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Review article

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Engram mechanisms of memory linking and identity

Ali Choucry [1,2,3], Masanori Nomoto [1,2,4,5] & Kaoru Inokuchi [1,2,4]

Abstract

Memories are thought to be stored in neuronal ensembles referred to as engrams. Studies have suggested that when two memories occur in quick succession, a proportion of their engrams overlap and the memories become linked (in a process known as prospective linking) while maintaining their individual identities. In this Review, we summarize the key principles of memory linking through engram overlap, as revealed by experimental and modelling studies. We describe evidence of the involvement of synaptic memory substrates, spine clustering and non-linear neuronal capacities in prospective linking, and suggest a dynamic somato-synaptic model, in which memories are shared between neurons yet remain separable through distinct dendritic and synaptic allocation patterns. We also bring into focus retrospective linking, in which memories become associated after encoding via offline reactivation, and discuss key temporal and mechanistic differences between prospective and retrospective linking, as well as the potential differences in their cognitive outcomes.

Sections

[1]Graduate School of Medicine and Pharmaceutical Sciences, University of Toyama, Toyama, Japan. [2]Research Center for Idling Brain Science, University of Toyama, Toyama, Japan. [3]Department of Pharmacology and Toxicology, Faculty of Pharmacy, Cairo University, Cairo, Egypt. [4]CREST, Japan Science and Technology Agency (JST), University of Toyama, Toyama, Japan. [5]Japan Agency for Medical Research and Development (AMED), Tokyo, Japan. e-mail: inokuchi@med.u-toyama.ac.jp

Introduction

Where our memories reside and how we can use them are questions that have baffled humans for centuries. Neuroscientists have long advocated the physical nature of memory traces: Richard Semon originally coined the term 'engram' to describe an enduring change in the brain that occurs as a result of a stimulus[1], whereas Donald Hebb later hypothesized that connections between two neurons that are coactive during an event will be strengthened, creating cell assemblies that can encode and recall memories[2]. Evidence for a physical memory substrate surfaced also from clinical observations, including the effects of electrical brain stimulation on memory recall[3] and the consequences of brain lesions[4]. Later, experimental studies in rodents systematically and unequivocally identified the memory engram as a memory trace that can be localized to a defined population of cells. This population of neurons, activated during learning, was shown to be reactivated by[5], necessary for[6] and sufficient for[7] successful memory recall. The sufficiency of memory engrams to recall a particular event means that mice will freeze in neutral environments in which they have experienced no adversity, when engrams of previous fearful memories are artificially activated (Fig. 1). This also paves the way for the creation of false memories and associations through the coactivation of engrams for unrelated events[8,9]. As more studies identified these engrams across different brain regions and behavioural paradigms (for examples, see refs. 6,9–15 and for comprehensive reviews of these discoveries, see refs. 16,17), both their necessity and their sufficiency to recall memories were firmly established. Some researchers went further, demonstrating that memories are housed at specific synapses within neurons, known as synaptic engrams[18–21].

Whether cellular or synaptic, a physical memory engram can explain the encoding and recollection of simple memories such as a shock–context association; however, many memories comprise multiple elements that need to be combined to create the final product that we perceive. It is also fundamental to our knowledge and decision-making (and, eventually, to our character) to have the ability to link distinct yet related memories. From linking events happening close in time[22–25] to deciphering hidden patterns to infer the solution to a problem[26,27], interactions between memory engrams may thus grant us higher cognitive abilities than the mere encoding of single memories. To complicate matters further, there must exist some mechanism(s) to preserve the individual identities of linked memories, as such engram interactions would otherwise be useless in the long term: if linking simply fused memories into a single large unit, we would effectively lose their characteristic details. These considerations meant that the next logical step in memory research after the discovery of memory engrams was an investigation of memory organization beyond the single-event level.

A plethora of studies in animal models have shown that when two memories are linked they are allocated to an overlapping population of engram cells[9,23,28–31], whereas others have pointed to synapse-specific events as the gatekeepers for memory identity[18,19,31–34] or to dendritic compartments as the true substrate for memory organization[34–36]. At a glance, it may therefore seem that the question of memory organization has been addressed: indeed, we do now have a strong basic understanding of its dynamics. However, adopting a broader perspective reveals that some facets of memory linking remain uncharted. For example, almost all of the engram overlap studies utilized prospective linking, in which two memories that occur within a short time frame of each other are linked through mechanisms that are already in effect after the first of the two events has occurred. It is far less well understood how a link between two memories can be established after both events have been encoded (retrospective linking). Understanding whether and how prospective and retrospective linking mechanisms are selectively recruited for specific cognitive outcomes will be essential to properly capture the ever-growing organization of lifelong memories.

In this Review, we summarize the evidence for engram overlap as a key mechanism for prospective linking. We then discuss key cellular and molecular mechanisms that are involved in this process, as well as insights from network simulation models designed to capture a comprehensive picture of the linking process. We highlight the involvement of dendritic compartmentalization and synaptic clustering in this process, and propose a model that connects the somatic events that link individual memories to the synapse-specific plasticity that preserves memory identities. We finally present retrospective linking as a potentially distinct form of memory association with its own unique set of cellular mechanisms and cognitive outcomes.

Engram overlap in memory linking

Evidence for engram overlap

The concept that overlapping populations of cells might store and associate multiple inputs emerged first from simple association studies, in which animals learn to associate a conditioned stimulus (CS) (such as a tone, light or context) with an unconditioned stimulus (US) (such as an electric shock or food) and thus develop a conditioned response (such as freezing or salivating) to the CS. This is also known as Pavlovian conditioning[37]. Although such conditioning does not necessarily reflect the linking of two distinct memories, it does necessitate the association of two stimuli to successfully develop a memory.

Early studies in mice assessed the expression of immediate early genes (IEGs) such as *Arc* — whose transcription is induced by neural stimulation — to visualize the convergence of multiple inputs onto the same population of neurons. *Arc* mRNA is restricted to the nucleus within 5 min after induction and then shifts to the cytoplasm, where it can be detected for another 25–30 min[38]. This means that if the CS and US are separated by around 25 min, it is possible to identify the neurons carrying their respective signals by examining *Arc* localization. Using this technique, a subpopulation of amygdalar neurons was found to be activated by both the CS and the US during associative learning[39–41] (Fig. 2a). Furthermore, the convergence of CS and US signals in this population was found to be required for successful taste associative learning[42]. Although these studies suggested input overlap as a candidate mechanism for associative learning, they lacked the temporal resolution to properly study the neural ensemble dynamics involved in learning each input and associating those inputs with each other. To address this, later studies used in vivo real-time calcium imaging in freely behaving mice to record ensemble activity during the presentation of the CS and US and subsequent periods. One study showed that the CS-responding neuronal ensemble in the amygdala changed to resemble that of the US following successful association[43], suggesting that there is crosstalk between sub-ensembles of the same memory. A second study revealed another form of neuronal crosstalk in the hippocampal area CA1 (ref. 44). As mice were presented with the CS and US, their respective ensembles responded separately to each input. However, following the conclusion of the inputs, a phase of network reverberation ensued, during which both ensembles displayed synchronized activity, resulting in successful CS–US association. This suggested that, in addition to cellular overlap, a temporal overlap of the activity of distinct ensembles can also link different aspects of a memory[8,9].

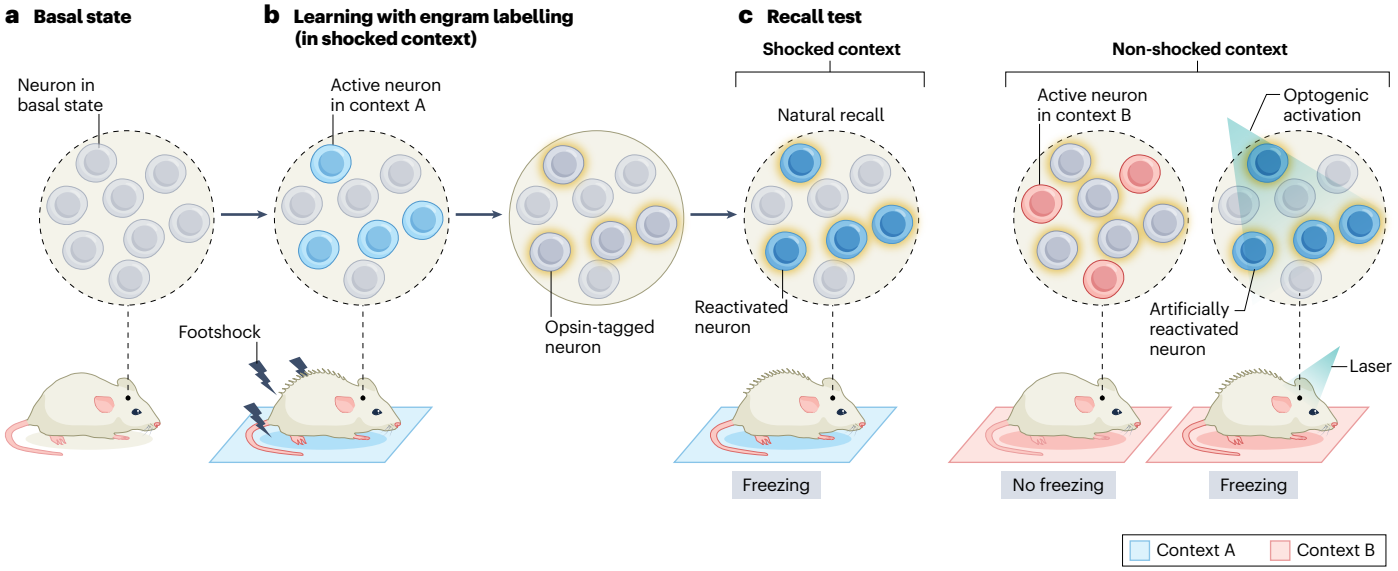


Fig. 1 | Sufficiency of engram cells for memory recall. Memory engrams that are active during encoding can induce memory recall when they are naturally or artificially activated[6,7]. A typical engram labelling experiment in mice illustrates these properties. **a**, Before learning (fear conditioning), all neurons are in the basal state. **b**, During fear conditioning, neurons that will form part of the engram (known as engram cells) are activated and will store the fear memory (blue-shaded cells). These engram cells are labelled with an activity-dependent photo-reactivatable opsin (yellow shading), usually expressed under the control of an immediate early gene promoter. **c**, Reactivation of engram cells, either naturally by a return to the shocked context (context A) or optogenetically in a completely neutral context (context B), is necessary and sufficient to recall the fear memory, resulting in freezing. Red-shaded cells represent naturally forming engram cells for the neutral context. The number of engram cells shown here is over-represented for clarity: in true experimental conditions, non-engram cells vastly outnumber their engram counterparts (for example, see refs. 9,11).

