.

**Learning and spine clustering.** There is growing evidence for the hypothesis<sup>77</sup> that inputs with functional similarities are organized in clusters within the dendrites of pyramidal neurons<sup>68</sup>. Spine clustering is thought to result in the amplification of synaptic inputs owing to the non-linear properties of the induction and propagation of dendritic spikes<sup>78</sup>. Recent findings reviewed above suggest that there are synaptic allocation mechanisms that account for the clustering of spine changes<sup>68</sup>.

Recently, two-photon *in vivo* imaging was used to demonstrate synaptic clustering of functionally related inputs in the motor cortex during a forelimb motor-learning task<sup>79</sup>. In this context, synaptic clustering refers to the addition of new spines during training to dendritic sites where other spines had been added in previous training trials. This study reported clustered addition of spines onto dendrites of layer 5 pyramidal cells in the motor cortex following learning of a

seed-reaching task. Furthermore, the authors found that clustered spines are more stable than non-clustered new spines. Finally, this clustered addition of spines occurs in a task-specific manner; that is, spines added after one task do not cluster with spines added after a different task, suggesting that spine clustering in the motor cortex reflects a morphological mechanism for synaptic storage of specific motor memories<sup>79</sup>. Although neuronal allocation mechanisms are thought to primarily link related but distinct memories, multiple exposures to the same motor-training patterns may result in spine clustering and thus strengthening of a given motor memory. It will be interesting to determine whether spine clustering in other regions of the cortex follow similar rules.

Although previous studies, including the one just reviewed above, indicate that learning can involve the net gain of new spines, learning can also be associated with a net loss of spines. A recent study reported a net loss of spines in the hippocampus after contextual fear conditioning<sup>80</sup>. This spine elimination was found specifically in active hippocampal neurons tagged by green fluorescent protein (GFP) under the control of a novel *Fos* tetracycline (tet) transgenic system. This net loss of spines in GFP-tagged hippocampal neurons required both exposure to the training context and conditioning (that is, footshocks). Remarkably, another study also reported that fear conditioning leads to the net loss of spines in the frontal association cortex, a region implicated in fear conditioning, which strongly correlates with memory on recall<sup>81</sup>. More striking is the finding that extinction of this specific fear memory induced the formation of spines within 2  $\mu\text{m}$  on either side of the spines that had been lost after conditioning. In addition, the spines added after extinction had a similar orientation to those lost during conditioning, as if they shared afferents. The implication is that the frontal cortex is involved in fear conditioning and extinction, and that in this region the synaptic allocation of memory for extinction is clustered around sites allocated to storing memory for conditioning. This is an interesting and surprising result, as there is a large amount of data demonstrating that extinction is not simply the reversal of conditioning<sup>82</sup> but instead involves new learning.

**Molecular mechanisms for synaptic clustering.** A potential mechanism for the clustered addition of spines is the aforementioned diffusible molecular crosstalk that occurs near activated spines. As mentioned above, previous studies suggested that signalling molecules synthesized at one spine, such as activated RAS and RHOA, diffuse out and may support spine changes in other nearby spines, thus possibly contributing to spine clustering. In addition, two-photon imaging studies of hippocampal slices also implicated a RHO GTPase (CDC42) in long-term spine volume increases. These increases were triggered by spine-specific stimulation using two-photon glutamate uncaging. These structural changes, as well as the activation of RHOA and CDC42, were shown to be dependent on CaMKII, a calcium-activated kinase that has a critical role in LTP and learning<sup>64,66</sup>. Induction of LTP leads to the addition

of new spines that contact the same presynaptic component<sup>83</sup>. This hints at a role for trans-synaptic signalling in synaptic allocation. Later work suggested that this process may be partly regulated by NMDA receptor activation and nitric oxide signalling<sup>84</sup>. Beyond RHOA, CDC42 and CaMKII, several other molecules have been implicated in spine formation and dynamics, such as TIAM1 and  $\beta$ -PIX (also known as ARHGEF7). These molecules may also be required for spine clustering<sup>85</sup> (FIG. 4).

