Title
Dimensions and mechanisms of memory organization

Journal
Neuron, 109(17)

ISSN
0896-6273

Authors
de Sousa, André F
Chowdhury, Ananya
Silva, Alcino J

Publication Date
2021-09-01

DOI
10.1016/j.neuron.2021.06.014

Peer reviewed

HHS Public Access

Author manuscript

Neuron. Author manuscript; available in PMC 2022 September 01.

Published in final edited form as:

Neuron. 2021 September 01; 109(17): 2649–2662. doi:10.1016/j.neuron.2021.06.014.

Dimensions and mechanisms of memory organization

André F. de Sousa[1], **Ananya Chowdhury**[1], **Alcino J. Silva**[1,*]

[1]Departments of Neurobiology, Psychiatry & Biobehavioral Sciences and Psychology, Integrative Center for Learning and Memory, Brain Research Institute, University of California, Los Angeles, California 90095, USA

Summary

Memory formation is dynamic in nature and acquisition of new information is often influenced by previous experiences. Memories sharing certain attributes are known to interact such that retrieval of one increases the likelihood of retrieving the other, raising the possibility that related memories are organized into associative mnemonic structures of interconnected representations. While the formation and retrieval of single memories have been extensively studied, very little is known about the brain mechanisms that organize and link related memories. Here, we review studies that suggest the existence of mnemonic structures in humans and animal models. These studies suggest three main dimensions of experience that can serve to organize related memories: time, space, and perceptual/conceptual similarities. We propose potential molecular, cellular and systems mechanisms that might support the organization of memories according to these dimensions.

In Brief

The biological mechanisms underlying memory organization remain largely unexplored. In this perspective, de Sousa et al. review some of the literature on memory organization in different species and propose circuit, cellular, and molecular mechanisms that might support the formation of mnemonic structures.

Keywords

Memory organization; Mnemonic structures; Inferential reasoning; Memory allocation; Memory Linking; Engram overlap

Introduction

Most memories are not acquired in isolation, but rather in a particular context (e.g., within a temporal window or a spatial context) that is often related to previous experiences and

[*]**Lead contact/corresponding author:** Alcino J. Silva (silvaa@mednet.ucla.edu).

Declaration of interests

The authors declare no competing interests.

affects further memory formation. Such interconnectedness of life experiences has been proposed to facilitate the organization of memories into associative mnemonic structures (reviewed in (Eichenbaum, 2017a)) according to different dimensions of experience, including space, time, and concepts (Morton et al., 2017). Nevertheless, the molecular, cellular and circuit mechanisms underlying the linking and organization of memories into these associative structures remain relatively unexplored (Rogerson et al., 2014; Silva et al., 2009).