Just as signals related to the CS and US converge on the same neurons within seconds or minutes to generate associations within the frame of a single episodic memory, studies have shown that different memories — encoded hours apart — may (under specific circumstances) be stored in the same population of neurons to induce memory linking.

One study has shown how neuronal co-allocation, that is, the allocation of the same population of neurons to more than one memory engram, in the hippocampus can naturally link contextual memories that are encoded close in time[22]. When mice were exposed to two contexts within a short temporal window (5 h), the memories of these contexts were linked so that receiving a foot shock in one chamber caused mice to significantly freeze in the other chamber. This fear was not merely an outcome of generalization, as the mice were able to discriminate between the two linked contexts and a neutral context that was never linked with the previous two, indicating that the linking was specific and that memory identity was preserved. Calcium imaging and engram labelling through genetic and immunohistochemical techniques revealed a higher overlap between the active ensembles encoding either context when the memories were linked, compared with the overlap when they were separated by a longer temporal window and hence were not linked (Fig. 2b). Another study using auditory fear conditioning (AFC) with two separate tones demonstrated similar co-allocation and memory linking in the mouse amygdala when the two tones were presented close in time[24]. This work further demonstrated that engram overlap and memory linking can also be induced by the mere recall (rather than learning) of an event soon before the encoding of the other.

Both of these studies consolidated the concept of ensemble overlap as a key mechanism for memory linking and instigated more experiments to explore different facets of this notion[23,28,29,45]. In one elegant study, two amygdala-dependent emotional memories — conditioned taste aversion and AFC — were linked through repeated co-retrieval sessions[28]. Linking was evident as mice froze (the behavioural response to AFC) when they received saccharin (the conditioned taste aversion stimulus). Labelling and optogenetically inhibiting the overlapping ensemble that was shared between both paradigms resulted in the preservation of both memories, but severed the link between them. This showed that connections between memories can be specifically altered without affecting the individual memories, providing insight into what exactly is encoded within the overlapping engrams.

In the studies described above, overlapping engrams were found and manipulated in the hippocampus and the amygdala, but whether higher cortical regions adopt the same mechanism for memory linking was unknown. A more recent study therefore targeted the posterior parietal cortex, which was shown to be involved in the association between an immediate shock memory (stored in the basolateral amygdala) and a contextual memory (stored in the hippocampus)[45]. Optogenetic activation of the same posterior parietal cortex ensembles during immediate shock and context exploration created an artificial link between these events, whereas inhibiting the posterior parietal cortex population that was active after experiencing both events specifically impaired the association but kept both memories intact. These results thus confirmed that engram overlap can be a brain-wide mechanism for memory linking that maintains memory identity. In line with this, it was also demonstrated

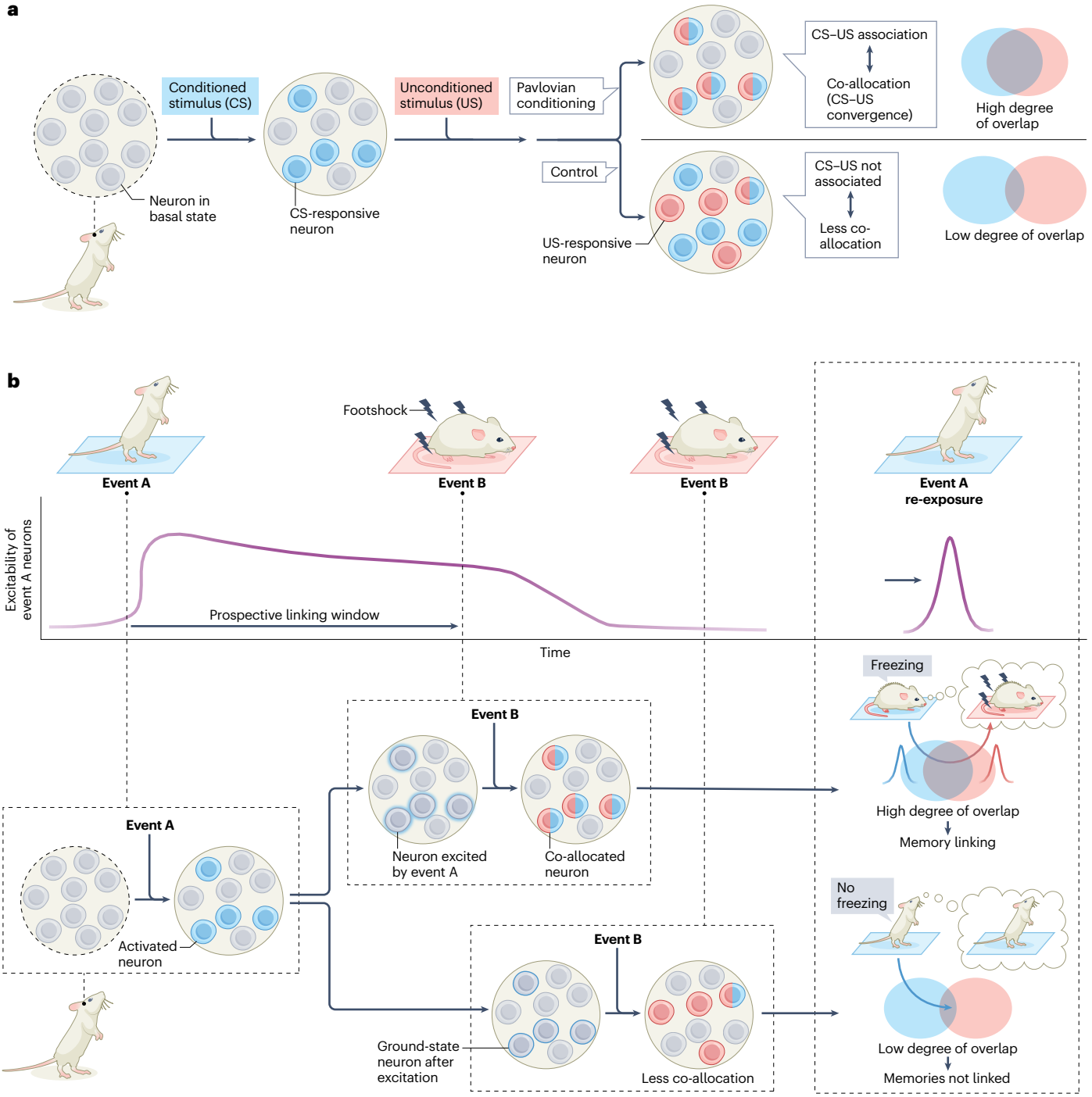


Fig. 2 | Associative learning and prospective memory linking. a, In Pavlovian conditioning, a form of associative learning, the converging influence of signals related to a conditioned stimulus (CS) and unconditioned stimulus (US) signals on the same neurons results in a high degree of overlap in their encoding engrams and mediates associative learning (top). This overlap is significantly lower in control mice that do not form associative memories (bottom)[39–42]. **b**, In prospective linking, the engrams encoding two events, or episodes, can be allocated to a shared population of neurons due to the heightened excitability of these neurons after encoding the first event[22,23,29,53,54]. When two distinct events undergo prospective linking, neurons recruited during the first event (event A) remain in a highly excitable state for a few hours and are thus readily co-allocated to another event (event B) if it occurs within this time window, creating an overlapping engram[22,23]. The high engram overlap between the events results in memory linking; mice will, for example, transfer a fear memory encoded in one context to the other context. However, if event B occurs after the excitability of the neurons activated by event A has normalized, there will be fewer overlapping engram cells and memory linking will not occur. Under these circumstances, the fear memory encoded during one event will hence not be transferred to the other event or context.

that memory formation and linking are separate processes that use different circuits in the hippocampus[23].

In addition to linking memories in terms of their behavioural outcomes, engram overlap can alter the fate of an encoded memory so that it matches that of another memory, a process called behavioural tagging[46]. In brief, a weak memory can be consolidated (stabilized for long-term storage) by virtue of its close temporal proximity to a much more salient event. Although such tagging does not necessarily mean that recall of one memory will induce recall of the other, it was found to depend on an overlapping engram population that is shared between both events[30].