#### *Synergism of synaptic and neuronal allocation.*

Although the study of synaptic and neuronal allocation mechanisms have separate histories, the studies reviewed here suggest that these two classes of processes use some of the same molecular mechanisms (for example, those involving CREB) and are closely interconnected. For example, without mechanisms that recruit a given neuron to encode both the initial strong or weak memory event, synaptic tagging and capture could not take place. Similarly, neuronal allocation mechanisms, which involve CREB-dependent changes in excitability, are dependent on mechanisms that recruit specific synapses to store the information in question. Therefore, we propose that synaptic and neuronal allocation mechanisms function hand-in-hand to determine where memories are stored in neurocircuits.

For example, suppose that the formation of a strong memory induces L-LTP in a subset of synapses in neuronal ensemble 1 but not in neuronal ensemble 2. For at least 1 hour after strong training, neuronal ensemble 1 would be able to share PRPs that could convert a weak memory into a strong one: the training for the weak memory would be able to elicit L-LTP in neuronal ensemble 1, owing to the presence of PRPs, but not in neuronal ensemble 2 because these proteins are absent there. This is an example of how synaptic tagging and capture could determine which neurons (not just synapses) would encode a given memory (FIG. 3). Conversely, mechanisms that are typically associated with neuronal allocation (for example, CREB-dependent changes in excitability) may also have a role in synaptic allocation. For example, increases in neuronal excitability in a given neuronal ensemble may affect some dendrites more than others, thus biasing memory storage to synapses in dendrites with higher excitability<sup>86,87</sup>.

#### **Memory allocation and schemas**

Studies by Piaget<sup>88</sup> and Bartlett<sup>89</sup> first introduced the idea that when new memories are related to previously acquired information, they are readily assimilated, perhaps because they are stored within pre-existing memory schema. Recent studies using rats suggest that organized schema in the neocortex, which are initially acquired gradually with the help of the hippocampus through many days of training, once present, account for the rapid acquisition and consolidation of related information<sup>90,91</sup>. Single-unit studies showed that many of the same neurons that fired in response to original goals early in training, presumably during schema formation, also fire in response to novel goals later in training<sup>92</sup>,

providing evidence that is consistent with the idea that memory allocation mechanisms assign new memories to neurons that were involved in encoding the original memories that shaped schema formation. Glutamatergic and dopaminergic mechanisms have been implicated in synaptic tagging and capture<sup>72,93</sup> and potentially schema learning, perhaps because these mechanisms are likely to be involved in the encoding and cellular consolidation of this rapidly acquired information. However, it is unclear what mechanisms are specifically responsible for the allocation of new memories to the same neurons that were initially involved in schema formation. Is the excitability of these neurons increased? If so, what mechanisms account for this increase? Is there a role for pre-frontal-hippocampal interactions in regulating the excitability of these neurons<sup>94</sup>?

#### **Memory allocation and cognitive deficits**

As memory allocation mechanisms are crucial for determining where memories are stored in neuronal networks, it is possible that deficits of memory allocation could lead to cognitive pathologies. Accordingly, aberrant levels of CREB expression and neuronal excitability have been reported in animal models of human neurological and psychiatric disorders, such as Alzheimer's disease (AD)<sup>95,96</sup>. Interestingly, overexpression of CREB-binding protein or CREB in the hippocampal CA1 region seems to rescue the spatial memory deficits in a transgenic mouse model of AD<sup>97,98</sup>. Furthermore, an increase in the levels of amyloid- $\beta$  causes deregulation of calcium and potassium channels, resulting in abnormal intrinsic neuronal excitability<sup>99</sup>. Taken together, these findings suggest that an increase in amyloid- $\beta$  levels results in altered CREB function, which then alters neuronal excitability and consequently could affect memory allocation mechanisms. Alterations of these mechanisms could contribute to the cognitive deficits associated with AD.

Age-related changes in neuronal excitability (unrelated to AD) may also lead to deficits in memory allocation. It is well documented that ageing leads to cognitive deficits, especially in hippocampus-dependent memory. It is also known that some of these deficits are related to decreases in intrinsic excitability, as characterized by larger afterhyperpolarization and an increased spike-frequency adaptation (accommodation) of hippocampal neurons in older mice<sup>100</sup>. These decreases in excitability may also lead to deficits in memory allocation; specifically, memories that would otherwise be linked and stored together or memories that might strengthen each other are unable to do so because of the lower excitability levels of the aged brain. Importantly, abnormalities in mechanisms that affect neuronal excitability are thought to contribute to a range of cognitive disorders<sup>39</sup>. For example, it is possible that changes in neuronal excitability and associated deficits in memory allocation could lead to inappropriate connections between memories and therefore contribute to the frequent loose association of thoughts or speech that is seen in schizophrenia. Indeed, changes in GABAergic function in schizophrenia<sup>101</sup> could potentially affect neuronal excitability and therefore memory allocation.