Mnemonic structures are evoked to explain the organization of multiple related events and, in our opinion, are considerably different from the concept of memory schemas previously introduced (Bartlett and Kintsch, 1932; Piaget, 1928). While some authors have resorted to memory schemas to explain different forms of memory organization (Preston and Eichenbaum, 2013), schemas are usually conceived as abstract, semantic structures of knowledge that result from the extraction of common elements present in multiple episodes (Ghosh and Gilboa, 2014). In contrast, mnemonic structures are associative networks that can be formed within just a few episodes and link related memories through a common representation while maintaining the details of each memory (Eichenbaum, 2017a; Rogerson et al., 2014; Silva et al., 2009). We share the view of Ghosh and Gilboa (Ghosh and Gilboa, 2014) who propose four necessary and sufficient features that define memory schemas: “(1) an associative network structure, (2) basis on multiple episodes, (3) lack of unit detail, and (4) adaptability” (Ghosh and Gilboa, 2014). Accordingly, mnemonic structures cannot be considered memory schemas and might actually support different cognitive processes (Table 1). For example, one of the primary functions of mnemonic structures might be to facilitate organized encoding of related information via memory allocation mechanisms (Silva et al., 2009) in order to maximize storage capacity and allow for the inference of indirect relations between specific events not experienced together (Eichenbaum, 2017a; Rogerson et al., 2014; Silva et al., 2009; Zeithamova et al., 2012a). In contrast, memory schemas are thought to influence perception, memory encoding, and action selection based on the cumulative regularities extracted from multiple episodes (Ghosh and Gilboa, 2014; Gilboa and Marlatte, 2017). Notwithstanding, mnemonic structures are likely to rely on previous memory schemas and might themselves influence the formation of memory schemas (discussed in next sections). Mnemonic structures operate at an inter-event level, becoming important when subjects try to relate information separated by event boundaries, such as when two memories are linked across time (Cai et al., 2016; Silva, 2017). These boundaries can be defined not only by significant changes in the spatial-temporal framework, but also by more subtle transitions including, but not limited to, changes in the relative relationship between the entities of an event, variations in task demands, and changes in goal-directed actions (Radvansky and Zacks, 2011). There is no clear consensus as to whether mnemonic structures are formed during learning (Eichenbaum et al., 1999; Rogerson et al., 2014; Shohamy and Wagner, 2008; Silva et al., 2009; Zeithamova et al., 2012a), or just become apparent during memory retrieval due to “memory search” strategies (Koster et al., 2018; Kumaran and McClelland, 2012; Polyn et al., 2009a). While both scenarios are not mutually exclusive, the work reviewed here suggests that either common elements between different experiences or a shared temporal window can lead to the formation of memory networks during encoding that can subsequently shape

behavioral responses during memory retrieval. Although the study of mnemonic structures has been primarily the purview of cognitive psychology, recent studies in humans and other animals have started to reveal their underlying physiological mechanisms (Eichenbaum, 2017a; Rogerson et al., 2014; Schlichting and Frankland, 2017; Silva et al., 2009). These studies suggest that the formation of mnemonic structures in different species relies on the co-allocation and integration of different memories into shared neuronal ensembles (Rogerson et al., 2014; Schlichting and Frankland, 2017; Silva et al., 2009), indicating that memory engrams are an integral part of these structures, which may involve individual memory representations in multiple brain regions. These exciting findings suggest that these structures are evolutionarily ancient, and that there is a shared core of mechanisms that could be studied in different model systems.

Here, we will first review different studies that suggest the existence of mnemonic structures in humans and other animals, with a special focus on the factors that might affect their formation. We will review examples from both episodic and semantic mnemonic structures but will focus on the biological mechanisms underlying the formation of structures with episodic and episodic-like memories that can be studied in animal models (i.e., memories that rely on *what, where, when* information (Clayton et al., 2001)). We will suggest potential molecular, cellular and systems mechanisms underlying the organization and linking of multiple memories, as well as review strategies that have been used to study memory organization in different species. We will focus mostly on rodent models, where recent ground-breaking methodological advances allow the observation and manipulation of neural activity with unprecedented temporal and spatial resolution. We propose that the framework and approaches described here could be used in studies designed to unravel the molecular, cellular, systems and cognitive mechanisms that the brain uses to organize, link, and relate individual memories into architectures that shape behavior and optimize evolutionary fitness.

Memory organization in humans and other animals

The key component of a mnemonic structure is the common element or feature that serves as a link between the individual memories of that particular structure. This common element can be, for example, a shared percept or concept, a temporal window, a spatial context, or even a shared causal relationship (Figure 1b) (Mace and Clevinger, 2019; Morton et al., 2017). The nature of the common element determines the nature of the mnemonic structure into which memories are integrated (see below). In general, the more elements two different representations share or the closer they are in any of the shared dimensions, the more likely it is that they will be recruited into the same mnemonic structure (Figure 1c). However, it should be noted that there are several examples where more similarities between two events actually lead to a stronger separation between 2 memories (e.g. of reviews (Brunec et al., 2020; Ritvo et al., 2019). It is currently not clear what are the conditions that determine whether two memories will be integrated in the same structure or not but some authors have proposed that motivational goals during the experimental task (Brunec et al., 2020), temporal proximity (Zeithamova and Preston, 2017), memory strength (Schlichting et al., 2015), or level of memory reactivation during encoding of related memories (Molitor et al., 2021; Ritvo et al., 2019) may play a role. This topic is currently under intense investigation and it is of great importance for a complete understanding of the processes involved in the

formation of mnemonic structures. However, in order to elucidate the biological mechanisms underlying the formation of mnemonic structures, here we will mainly focus on examples that reveal the successful formation of these structures.