It is important to note that, in all the aforementioned studies, engram overlap occurred even in situations in which the memories were not linked, albeit to a lesser degree. The absolute presence of overlapping engrams is therefore not an accurate predictor of memory linking; rather, the magnitude of the overlap may be the key determinant of linking[47]. For example, mice have been shown to be able to link two contextual memories when they are separated by 5 h, but not when they are separated by 7 days[22]. In both situations the mice showed hippocampal engram overlap; however, this overlap was significantly higher in the 5-h group[23,29]. Similarly, in a study in which conditioned taste aversion and AFC linking was induced by repeated co-retrieval sessions[28], both the test group (those in which linking was induced) and the control group also exhibited overlapping engrams in the basolateral amygdala (albeit to a lesser degree in the control group). Although the overlapping engrams in the control groups in the aforementioned studies did not surpass those that would be expected to occur by chance, their presence across different studies and paradigms may support the existence of a small overlapping population that does not necessarily mediate memory linking.

A recent study used a hippocampal circuit model to simulate the linking of multiple memories or 'concepts' and investigate the effect of manipulating the extent of shared 'concept cells'[47]. This revealed a threshold of overlap required for successful linking, below which concepts remained separate and above which concepts fused into a larger unit that could no longer be segregated. Although not explicitly stated, these results may support the proposed quantitative nature of memory linking: too weak an overlap may not be sufficient to link memories (but could prime the circuit), whereas overly overlapping the engrams merges memories into one, losing their identities. Overall, the experimental and simulation data both suggest that the degree of engram overlap, rather than its existence per se, may be the key determinant of memory linking and identity (Box 1).

In this section, we drew similarities between associative learning and memory linking to bring into focus a common concept, that of information overlap within a neuron or population of neurons. Whether association and linking represent distinct or unified mechanisms, however, remains unknown. In associative learning, the CS and US are presented within a narrow temporal window (seconds to minutes) (for example, see refs. 31,44). Both stimuli are merely considered to be components of a single memory, and their timely presentation creates a temporal map (a representation of the associative and temporal relationships of the stimuli) leading to successful association (for a review on temporal coding, see ref. 48). On the other hand, memory linking involves completely distinct episodes encoded hours apart (for example, see refs. 22,23,29). As such, it seems reasonable to consider associative learning and linking as completely distinct processes. However, it is possible to challenge this divide. For example, a contextual memory — which is used as the CS in many associative learning paradigms — can, by itself, induce a behavioural response[49]. Both the CS and the US can also produce distinct neural activity patterns[50] or even produce separate engrams encoding their respective contents[9]. Moreover, the temporal gap between stimulus or episode presentation may be similar in associative learning[39–41] and memory linking[30]. It is hence possible that association and linking exist within a single continuum of learning at different time scales (ranging from seconds to hours), in which eligible information is bound together to create a complete memory. Indeed, it was proposed that the temporal aspect (the interval between the encoded stimuli) is a fundamental component of temporal maps, but is not the only one[51].

Mechanisms underlying engram overlap

As discussed in the previous section, the two main experimental paradigms in which memories have been shown to exhibit overlapping engrams are behavioural tagging and the linking of two contextual

Box 1

The quantitative nature of engram overlap

If engram overlap is the mechanism for prospective linking, how can it occur to any degree in conditions in which memories are not linked? What exactly do the neurons that are shared between the overlapping engrams encode or do that wires the memories together? How can linked memories retain their individual identities? These questions have been approached using a network simulation model of shared memory cells (called shared concept cells)[47] that incorporates various aspects of the hippocampal circuitry, including inhibitory control, oscillatory rhythms and the existence of overlapping memories or 'concepts'. By manipulating the identity and strength of the inputs (external stimulation) to the model as well as the degree of overlap between the concept cells associated with different memories, the authors created a model that in various aspects fits experimental data from higher primates[187] and humans[187,188]. In brief, it was shown that, for successful memory linking, the proportion of shared concept cells must exceed a minimum threshold value (5% in sparse neural assemblies). The higher the degree of sharing, the more likely it is that the activation of one memory will spontaneously activate the other. However, should the shared proportion exceed a maximal threshold (50%), the two concepts or memories fuse into a larger unit that can no longer be dissociated. Although this study did not directly use a specific time window between the events, the findings suggest that there must be a control mechanism to constrain engram overlap in order to prevent erroneous associations. This is strikingly similar to the narrow temporal window for prospective linking as well as the scaling down of excitability at its end[29]. This simulation thus logically modelled the trade-off between the strength of memory linking and identity preservation.

memories. In behavioural tagging, two seemingly unrelated memories are bound together during consolidation[30,52] but are not necessarily linked at the recall level. In contextual memory linking, the attributes related to one context or event (such as fear) are transferred to another so that both eventually induce memory-specific behaviour[22–24,29]. Despite their differences, both paradigms show significant engram overlap and are time-sensitive, as the two events need to occur within 3–5 h of each other for the memory interaction to occur. This narrow time window suggests that such linking is mediated by short-lived mechanisms that are put into action during or after the first event.

One of the earliest indications of the mechanisms underlying prospective linking was revealed in an experiment in which rabbits learned to anticipate an air puff to their eyes following a 6-kHz tone[53]. Within 1 h of learning, hippocampal CA1 neurons began to increase their excitability (reaching a maximum by 24 h after learning) in a learning-specific, but not memory-specific or performance-specific, manner. The authors suggested that this temporal window of heightened excitability is important for learning or consolidating the association. This concept was brought further into focus by the discovery of various molecular mechanisms that can modulate memory allocation by affecting neuronal excitability. For example, the transcription factor cyclic adenosine 3′,5′-monophosphate response element binding protein (CREB), which is encoded by an IEG, was found to increase the synaptic efficacy and excitability of mouse amygdalar neurons[54] and the allocation of fear memories was biased towards neurons with higher CREB levels in the amygdala[6,54,55], the insular cortex[56], the hippocampus[57] and other brain regions[58]. Although CREB has many effects on neurons[59], its influence on neuronal excitability is likely to be the key factor determining neuronal allocation, as artificially activating or inhibiting a subset of amygdalar neurons immediately before encoding a fear memory preferentially recruits or excludes those neurons to or from the memory trace, respectively, even without direct modulation of CREB[60].

Several other IEGs also regulate excitability, as well as other cellular processes that may contribute to the memory trace, including synaptic plasticity, neuronal communication and neuronal survival. For example, *Fos* was shown to regulate both the excitability and the survival of hippocampal neurons[61]. The activation of ensembles of hippocampal neurons labelled by their *Fos* expression during memory encoding is required for the reactivation of their counterparts in the cortex in mice[62]. As cortical *Fos*-expressing ensembles were sufficient to recall a fear memory[10], this suggests that the *Fos*-expressing neurons that constitute a particular memory engram communicate across brain regions[62]. In the cortex, most neurons co-express multiple IEGs[63,64]. One of these, *Arc*, directly affects synaptic properties and plasticity[65], is required for memory consolidation[66] and may prime neurons for reactivation by modulating their excitatory input[67]. Another IEG, neuronal PAS domain protein 4 (*Npas4*), regulates inhibitory synapse development[68], excitatory–inhibitory balance[69] (the net weight of the excitatory and inhibitory inputs impinging on a neuron) and fear memory formation in the amygdala[70]. Yet another IEG, Homer protein homologue 1a (*Homer1*), regulates network excitability by negatively regulating excitatory synaptic transmission[71], and also has a role in memory consolidation[72]. In the cortex, in vivo imaging of early growth response protein 1 (*Egr1*), an IEG whose expression is associated with high-frequency stimulation and learning-induced plasticity[73,74], revealed context-specific neuronal ensembles that were segregated both in their anatomical allocation as well as in their activities from other, non-specific neurons[75]. Overall, these findings suggest that various IEGs collectively dictate network excitability as well as synaptic plasticity, contributing to learning and memory[76,77]. Aside from being used to visualize and manipulate engram cells in memory linking studies, whether IEGs exert more direct roles in memory linking remains to be thoroughly investigated.

The importance of neuronal excitability for memory linking is supported by studies of dopamine, which has been shown to control the encoding of cue–reward association in the lateral entorhinal cortex[78], to increase neuronal excitability in the hippocampus and to be involved in linking contextual memories[23], and to induce engram overlap during behavioural tagging[30]. These studies suggest that increased neuronal excitability following learning may be a central mechanism for engram overlap between temporally proximate events. The relatively narrow temporal window that limits the natural linking of contextual events through co-allocation of both memories onto a shared engram ensemble[22,23] was recently found to be terminated by the expression of C–C chemokine receptor type 5 (ref. 29), whose delayed induction in response to neuronal activity acts to reduce neuronal excitability.

This work indicates that neurons encoding a single memory remain, through various mechanisms, in an excitable state for some time after the encoded episode, allowing them to be preferentially allocated to a second memory occurring soon after the first. This could enable the brain to remain alert for successive events, which are likely to be connected, whereas the narrow temporal window could prevent non-specific linking beyond a certain time. From the available experimental data, this prospective linking does not seem to be selective in terms of the memories that are included, so long as they both fall within the allotted temporal space. In other words, prospective linking mechanisms passively link a second event to the first regardless of its content. It remains possible that there are mechanisms that exclude the inclusion of irrelevant events happening within the linking window, but this has not yet been shown experimentally. As such, it appears that prospective linking would not provide an ideal mechanism for higher-order inference and associations, in which specific pieces of information need to be extracted and compiled across longer time intervals. Furthermore, it remains to be seen whether the excitability-based mechanisms that drive prospective linking can induce associations between events that are further apart in time.

Memory linking and identity maintenance

Although the aforementioned studies have established some general principles for memory allocation and linking, we are still far from truly understanding how memories maintain their individual identities following engram overlap. Investigating subcellular compartments, namely dendrites and spines (or synapses), is paramount to fully grasp such dynamics.