### Future studies of memory allocation

Although there is strong and growing evidence for synaptic and neuronal allocation, there is much to be done in this exciting, young field. For example, there is no clear integration of the various mechanisms implicated in memory allocation, including synaptic tagging and capture, metaplasticity, spine clustering and CREB-mediated neuronal excitability. Understanding the molecular, cellular and systems mechanisms and implications of these processes may elucidate how they are coordinated and integrated during memory formation. For example, it would be crucial to determine the molecular mechanisms involved in these processes, such as the PRPs that are captured by tagged synapses.

In addition, there is a pressing need for tools to image and manipulate spine clustering and tagging, so that it is possible to study the functional significance of these allocation mechanisms. For example, it would be important to carry out behavioural studies using approaches capable of promoting, preventing and imaging *in vivo* synaptic tagging and spine clustering. Although the elegant studies reviewed here have uncovered behavioural evidence that is consistent with the synaptic tagging and capture hypothesis, there is still no direct evidence that the interesting behavioural interactions ascribed to synaptic tagging and capture actually involve these mechanisms. It is possible that the behavioural interactions ascribed to synaptic tagging and capture are caused by protein synthesis-dependent increases in neuromodulators, such as dopamine, that are unrelated to synaptic tagging mechanisms. To obtain direct evidence of the tagging hypothesis, it will be essential to pair behavioural analysis with techniques that enable the labelling, tracking and manipulation *in vivo* of synapses that are involved in memory. These experiments should not only be able to visualize the synaptic events underlying the behavioural interactions that are consistent with the synaptic tagging hypothesis, they also ought to manipulate these synaptic changes directly and specifically and study the impact on the behavioural interactions. Convergence between these tracking and manipulation studies would make a compelling argument for the behavioural function of synaptic tagging and capture mechanisms.

Similarly, much remains to be done in neuronal allocation research. Most studies of this class of mechanisms have focused on the effects of CREB. Nothing is known about the molecular cascades upstream and downstream of this transcription factor that are specifically involved in memory allocation. What are the receptor systems and signalling cascades that activate CREB and affect allocation? What are the channels that mediate the increase in excitability that is thought to underlie neuronal allocation? The answers to these questions, not only in the amygdala, in which most previous studies of neuronal allocation have been carried out, but also in other brain regions, will be crucial for increasing the understanding of these important phenomena.

In addition, it would be of great interest to determine how phenomena such as extinction and reconsolidation affect synaptic and neuronal allocation of information in the amygdala, prefrontal cortex and hippocampus<sup>82,102</sup>. Furthermore, at a circuit level, it is important to determine how neuronal allocation in one brain region affects allocation in other interacting regions. In this respect, it would be especially interesting to study neuronal allocation during systems consolidation, in which interactions between hippocampal and cortical ensembles may shape the semantic structure of information<sup>103</sup>. For example, how are memory allocation mechanisms coordinated between hippocampal and neocortical networks during systems consolidation? Although most studies of neuronal allocation have focused on molecular and cellular mechanisms, future studies will need to integrate these findings with the circuit mechanisms of memory storage.

### Conclusions

The studies reviewed here conclusively demonstrate that there are mechanisms that can determine which synapses and neurons in a neurocircuit go on to encode a given memory from a pool of synapses and neurons that receive similar input. This process is not random and instead is likely to involve mechanisms such as synaptic tagging, spine clustering, metaplasticity and CREB-dependent changes in excitability. The results reviewed also suggest that synaptic and neuronal allocation mechanisms work closely together in shaping the networks of cells involved in the acquisition, stabilization and recall of information in the brain.

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#### Competing interests statement

The authors declare no competing interests.

#### FURTHER INFORMATION

P. Golshani's laboratory homepage: [www.golshanilab.neurology.ucla.edu](http://www.golshanilab.neurology.ucla.edu)

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