In humans, the relative organization of different memories can be directly inferred from retrieval studies, whereas evidence for the existence of mnemonic structures in animal models is primarily obtained by the observation of functional relations between memories, such that manipulations of one memory lead to modifications in the other (Cai et al., 2016; Rashid et al., 2016; Rogerson et al., 2014; Schlichting and Frankland, 2017; Silva et al., 2009; Zeithamova et al., 2012a). These modifications can be directly assessed by behavioral studies or indirectly probed by imaging, electrophysiology and other methods for observing neural activity.

Finally, even though the classification of mnemonic structures according to different dimensions of experience (percept, concept, time, and space) outlined here is useful to establish a framework that can help one to interpret and guide experimental research, the formation of any mnemonic structure is likely influenced by different combinations of all dimensions.

Percept- or concept-based mnemonic structures

One of the most commonly studied type of mnemonic structures are those based on a perceptual or conceptual element (e.g., an item, a person, an abstract concept, a causal relation) that is common among a group of memories. This type of memory organization has been studied in humans and rodents in the context of different cognitive/behavioral tasks including, but not restricted to, retrieval-mediated learning (Hall, 1996; Holland, 1981; Iordanova et al., 2011; Zeithamova et al., 2012b), inferential reasoning (Bunsey and Eichenbaum, 1996; Zeithamova et al., 2012a), and free recall clustering (Brown and Schopflocher, 1998; Shuell, 1969). These studies suggest that the encoding of novel information can be affected by prior related memories, such that independently generated memories can become integrated into a mnemonic structure through a common element.

In humans, the ability to recognize connections between indirectly related events or items has been proposed as evidence for the existence of mnemonic structures (Morton et al., 2017; Zeithamova et al., 2012a). For example, witnessing two different people on separate occasions walking home with the same child would lead most people to infer that the two individuals are related in some way. A mnemonic structure that includes the two memories of the two separate individuals walking with the same child, and the fact that both memories have the same child in common may be key for the inference that the two individuals might be related. Even if the two memories were encoded on different days and in different locations, the common element (i.e., the child) would serve as the node that relates and organizes them into an associative structure. Note that the formation of this particular mnemonic structure might be highly dependent on the existence of a previous memory schema representing a “traditional” family structure (Figure 1a) since the ability to suppose the existence of this family arrangement in this situation depends on a memory schema that is formed following multiple contacts with such family arrangements. Thus, memory

schemas might guide the formation of mnemonic structures by providing a general layout of expected relationships on each situation. In turn, mnemonic structures can influence schema formation/update by providing the backbone of common relationships that occur across multiple mnemonic structures of the same type.

Percept-based memory organization has been studied using inferential reasoning tasks (reviewed in (Zeithamova et al., 2012a) in which human participants first learn a given pair of items, such as the image of a face paired with the image of a house (Face1-House A), and then learn a second pair involving a common element (House A-Face2). During the test phase, subjects are probed for their ability to infer the existence of an indirect relationship between the first and second faces (Preston et al., 2004). Similar to the case of the couple mentioned above, the same house in both memories functions as a node in a memory structure relating the first and second faces. Functional magnetic resonance imaging (fMRI) studies demonstrate that activity patterns associated with a given memory (e.g. Face1-House A) are reinstated during encoding of a related memory (House A-Face2), thus leading to an increase in the similarity of multivoxel patterns between the two memories (reviewed in (Schlichting and Preston, 2015; Zeithamova et al., 2012a)). This increase in pattern similarity observed during learning was further demonstrated to correlate with the strength of inference during the test phase, suggesting that links between related memories are formed during memory encoding, which might be essential for the formation of mnemonic structures (Zeithamova et al., 2012b). Reciprocal interactions between the hippocampus (HPC) and the medial prefrontal cortex (PFC) seem to be critical for establishing this pattern similarity, where the PFC is thought to guide the reactivation of relevant neural representations in the HPC during encoding and retrieval of related memories (Backus et al., 2016; Preston and Eichenbaum, 2013; Schlichting and Preston, 2016; Zeithamova et al., 2012b). Similar inferential tasks involving discrimination of different odors had previously been used in rodent studies and both rats and mice were shown to successfully infer relations between indirectly related odors (Bunsey and Eichenbaum, 1996; DeVito et al., 2010). Interestingly, HPC and PFC lesions in these studies impaired correct inferences without affecting memory for direct associations, possibly suggesting an evolutionary conserved role for these brain regions in organizing information into percept-based structures.