Synaptic dynamics

Synapses have emerged as a prime candidate site for subcellular memory storage that could expand a neuron's encoding capacity by orders of magnitude[79]. An early study investigated synaptic remodelling — changes in spine shape, structure and/or number — following motor learning and novel sensory experiences in the mouse cortex[80]. The extent of such remodelling, which included both spine elimination and formation, correlated with behavioural performance in the motor learning task. Furthermore, a small fraction of the newly formed spines survived for weeks, providing what the authors suggested to be a structural basis for lifelong memories. Another study demonstrated that AFC memories could be switched on and off by bidirectionally manipulating

synaptic plasticity in the auditory input pathway, but did not investigate spine remodelling[32]. Later that year, two-photon imaging of head-fixed mice training in a motor learning task revealed task-specific spine addition to a subset of dendritic branches in neurons in the motor cortex. This remodelling required a period of non-rapid eye movement (NREM) sleep after learning, during which task-activated neurons were naturally reactivated[33]. Interestingly, when the mice performed two slightly different tasks (involving forward or backward movement), the spines created in response to each task were added to different dendritic branches, whereas retraining on the same task led to the formation of additional spines on previously engaged branches. This suggested that neurons might encode two related events by allocating their memories to spines on different dendritic branches. This notion of dendritic selectivity resurfaced in a more recent study, in which mice learned associations between different tones and shocks[81]. In this study, learning induced spine elimination, not formation, whereas extinction of the fear memory (through the repeated administration of the CS without the US) induced spine formation. Interestingly, mice could learn two different CS–US associations by eliminating spines from distinct dendritic branches for each pair, and extinguishing one memory did not affect the spines involved in the other association. When mice were overwhelmed with multiple CS–US associations, however, the same dendritic branch was affected by all pairs, and the extinction of the memory for any one CS–US pair generalized to all others.

A closely related notion suggests that offline dynamics (neuronal activity occurring during rest or sleep) may influence the allocation of memories to spines and, subsequently, behavioural outputs. For example, in one study, neuronal allocation (the selection of specific neuronal ensembles to encode a specific event) — occurring as mice performed the task — seemed to precede the allocation of the memory to specific dendrites and the formation of novel task-induced spines, which occurred in the subsequent sleep[33]. A recent study also showed that synaptic plasticity during consolidation refines the behavioural responses to concomitantly encoded stimuli of distinct valence[82]: mice froze similarly to safe and danger-related cues before consolidation, but were able to distinguish between them the next day, after enough time and sleep to consolidate the memory. This prompts us to ask whether, if the spines that encode a particular memory or memories are indeed assigned to dendritic branches after their parent neurons have already been selected, network reorganization — especially that occurring during offline states — can alter spine allocation to favour engram similarity or segregation.

Further evidence of the importance of spine allocation for memory identity came from another study in which a synaptic probe, a photoactivatable form of the activated synapse-targeting protein RAC1, was used to selectively label and manipulate spines that were potentiated by motor learning in freely moving mice[18]. Optically shrinking the labelled spines selectively impaired subsequent performance in the task with which they were associated, whereas a distinct motor task encoded by the same cortical region remained unaffected. This manipulation was spine-specific, but not branch-specific, providing strong, unequivocal evidence that synapses (or spines) are the subcellular units of memory storage (at least for motor memories) and further developing the case for synaptic gatekeeping of memory identity. Another study used a technique in which fragments of fluorescent proteins are reconstituted via connections between pre-synaptic and post-synaptic compartments, allowing interregional synaptic partners to be visualized and quantified after fear conditioning. This unveiled a selective enhancement of synapse density among the CA3 and CA1 cells that were part of the memory engram, which correlated with memory strength[79,83]. A recent study using the same method reproduced these results, showing enhanced synaptogenesis in CA3 and CA1 engram-related neurons, which disappeared with extinction learning[19]. These results further confirm that memories are stored as patterned spine allocation across engram partners.

In a study using a more straightforward strategy to assess how neurons preserve a memory's identity[31], mice underwent AFC with two different tones (7 and 2 kHz) separated by either 5 h (to induce memory linking) or 7 days (to keep memories segregated). The study asked whether memories that are linked and stored in the same neuron can still be differentially processed and/or expressed. The authors demonstrated that synaptic plasticity processes, namely long-term potentiation (LTP) and long-term depression (LTD), are synapse-specific and memory-specific, even for linked memories in overlapping neurons. To do so, they made use of an earlier observation that linked tone–shock memories exhibit overlapping engrams in the amygdala but not in the auditory cortex. Thus, they could specifically target synaptic connections from the auditory cortex to the amygdala that corresponded to either of the two tones. Through this approach the authors demonstrated memory-specific and synapse-specific gain and loss of function with LTP and LTD, respectively, providing strong causal evidence that memories and their identities are managed by synaptic plasticity components and that memories that are encoded by the same neuron can have different fates.

Dendrites as independent memory compartments

Dendrites, with their elaborate morphology and rich ionic repertoire, are involved in various cognitive processes[84–90]. Of particular relevance for memory linking and identity maintenance, dendrites can act as semi-independent subcellular compartments[91,92] and thus present another candidate mechanism for refined memory organization[93–95].

Dendrites generate spatially localized regenerative events called dendritic spikes[96–102], which are important for compartmentalized plasticity[103–108] and can induce temporally precise somatic action potentials[109]. This compartmentalization is so pronounced that dendritic activity can be different from that of the parent soma[110], or even from one branch to another[105,111–114]. Furthermore, synaptic integration may also differ between branch points. LTP is more likely to occur within a dendritic branch when multiple spines on the same branch are stimulated than when the stimulated spines are divided across two sister branches[107], whereas input summation — the net amplitude of the excitatory potential resulting from the activation of multiple sites — differs between branches, and even on the same branch as a function of within-branch distance of the stimulated sites[115]. Such dendritic non-linearities create a complex manifold of computational abilities, comparable with that of two-layer[116–118] or multilayer[119] neural networks. Not surprisingly, therefore, dendritic activity orchestrates the integration of multiple synaptic inputs into a unified change in membrane potential[120,121]. More importantly, modelling studies have revealed how dendritic non-linearities could mediate both memory linking[118,122] as well as feature binding, in which the same neuron stores multiple features of an event[35]. Both of those features are crucial for our proposed model for memory linking and identity, which will be discussed later.

A recent study followed the evolution of dendritic (and spine) plasticity in amygdalar neurons[110] as mice learned a tone–shock association. Somatic and dendritic responses were measured with two-photon calcium imaging in head-fixed mice. Before learning, tones elicited no

characteristic dendritic responses. After learning, however, in a fraction of neurons, dendrites and dendritic spines upregulated or downregulated their responses to tones, and tone-up dendrites (and spines) could be found in tone-down neurons, essentially de-coupling somatic and dendritic calcium responses. On the other hand, the responses of spines and dendrites to tones were matching, so that tone-up spines were allocated only to tone-up dendrites, and vice versa. Learning also increased the probability of tone-induced transients that appeared only in dendrites and not in the soma, suggestive of independent dendritic responses to salient cues: indeed, one-fifth of all dendritic calcium transients occurred without concomitant somatic activity. Overall, this study provided an elegant demonstration of compartmentalization in dendrites and their independence from parent soma and sister branches following learning. This independence provides neurons with network-level computational capacities, as memories are not defined solely by the neurons to which they are allocated but also by their allocation to sub-neuronal compartments with semi-independent plasticity that can alter their linking and identity. A recent review of this dendritic compartmentalization advocated a very interesting concept, that of "dendritic engrams"[36]. In brief, it was suggested that dendritic compartmentalization acts upstream of synaptic engrams, orchestrating their spatial and functional distribution as well as the plasticity events to which they are subjected and that may not be shared with other spines on the same dendritic branch.

Synaptic allocation and clustering

In line with the proposed contribution of dendritic compartmentalization to memory linking and identity maintenance, modelling studies have predicted that synaptic stimulation differently affects dendritic and neuronal outputs, depending not only on the dendritic allocation of the stimulated synapses (within-branch versus across-branch stimulation) but also on their location within the dendritic branch[117,118,123–125]. Spines display a wide range of types of plasticity, including metaplasticity[126,127] (in which the history of synaptic activity affects how a synapse responds to future events) and synaptic crosstalk in which strong inputs to one synaptic pathway can potentiate weaker inputs that impinge on a different pathway[128]. A mechanistic explanation for the latter phenomenon is provided by the synaptic tagging and capture hypothesis[129,130]. According to this theory, weak synaptic stimulation produces an early (temporary) form of LTP, but also attaches a synaptic tag that primes this synaptic pathway for a few hours. During that period, if a stronger stimulation results in a more persistent form of LTP (late LTP) in another synaptic pathway in the same neuron, it induces the synthesis of plasticity-related proteins (PRPs) in soma or dendrites. These PRPs can be captured by the previously tagged synapse, which will then develop late LTP. It is not completely understood whether PRPs are available throughout the whole neuron or are localized to strongly activated branches[107,131], and it is thought that there may be competition between synapses for a common pool of those proteins[130,132]. Important for such synaptic crosstalk is the distance between the spines receiving the inputs and the timing of their activation[133–135]. This can be attributed, at least in part, to the requirement for key signalling molecules to diffuse to nearby synapses. Synaptic tagging and capture mechanisms can therefore explain the potentiation of weak memories that can occur when they are temporally proximate to stronger events[46,136,137] (but also see ref. 138 for an alternative viewpoint).

Of particular importance for our understanding of memory linking is the phenomenon of synaptic clustering, in which a cluster of spines that share similar inputs and/or response characteristics are located within a confined dendritic domain[94,139]. Such clusters were predicted to maximize neocortical neuronal responses, as opposed to randomly distributed inputs (an effect termed cluster sensitivity[140]), and to induce dendritic non-linearities via induction of dendritic spikes[123], which was shown experimentally[115]. The first evidence of such clustering was found in the auditory localization circuit of the barn owl[141], and this discovery was later reproduced in mice, where spines in the barrel cortex were shown to form synchronized 'assemblets' of 2–12 spines located within 10 µm of each other[142]. Synaptic clustering was also observed in the visual cortex of mice and ferrets[89,143]. A computational study suggested that the stimulus selectivity (the preferential response to a certain stimulus more than others) of the neuronal soma can differ from the mixture of selectivities of its dendrites[144] and that the spatial arrangement of spines can bias the stimulus selectivity of the soma even if the total number of synaptic contacts that are stimulated by the two stimuli is comparable. In vivo studies did not, however, find any special arrangement of spines in sensory cortices[145–147]. An excellent review of synaptic clustering[139] suggested an interesting reconciliation of these apparently contradicting findings, proposing that clusters of synapses do not code for a continuum of sensory information but, rather, for meaningful combinations of stimuli that are behaviourally relevant (for example, tones associated with a shock[110]). In accordance with this view, the degree of synaptic clustering in the retrosplenial cortex was indeed correlated with behavioural performance in contextual fear conditioning[148]. Clustering of spines was reported in 'hot spots', dendritic sites in which synaptic turnover rates are high[94,148], and was recently shown to occur in interregional engram populations involving neurons in both the CA3 and CA1 areas of the mouse hippocampus[19]. Spine clustering is also predicted to bind information by enhancing the coupling between the spikes of the dendrite housing those clusters and the somatic membrane potential[35]. In the motor cortex, spine clusters are generated following repetitive motor learning in a coordinated manner, such that spines that are induced by different tasks have a low incidence of clustering with each other[149].

A computational model of generic neurons that incorporated dendritic non-linearities, intrinsic excitability and homeostatic plasticity predicted that memory linking is associated with clustering of learning-induced spines[122]. According to this model, the locus of PRP synthesis affects the degree to which the engrams encoding each linked memory overlap (and thus the degree of memory linking), the sparsity of the engrams and the signal-to-noise ratio (the contrast between coding (engram) and non-coding neurons). For a single associative memory, soma-derived PRPs produced engrams with higher activity and sparsity/contrast, in which the synaptic trace was limited to a smaller population of neurons, and smaller synaptic clusters were found in many dendrites. When PRPs were localized only to strongly activated branches, however, engrams showed lower activity and sparsity, as the synaptic trace was widely distributed across the majority of neurons, and larger synaptic clusters were confined to fewer dendritic branches. Eliminating dendritic spikes from the model made the two conditions (somatic versus dendritic PRPs) indistinguishable, further demonstrating how dendritic plasticity may control not only synaptic arrangement but also engram dynamics. On the other hand, when two strong memories were linked, soma-derived PRPs resulted in higher engram overlap than locally derived PRPs, but dendritic co-clustering was comparable between the two conditions. It is thus plausible that dendritic allocation may proceed differently from neuronal allocation, a notion we will discuss later in our model.

In conclusion, both dendritic and synaptic non-linearities have been predicted and proven to have roles in higher-order computations. It is thus possible to assume that these subcellular compartments can also control both the linking of multiple memories and the maintenance of their identities.

Somato-synaptic model for memory linking

Many previous models of memory linking describe engram overlap as the key dynamic, whereas more recent models suggest synaptic clustering to be the true subcellular mechanism. As we have discussed, there is experimental and computational evidence supporting both views. In attempting to create a single model to reconcile the cellular and synaptic underpinnings of memory linking while simultaneously accounting for the maintenance of memory identity, we suggest that several assumptions need to be met. First, even with engram overlap, individual identities must be able to be preserved. Second, not all overlapping engram cells will induce memory linking. Third, subcellular (dendritic and spine) allocation must be a key regulator of a memory's fate. Finally, the link between memories must not be a rigid process: it can be possible to strengthen the link up to the point at which fusion occurs (resulting in loss of identity, for example with repeated linking reinforcement) or weaken the link up to the point at which dissociation occurs (for example, in case of incidental associations)[47].

With these assumptions in mind, we propose a model that integrates engram overlap, spine clustering and key experimental and modelling literature to create a dynamic scale of memory linking and dissociation that is constantly modulated by learning (Fig. 3). Following the linking of two events (or episodes), A and B, our model predicts the existence of four functional neuronal populations that can be differentiated based on the neuronal and dendritic allocations of the memories of the two events, as well as their function. The first population is the linking population, in which overlapping neuronal allocations between events A and B connect both events[22,23,28–30,47]. In these neurons, spines corresponding to both events are co-allocated to the same dendritic branches in a clustered manner[19,34,122,148], allowing them to 'share' their synaptic plasticities[107,128,130,133–135]. This will mean that activation of the inputs corresponding to one event leads to concomitant recall of the other event[19,34,94,110,122,139].

The second neuronal population responds to both events A and B yet does not mediate their linking[22,23,29,30,47]. This seems paradoxical until we consider the semi-independent subcellular compartmentalization and the reversibility of association in healthy brains. As we have discussed, neurons may allocate similar yet distinct episodes with distinct behavioural outputs – such as forward and backward running[33] or different CS–US associations[81] – to different dendritic branches. We propose that whereas responses to both events A and B overlap

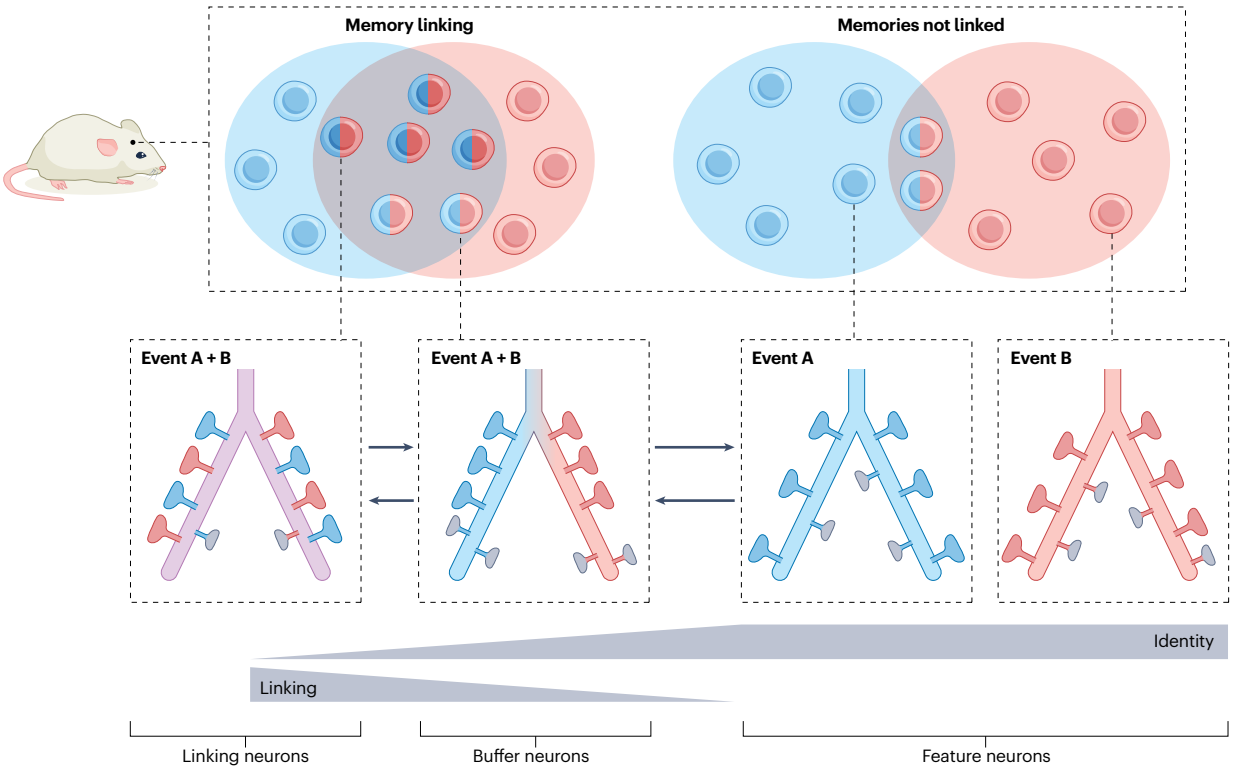


Fig. 3 | A somato-synaptic model for dynamic memory linking and identity preservation. We hypothesize that four neuronal populations with distinct patterns of dendritic and spine memory allocation control the degree of memory linking or segregation. In linking neurons, spines that are activated by event A (shown in blue) and those activated by event B (shown in red) are clustered on the same dendritic branch. These overlapping neurons are necessary for memory linking, which is severed if they are inhibited. Buffer neurons also possess spines for both events, or episodes, but these are located on distinct dendritic branches. These neurons are among the overlapping population yet do not mediate linking of events A and B. They are, however, primed to cluster spines and become linking neurons. Feature neurons for event A and event B are specific for their corresponding events, binding their unique features and maintaining their identity. We propose the balance of all four populations to be dynamic, skewing more to the right side (identity) when initially coincident events become more segregated, or to the left (linking) when the link is repeatedly reinforced, so much so that memories merge into a single entity with loss of their individual identities.