In addition to mnemonic structures formed by tangible common elements, information can also be organized according to common concepts, task rules, or even subjective hedonic value (Honey and Watt, 1998; Long et al., 2015; Polyn et al., 2009b). For example, semantic clustering is a well-known phenomenon in the human memory literature where conceptually-related items that were learned in the same list tend to be co-retrieved during testing (Shuell, 1969). Moreover, human studies show that both directed and spontaneous recall of certain episodic memories increases the likelihood that other conceptually-related events are also retrieved, suggesting that these types of memories are highly organized by conceptual similarity (Mace, 2014; Mace et al., 2010). Both humans and rodents were shown to link information from separate events that share common task rules (Honey and Watt, 1998; Polyn et al., 2009b), and in rodents this was dependent on intact HPC and PFC, suggesting a general role of these brain regions in organizing information according to different dimensions of experience (Coutureau et al., 2002; Iordanova et al., 2007).

Overall, the studies reviewed in this section suggest that events sharing either perceptual elements, common events, or abstract concepts, tend to become associated, possibly contributing to the formation of integrated mnemonic structures that support different cognitive processes. In addition, both the HPC and the PFC appear to be critically involved in the formation of these mnemonic structures in both humans and rodents.

Time-based mnemonic structures

Time may be the most natural way to organize distinct memories, since events experienced close in time are more likely to be meaningfully related than events experienced far apart in time (Cai et al., 2016; Rogerson et al., 2014; Silva, 2017; Silva et al., 2009). While it is often difficult to clearly disentangle time and space in ongoing experience (Buzsáki and Llinás, 2017), time can been treated as an independent entity that affects the different aspects of learning and memory (Eichenbaum, 2017b; Howard and Eichenbaum, 2015). Evidence from human studies suggests that even unrelated items encoded within close temporal proximity tend to become associated, such that retrieving one increases the likelihood of retrieving the other (Kahana, 1996). One theoretical model, known as the Temporal Context Model (TCM), attempts to explain this phenomenon by proposing that the brain integrates changing sensory inputs as a sequence of occurrences through time and attributes different “time tags” to each sequential change (Howard and Kahana, 2002). This model predicts that there is a slowly-changing representation of a “temporal context” that is co-encoded with different items, and that allows for items encountered in close temporal proximity to share similar time tags. During memory retrieval, the time tag associated with a particular element increases the likelihood that other elements associated with the same temporal context are also retrieved. While the time scale proposed in this model is suited for tracking changes occurring within events (seconds to minutes apart), one can imagine that a similar process may track and label sequences of events across longer time scales (Brunec et al., 2015; Eichenbaum, 2017b). In this view, different events that unfold in close temporal proximity (hours apart) would share a more similar temporal context and could therefore become integrated into a time-based mnemonic structure. Thus, temporal context could serve as a common node connecting or biasing the encoding of multiple events in this mnemonic structure, not unlike the examples of common items described for percept-based mnemonic structures. This framework could explain the well-known temporal clustering of reported events observed during retrieval of autobiographical memories in humans, where retrieval of one event often increases the likelihood of retrieving other events experienced in close temporal proximity (generally within the same day) (Mace and Clevinger, 2019).