Glossary

Behavioural tagging
A phenomenon in which memories for non-salient experiences are strengthened when they are immediately followed or preceded by an event of greater salience. As a result, weak events that would otherwise only elicit short-term memories are stored as long-term memories.

Dendritic compartmentalization
The non-linear segregation of dendrites by various mechanisms, such as dendritic spikes and intrinsic excitability, as well as their anatomical configuration. Synaptic potentiation or depression can thus be restricted within those compartments.

Dendritic spikes
Spatially restricted spikes in potential occurring in a localized area of the dendrite when synaptic inputs are temporally or spatially clustered. Such localized spikes may occasionally propagate to the soma and can trigger axonal action potentials. As such, dendritic spikes underlie dendritic non-linearities and compartmentalization.

Immediate early genes
(IEGs). A subset of neuronal genes that are rapidly and selectively upregulated in response to neuronal stimulation by a wide variety of stimuli. IEGs are implicated in synaptic plasticity, learning and memory.

Inferential reasoning
The ability to deduce relationships among events that were never co-presented, through common intermediaries. Using such intermediaries allows one to infer the whole hierarchy of events, from highest to lowest, on an arbitrary scale.

Long-term depression
(LTD). A synaptic plasticity mechanism in which there is a decrease in the strength of synaptic efficacy, following low-frequency stimulation.

Long-term potentiation
(LTP). A synaptic plasticity mechanism in which there is an increase in the strength of synaptic efficacy, following high-frequency stimulation. Together with LTD, LTP is believed to have a major role in various forms of learning and memory.

Memory engram
A group of neurons that are activated by an event, resulting in enduring cellular changes, and whose reactivation results in the recollection of the memory of that event.

Memory replay
The offline reinstatement of the cellular activity patterns that encoded a particular event. This replay is often observed during subsequent rest or sleep periods in a compressed manner, and is thought to have a key role in memory consolidation.

Network reverberation
A mechanism by which neuronal circuits maintain patterns of activity after an initial stimulus has ceased, by forwarding the signal from one neuron to another within a specific circuit or ensemble. This signal may coincide with a new input converging on the same ensemble, which may create an association.

Pavlovian conditioning
Behavioural and physiological changes that occur when an animal learns that a naturally neutral stimulus predicts a biologically salient event. In the original studies conducted by Pavlov, dogs salivated in response to the ticking of a metronome (a neutral stimulus), because this sound immediately preceded food delivery (a salient event) on previous occasions.

Plasticity-related proteins
(PRPs). Proteins that are synthesized in response to synaptic stimulation and are required for maintenance of the ensuing synaptic plasticity. The diffusion and capture of these proteins by weakly activated or inhibited synapses may stabilize their synaptic plasticity, according to the synaptic tagging and capture hypothesis.

Synaptic clustering
The grouping of synapses with similar response and/or input properties within relatively short stretches of the dendritic branch.

Synaptic engrams
A subset of synapses in engram cells with altered synaptic plasticity following learning.

in these neurons, they are allocated to distinct dendritic branches, and hence may be considered as distinct features or events[33–35,150,151]. The dendrites responding to events A and B may initially show similar branch strengths and somatic coupling, meaning that the neurons respond equally to both events even though they are segregated in terms of subcellular allocation. Therefore, activation of or plasticity in spines related to event A will not affect spines related to event B[18,152], and these neurons may alter their responses through mechanisms such as rate or phase coding[153,154] or differential spike generation[155]. We call this population 'buffer neurons' and will describe its function later.

The third and fourth populations are separate 'feature populations' for events A and B. They constitute neurons that exclusively encode either event, but not both, and are necessary for preserving the details of their respective memories[28]. They may show clustered spines corresponding to their respective coding event (for example, event A), with either a complete lack of spines for the other event (in this case, event B) or a weaker spine allocation on distinct dendritic branches. Hence, the branches coding for event A will dominate the competition for somatic coupling, driving the neuronal response to event A, but not event B. Distinct dendritic branches in these neurons may contribute to binding different features of event A, hence conferring a detailed episodic memory recall even if the neuronal activity of the linking population was inhibited[28,33,35].

In this model, memory linking and memory identity are located at the opposing ends of a cognitive balance that we propose is under the control of buffer neurons. Following the initial linking and allocation of the memories to all four neuronal populations, subsequent learning (or recall) events determine the need for more association or segregation. Should the link between events A and B be further reinforced in subsequent events, new spines can be specifically added to opposing branches in buffer neurons, so that the spines responding to events A and B will eventually be co-allocated on similar dendritic branches. Ensuing spine clustering will effectively convert these buffer neurons into linking neurons, increasing the strength of memory linking and co-recall of both events A and B.

This hypothesis suggests that separately encoded events may be successfully linked, post encoding, at time intervals much longer than commonly reported. Indeed, it has been shown that associative synaptic plasticity may increase ensemble similarity post encoding, by conjoining neurons from different ensembles[156], and that repeated co-recall can induce linking of two independently encoded memories[28]. Both incidents depend on repeated co-presentation of previously

encoded elements, instigating a logical motif for linking and generating overlapping engrams. Furthermore, a recent preprint has shown that complementary bits of information encoded across days and weeks can be logically linked to generate a comprehensive knowledge[157], a process that involves idling reactivation (neuronal reactivation during rest or sleep).

Alternatively, should events A and B become more independent in subsequent learning (by having distinct outcomes or unique characterizing features, or becoming more temporally dissociated), buffer neurons may act to counteract linking and enhance memory independence, by converting to feature neurons. For example, following repeated or strong stimulation that reinforces event A, a buffer neuron may enhance the branch strength for dendrites carrying A spines more than it does for dendrites carrying B spines (possibly by clustering A spines), progressively steering somatic responses until the buffer neuron eventually becomes an A-feature neuron. This assumption is based on the capacity of clustered spines to induce dendritic spikes, which can modify somatic firing[158], and increase the coupling of the dendrite to the soma (branch-coupling strength[105]), thus skewing inter-branch competition. Our model also predicts the conversion of linking neurons into buffer and/or feature neurons, possibly through weakening or deletion of spines from clusters. This assumption is more challenging to prove, as there is no direct experimental evidence of the deletion of clustered spines in cases of memory unlinking. However, if events A and B are no longer linked at the behavioural level, one can assume that their respective spines would no longer need to coactivate. In developing hippocampal neurons, a neurotrophic factor-dependent mechanism was recently shown to modulate spines within clusters, maintaining synchronized clusters while downregulating 'out-of-sync' synapses[159]. Furthermore, a recent computational model of associative learning revealed that, despite the continuous turnover of synapses, spontaneous offline reactivation of assemblies maintains more synapses than those removed, hence maintaining the overall strength of the assembly[160]. Synchronized offline reactivation of event A and B synapses may thus be a key requirement for their persistence in a clustered state, and eventually the maintenance of the assembly as a whole[161].

At the ensemble level, how can linked memories separate post encoding? Dissociation of neuronal activation patterns seems to be a key mechanism for such unlinking. Indeed, in humans, overlapping memories can be dissociated by selectively reactivating a subset of those memories during sleep[162], and the human hippocampus decreases the representational similarity of overlapping spatial events with distinct outcomes, to become less similar than even non-overlapping ones in a learning-dependent manner[163]. Moreover, competing memories can be temporally segregated with respect to the hippocampal theta rhythm[164], which may reflect different activation dynamics of their respective spines and dendritic branches as a result of our proposed spine rearrangement.

Through buffer neurons, the four populations can dynamically change their respective weights in response to learning. More linking merges more neurons into the linking population, which sacrifices memory identity to enhance linking, eventually creating a single 'A and B' representation that no longer dissociates either event[47]. On the other hand, less linking gradually leads to a stronger representation of details of both memories but with a severed link. Such dynamism may explain why individuals who are amenable to forming stronger associations may show deficits in pattern separation (as has been seen, for example, in people living with schizophrenia[165,166]) and those who form weaker associations may have enhanced pattern separation (as seen, for example, in people with savant syndrome[167]).

We must clearly state that, although strong experimental evidence exists for an overlapping engram population that links two events, as well as for non-overlapping populations encoding either event, no conclusive experimental evidence exists for the population that we have here called 'buffer neurons'. We have hypothesized that such a population exists, based on multiple reproducible reports of overlapping engrams in situations in which memories are not linked, as well as the computational evidence for the quantitative nature of memory linking[47]. However, even in the absence of buffer neurons, the rest of our model would remain mostly intact.

In summary, our model incorporates subcellular mechanisms as well as experimental and modelling results into a single dynamic model that grants more fluidity to overlapping memories in terms of linking and identities. Based on the available experimental, computational and clinical evidence, we postulate the existence of four distinct populations that maximize the use of dendritic non-linearities to exert unique effects. The accuracy of both our allocation and functional predictions for each population, and whether the size of each ensemble changes through learning events that favour more linking or dissociation, remain to be proven experimentally.

Retrospective memory linking

Our knowledge is usually built gradually, across days, weeks and even months, as we constantly review what we have learned and rehearse previous events that may complement what we currently understand. In simpler terms, we must have the ability to look back in time, scan our memory repertoire and mix and match relevant (but not irrelevant) events to infer relationships, solve outstanding problems or make sense of previously incomprehensible bits of information.

As discussed above, prospective linking strongly depends on temporal proximity, and exploits the transient increment in neuronal excitability to co-allocate neurons to both events. This mechanism indiscriminately links both events that are similar to each other (such as contextual memories[22,23,29]) and those that differ from each other (as in the case of behavioural tagging[30,52]). Although such dynamics offer clear cognitive advantages, as temporally close events are likely to be related, they are unsuitable for higher-order associations, where the relevant knowledge may be fragmented across multiple distant episodes. Thus, prospective linking cannot selectively piece together cognitively relevant pieces of information encoded across long temporal intervals. To that end, mechanisms that become active following an event that bears specific significance to a previous one are required. These retrospective mechanisms should be able to transcend the strict temporal window for prospective overlap, possibly conferring a different scale of cognitive capabilities in the process. Indeed, it has been shown that we can bridge such temporal gaps to link episodic fragments that share the same narrative[168], even at intervals as long as 18 months[169]. Moreover, it has recently been shown that both the hippocampus and the entorhinal cortex can reinstate specific activity patterns to identify the temporal context for memories, several months after encoding[170].

Some of the few reports of retrospective linking highlight how both its mechanism(s) and outcome(s) can be fundamentally different from those of prospective linking.

For example, to understand how neural circuits filter a group of stimuli with variable pertinence to an ongoing behaviour, two-photon calcium imaging was performed on the Schaffer collaterals of neurons in hippocampal area CA3 that project to CA1 (CA3SC neurons) as mice

ran on a voluntary treadmill with either random or fixed-location cues. At the same time, CA1 sharp wave ripples (SWRs)[171] – high-frequency events during which memory replay is thought to support memory consolidation[172–174] – were recorded. Random cues carried no valuable spatial information, and the CA3SC neurons that were activated by these cues were silenced during SWRs. When the cues were spatially fixed, however, SWRs preferentially activated the CA3SC neurons with which they were associated. As such, discrete assemblies were favoured for reactivation during replay. A more recent study in human participants watching natural narratives with scene transitions (event boundaries) showed how, during those boundaries, the hippocampus may preferentially reactivate relevant past events, even if they are temporally distant[175]. These studies show how retrospective mechanisms can be selective when extracting useful pieces of an encoded experience.

Two recent studies investigated retrospective linking for contextual memories. One study showed that the anterior cingulate cortex acts retrospectively to specifically link two relevant contextual memories (and leave less related ones unlinked) even when the events occurred at intervals of 1 day or 5 days[26] (Fig. 4). The authors developed a paradigm in which mice linked memories based on the geometrical features of the different contexts in which they occurred, so that

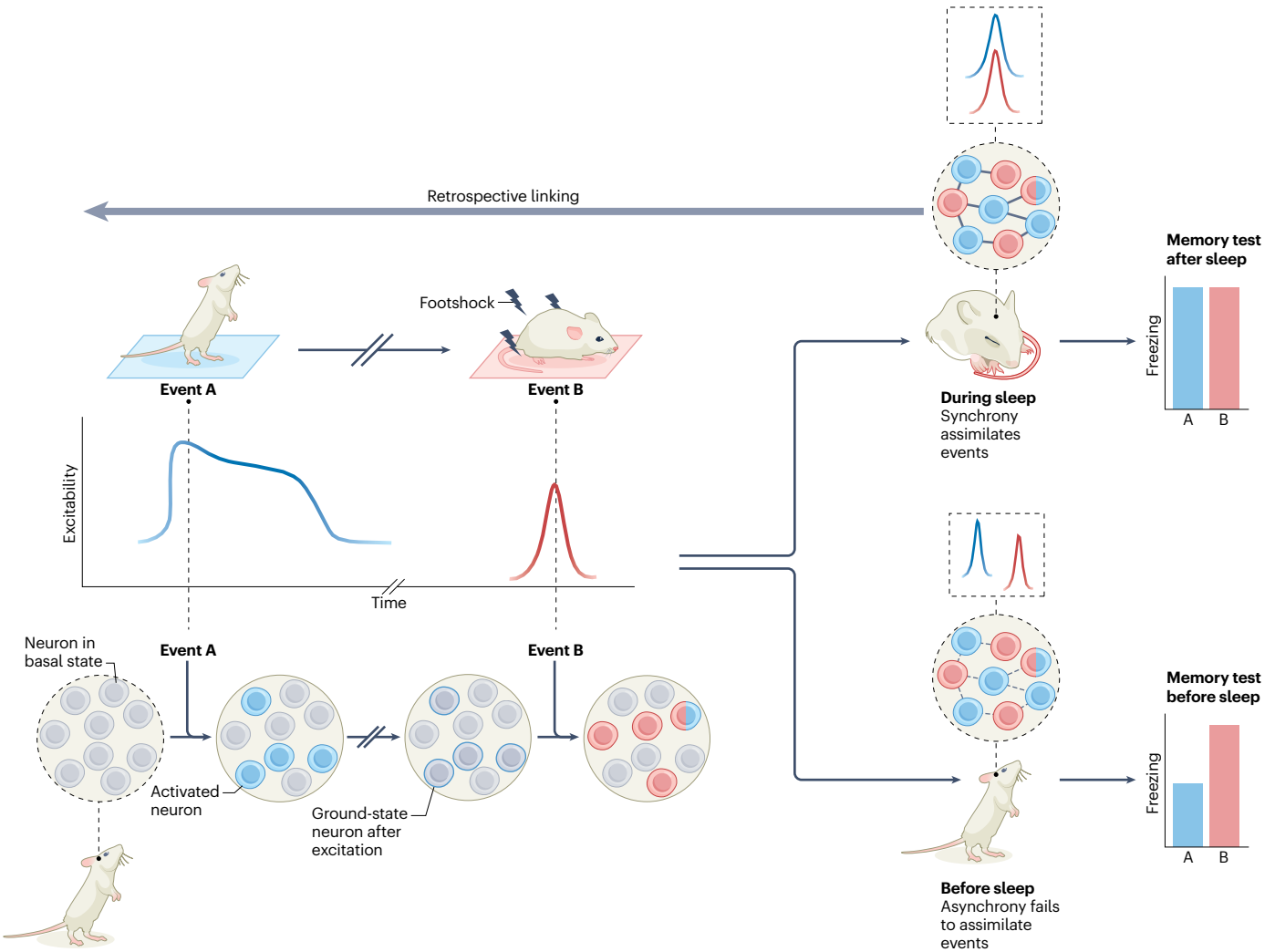


Fig. 4 | Retrospective linking through offline reactivation. Selective offline reactivation of previously encoded relevant information has been shown to mediate a specific form of memory linking at longer temporal intervals[26,157,176] Mice are exposed to one context (event A), followed by fear conditioning in a different context that shares common features with the first context (event B) 1 day later. By the time the mice are exposed to event B, the neurons that were activated by event A have returned to their normal (ground level) excitability levels (blue curve). Thus, exposure to event B leads to a small overlap between those engrams. During subsequent sleep, strong synchronous reactivation of event A and B engram cells (indicated by the thick connecting lines between red and blue cells) links both events, or episodes, so that mice equally freeze in both contexts[26]. Before sleep, mice freeze significantly more in the conditioning (red) context, as engram cells for both events A and B fire asynchronously (indicated by the dashed connecting lines between red and blue cells). From a cognitive perspective, during such retrospective linking the brain looks back in time, extracting eligible events whose engrams have returned to baseline excitability levels and reactivating those events synchronously to link them during sleep.

Box 2

Memory linking in humans

In rodent studies, a wide array of techniques allow for selective tagging, manipulation and online and post hoc analyses of the cellular and subcellular components of memories. Although it is understandably challenging to recreate many of those experiments in a clinical setting, human studies have revealed striking similarities to rodents that span the whole arc of memory processing, from encoding to recall. For example, in both humans and rodents offline reinstatement of learning patterns for consolidation[11,189–194], the need for memory reconsolidation following retrieval[195,196], the existence of a gradient for spatial information coding along the hippocampal axis[197,198] and the presence of time cells in the hippocampus and entorhinal cortex for temporal coding and time tracking[199,200] have been observed.

Importantly, the similarities between rodents and humans also involve processes that may directly influence memory linking. For example, human studies have shown that neural engagement prior to a task may affect the learning and recollection of the task[201–205]. Although this cannot provide a direct causal link between excitability and allocation, it shows a link between neuronal activity before learning and the cognitive outcome. This mirrors, to an extent, what we have learned from engram studies in rodents. Another interesting similarity to rodents is that, in human subjects, pre-event neuronal activity may contribute to the linking of the event to a temporally proximate memory. Indeed, elements encoded close in time evoke similar hippocampal activity patterns[206] and, inversely, hippocampal activity patterns support judgement of temporal relationships[207]. Moreover, an elegant study demonstrated an enhanced ability to infer relationships and integrate information among memories that were learned on the same day, compared with those encoded days apart[25]. Another study of interest closely mimicked a well-established paradigm for contextual memory linking in rodents[22,23,29], by fear-conditioning human participants with an electric shock that was paired with one of two previously encoded memories[208]. Only when these memories were encoded within a short temporal window (3 h, but not 7 days) did the fear produced by the shock transfer to the other memory, demonstrating behavioural linking that is strikingly similar to that seen in rodent studies.

Memory recall destabilizes previously consolidated memories until they undergo reconsolidation[195,196]. Until such re-stabilization occurs, memories are labile and prone to modification or update. For example, college students learning a word list and receiving a reminder of that list before learning a different one show significant intrusions of the original list with many items from the second list[209]. The brief reminder destabilized the original list enough to incorporate items from the second list that was encoded shortly after, indicating memory integration/update. This task has also been repurposed in rats, in which word lists are replaced with feeder tube locations[210], achieving similar results.