In addition, the same framework could explain recent results obtained in human and rodent studies that explore the linking of two different memories acquired hours apart. Rodent studies demonstrated that related events (e.g., explorations of novel contexts) experienced within a day become functionally linked such that updating the memory of one event (e.g., with an unconditioned stimulus) directly affects the memory for the other. In contrast, if the same events are experienced days apart, memories appear to become independent with no evidence of functional linking (Cai et al., 2016). Similar experiments in humans showed that subjects were more likely to link two memories when they were encoded hours versus days apart (Yetton et al., 2019). Rodent studies further demonstrated that the

two functionally linked memories shared a higher number of encoding cells in the HPC (Cai et al., 2016), suggesting that time-based structures rely on cellular mechanisms similar to the ones described in the previous section for percept-based structures. Human studies have also demonstrated that events experienced in close temporal proximity (seconds to minutes), while participants navigate a virtual town, tend to be retrieved together, and have a higher similarity of voxel patterns in the HPC than events or items experienced further apart (Deuker et al., 2016). Remarkably, this relationship between similarity of voxel patterns and temporal distance was also observed in a study where participants were cued to retrieve memories encoded during daily life over a span of 30 days, possibly indicating that in humans the HPC also organizes experiences over extended time periods through encoding mechanisms that result in increased pattern similarity between memories within the same extended temporal context (Nielson et al., 2015). Given the potential parallels observed between the neural mechanisms operating during time-based memory linking and the inferential reasoning experiments described in the previous section, it is tempting to hypothesize that an increase in the number of shared neurons encoding both memories might be a general mechanism to integrate information from different events into a given mnemonic structure (Morton et al., 2017; Schlichting and Frankland, 2017). It remains to be tested whether time-based structures also allow for the inference of indirect relationships between multiple events experienced within the same temporal context, in a way similar to percept-based structures.

Space-based mnemonic structures

Another major dimension that can affect memory organization is the presence of a common spatial context. Much like a temporal context, a spatial context can have a predictive impact in the life of any organism capable of exploration. Not surprisingly, neural mechanisms dedicated to encoding spatial information have been described in multiple species (Moser et al., 2017), and the spatial context is well known to affect learning and memory processes (Metzger, 2014). In humans, spatial contexts are often used as mental landmarks for clustering episodic memories and determine temporal sequences of events (Barsalou, 1988), suggesting that they serve as a common element that integrates different memories into mnemonic structures. However, the formation of space-based mnemonic structures might partially depend on different mechanisms than the percept-based mnemonic structures described above since it is difficult to see how the same context could continue to serve as a strong cue that links novel memories together as one spends more time in it (Hupbach et al., 2011). Perhaps, spatial contexts operate in a similar way as temporal contexts, providing a slowly changing representational framework that is co-encoded or bias the encoding of events unfolding over time. Accordingly, there is now compelling evidence that aspects of the spatial context are co-encoded with different items during a learning episode in both humans and rodents (Komorowski et al., 2009; Miller et al., 2013a; Staresina and Davachi, 2008). Furthermore, studies from both species demonstrated that spatial context modulates the way different items/events are represented in the HPC, with items/events experienced in close spatial proximity or in the same context sharing more similar activity patterns (Deuker et al., 2016; McKenzie et al., 2014; Miller et al., 2013b).