Another interesting facet of memory linking is that of emotional binding. In simple terms, memories are more easily recalled when their valence matches the current state we are in, so that a low mood enhances recall of bad memories whereas positive states recruit more joyful memories[211,212]. This suggests some sort of biased memory crosstalk. In rodents, the activation of engrams for positive memories was indeed shown to reduce the negative effects of stressful episodes[213]. Recently, the memory trace for a stressful episode was identified in the human amygdala[214]. It remains to be unequivocally demonstrated, both experimentally and clinically, whether and how memories of similar valence, such as a pair of aversive or rewarding memories, selectively interact and integrate with one another. Such a valence-dependent interaction may reveal a novel layer in memory linking that is more influenced by the meaning than the timing of an experience.

attributes associated with a triangular context (an arena with three corners) are transferred to a square context (four corners) that was encoded 1 day or 5 days earlier, but not to a circle (no corners) encoded at similar intervals. This linking, or assimilation, was dependent on sleep following the second event, during which the neurons encoding relevant events displayed significant co-reactivation, compared with neurons activated during less relevant contexts. Inhibiting anterior cingulate cortex activity during sleep following the second event blocked this memory linking, which strongly suggests that engram co-reactivation during sleep is the key mechanism for retrospective linking. Findings reported in a recent preprint corroborated these results in the hippocampus, in which a fear memory was retrospectively linked to a neutral event encoded 2 days prior[176]. Interestingly, this retrospective linking was also mediated by offline reactivation of neuronal ensembles encoding both events, and it was not observed prospectively for memories encoded after the aversive event.

Another recent preprint has reported interesting linking dynamics in mice undergoing a much more demanding cognitive task: inferential reasoning[157]. In this study, mice learned the hierarchical order of five contexts (A > B, B > C, C > D, D > E). When mice were then presented with a previously unseen combination of contexts (B and D), they could indirectly infer which context is higher (that is, rewarded) based on the previously learned hierarchy. Offline reactivation of the learned context combinations was shown to be key to this inference behaviour, with the authors suggesting that different stages of sleep have distinct roles in the emergence of inference in the cortex. This conclusion fits the hypothesized duality of sleep functions[177] and mirrors the sequential hypothesis of sleep[178], which suggests that NREM sleep classifies information whereas rapid eye movement (REM) sleep processes and integrates information that has been tagged as relevant into existing knowledge. The sequential hypothesis of sleep was supported by findings in an emotional learning task[179], and explains how sleep can help to both maintain[180] and forget[181] memories. A more recent report demonstrated that REM-rich sleep 'distorts' or destabilizes memories, facilitating their integration into existing knowledge, whereas NREM stabilizes them[182]. The nature of the proposed tag that denotes memories as being relevant remains elusive and is a key outstanding question that must be addressed if we

are to conclude that memory reactivation during sleep is structured, as opposed to random[183].

Another insightful study taught human participants how to identify the correct order of a series of images and followed that by displaying novel images in a scrambled order, while using magnetoencephalography to detect item representation[184]. In a brief rest following the encoding session, item representations were replayed (similar to the memory replay seen in rodents) in a temporally compressed manner and coinciding with hippocampal SWRs. Interestingly, the representations of items from the scrambled list were replayed in the correct sequence, indicating that this replay used the learned sequences displayed earlier to infer the correct order of a novel problem. Whole-brain imaging with magnetoencephalography makes it difficult to pinpoint where these replay events originated, but the authors suggested that they are of neocortical origin. This study, and others, show that there are similarities in memory linking dynamics between humans and rodents (Box 2).

Importantly, offline memory reactivation is not exclusive to sleep periods and can occur during brief rest periods in awake rodents[171] and humans[184]. Regardless of its timing, it seems plausible that such offline reactivation for retrospective linking is the counterpart of excitability for prospective associations. However, whether offline co-reactivation can induce engram overlap remains an important outstanding question[26,157,176]. Retrospective linking should, by definition, occur on a need-only basis. This means that if the engrams eventually overlap, they may not do so at the time of memory encoding. Our question hence crystalizes further: can distinct engram populations become more fluid post encoding via retrospective mechanisms, allowing them to achieve overlap and association? Indeed, some experimental and computational evidence exists in favour of such engram fluidity. For example, as discussed previously, associative synaptic plasticity can change the composition of a neuronal ensemble by incorporating more neurons from a different ensemble and, eventually, increasing inter-ensemble similarity[156], and engrams for two separately encoded events can be driven to overlap by repeated co-retrieval sessions[28]. A more recent study developed a recurrent network model to investigate the dynamics of retrospective memory integration at the circuit level, measuring both the connection weight and the level of ensemble overlap[185]. Using an associative inference paradigm, the authors demonstrated many interesting network features following memory association. Of note is the observation that association is not accompanied by addition of novel neurons to the active ensemble but, rather, by expanding the tuning of the existing neurons to encode more than one item. Furthermore, and probably of significant relevance to this Review, is the authors' demonstration that neural overlap develops for directly presented and indirectly inferred associations as a function of the number of times that their stimuli are co-presented. Although this form of direct stimulus presentation does not necessarily match the spontaneous and naturalistic offline reactivation that occurs as one ponders upon a problem, it does provide supporting evidence for the concept of fluid memory representations that may drift to favour ensemble overlap when previously encoded pieces of information are sewn together into knowledge.

In conclusion, although prospective linking through engram overlap appears to be well established, its temporal restraints and permissive nature suggest that it cannot account for our ability to perform selective associations comprising bits of knowledge that have been acquired in a scattered manner throughout our daily lives. It is likely that prospective and retrospective mechanisms are cooperative, rather than mutually exclusive, as previously shown in the hippocampus during a spatial memory task[186]. It is thus paramount to consider how and when retrospective dynamics spring into action, and whether they complement, enhance or exclude prospective mechanisms in various tasks (Fig. 5).

Conclusions and future perspectives

In this Review we have highlighted progress in deciphering the mechanisms of memory linking, with a focus on engram overlap. We have also revisited evidence of synaptic memory substrates to provide a complete and logical picture of memory linking, in which memories can be shared yet remain sufficiently separable. We have compiled cellular, dendritic and synaptic mechanisms to create a somato-synaptic

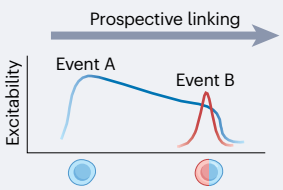
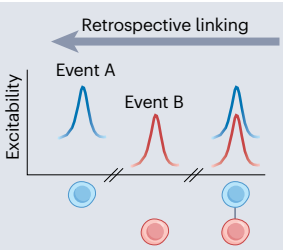
Linking type	Brain state and activity	Mechanism	Interval required to link events	Specificity for link	Related cognitive function	Creativity
	• Awake (conscious) • Cellular excitability	Excitability-based co-allocation	Seconds to 6 h	Closely timed events (present events) are linked	• Passive linking of events • CS1–CS2 linking	Low
	• Quiet awake or sleep (subconscious) • Slow-wave sleep • Spindles • Ripples	Sychronized co-reactivity	Seconds to days	Selective linking for relevant information (past events)	• Selective adaptation/ linking • Inference • Re-sorting • Dreaming	High

Fig. 5 | Mechanisms and characteristics of prospective versus retrospective memory linking. Prospective and retrospective memory linking work when the brain is in different states and at different temporal scales, and have different specificity requirements. They provide distinct outcomes, ranging from rapid and permissive associations to more laborious forms of knowledge and creativity. CS, conditioned stimulus.

model, in which distinct neuronal populations mediate memory linking and discrimination across a fluid and dynamic scale.

Both engram overlap and synaptic clustering are quickly becoming established in the neuroscientific community as key mechanisms for memory linking, with many powerful and insightful supporting studies. We note, however, that most of these studies utilized similar behavioural designs, examining what we here refer to as prospective linking. As such, these studies may in fact be exploring a single concept to exhaustion, while ignoring others. We have therefore also shed light on a less explored side of memory linking, in which the brain has to 'think back' and selectively connect matching events: or what we here call retrospective linking. The few studies that used study designs that examine retrospective linking have revealed interesting mechanisms, such as offline engram co-reactivation. It is not yet clear whether retrospective linking also uses engram overlap or other dynamics that are characteristic of prospective linking. Thus, whether and how these two forms of memory linking interact, and whether they are reserved for specific cognitive outputs, are exciting avenues that should be pursued in our quest to understand the complicated and fascinating process of memory organization.

There are many key outstanding questions that relate to prospective linking. For example, how specific or permissive is prospective linking within its allotted temporal window — that is, are all events linked, regardless of their relevance, or are there mechanisms in place to prevent erroneous linking of unrelated events? Can prospective linking mechanisms accommodate multiple events to successfully extract complex knowledge? Is offline reactivation required for prospective linking? Is engram overlap also the mechanism for memory linking in humans?

Similarly, there are numerous unresolved issues in our understanding of the role of synaptic dynamics in memory linking. For example, do spines communicate with, or alter the plasticity of, spines on different dendritic branches during memory linking and/or offline processing? Can this interaction alter the function of a neuron for memory linking? How does sleep affect clustered synapses for linked memories? Can a population of neurons encode two events without linking them? Do dendritic and spine allocation patterns create subpopulations of engram cells for linked memories with distinct functions?

In relation to retrospective linking, there are numerous additional questions to be answered. Can engram overlap occur after the encoding of distinct engrams and, conversely, can overlapping engrams drift apart as memories become evidently unrelated? Is offline co-reactivation of relevant information the underlying mechanism for retrospective linking? Does offline co-reactivation randomly select from the pool of stored information of currently and previously encoded memories? If not, how are the relevant combinations tagged for co-reactivation? Do different sleep stages (REM and NREM) have distinct roles in retrospective linking?

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