These effects of the spatial context on memory encoding have been shown to directly affect memory organization. For example, human studies demonstrate that items encountered in close spatial proximity tend to be retrieved together during free recall tests, mirroring the effects observed for items acquired in close temporal proximity (Miller et al., 2013b; Pacheco and Verschure, 2018). Studies in both humans and rodents have further demonstrated that two perceptually different cues come to be treated as equivalent during a test phase if they were presented in the same context during learning (Molet et al., 2011, 2012). In one of these studies, rats were trained in a flavor conditioning task by providing water containing two distinct novel flavors either in the same spatial context or in different contexts. Following this learning phase, one of the flavors was mixed with sucrose to update its valence. On the testing day, the rats consumed significantly more water mixed with the flavor that had been presented in the same context with the updated flavor during learning, than the one presented in a different context (Molet et al., 2012). These results indicate that following changes in the valence of one flavor, rats change their relative preference for flavors that had been presented in the same context, suggesting the existence of an organizational relation that affects independent memories in a similar way as time-based mnemonic structures described in the previous section. In summary, the studies reviewed in this section suggest that, similarly to the temporal context, the spatial context of memories allows for the attribution of “spatial tags” that enable the organization of multiple memories according to common places or contexts where they are encoded. Moreover, these studies suggest that space-based mnemonic structures might involve an increase in the similarity of representation patterns between memories encoded in the same spatial context, similar to percept- and time-based structures. However, spatial contexts might exert their organizational role in ways that differ from simple items (physical or abstract), in part due to differences in the circuits used to encode each of these dimensions, as proposed in the next sections.

Biological mechanisms of memory organization

The studies reviewed in the previous sections suggest the HPC and the PFC are important for the formation of different mnemonic structures during learning. Moreover, several studies demonstrate that hippocampal neuronal ensembles of related memories are more similar than those of unrelated memories, suggesting that overlap between memory ensembles could be an essential mechanism for the formation of mnemonic structures (Morton et al., 2017; Rogerson et al., 2014; Silva et al., 2009). A better understanding of the mechanisms regulating neuronal memory allocation and overlap during the tasks mentioned above would be crucial to elucidate the general mechanisms underlying memory organization in the mammalian brain. In the next sections, we will first review the participation of the HPC and PFC in memory processes that might be relevant for the formation of mnemonic structures. We will then propose how biological mechanisms operating at different levels (circuit, cellular and molecular levels) in these brain regions might contribute to the formation of organized mnemonic structures.

The role of HPC in memory

The HPC and surrounding medial temporal lobe (MTL) have long been implicated in the formation, consolidation, and retrieval of episodic memory in different species (e.g. of review (Squire et al., 1993)). Multiple studies in humans and animal models have determined that the HPC plays a critical role in combining different types of information (*what, where,* and *when* information) (Sugar and Moser, 2019) characteristic of episodic memory. One influential theory proposes that these types of information are conveyed to the HPC by different neural circuits involving surrounding parahippocampal regions (reviewed in (Eichenbaum, 2017b; Eichenbaum et al., 2012), but see (Save and Sargolini, 2017) for a review on recent studies challenging a clearcut view of this hypothesis). The *what* pathway involves the perirhinal cortex that projects directly to the lateral entorhinal cortex (LEC), which in turn has reciprocal connections with the HPC. In contrast, *where* information involves activity in the parahippocampus cortex (known as postrhinal cortex in rodents) that projects to the medial entorhinal cortex (MEC), which has reciprocal connections with the HPC. Information about *when* an event is experienced has been detected in the HPC, MEC and LEC, and is thought to involve additional brain regions (reviewed in (Eichenbaum, 2017b)). The *what, where, when* information remain largely segregated by these two pathways until combined by entorhinal projections in the HPC (Witter et al., 2000). Hippocampal neural activity is thought to encode, amongst other things, the identity of items and stimuli (Wood et al., 1999a), the position of the animal in space (place cells) (O'Keefe, 1976), and the time elapsed in task-relevant intervals (time cells) (Pastalkova et al., 2008), suggesting that the HPC processes all these different types of information.

Traditionally, the HPC has been viewed as a brain region essential for the encoding and retrieval of unique episodes via pattern separation and pattern completion mechanisms supported by different subfields (Marr, 1971; McClelland et al., 1995; O'Reilly and McClelland, 1994). However, several studies have demonstrated that this brain region is also able to represent common features between different episodes (e.g. (Cai et al., 2016; McKenzie et al., 2014; Schlichting et al., 2015; Shohamy and Wagner, 2008; Wood et al., 1999a; Zeithamova et al., 2012b)). In rats, responses of individual cells in the dorsal HPC have been found to correlate with both unique events and multiple related events, suggesting that cells in this brain region might encode both specific events and common features present different events (McKenzie et al., 2014; Wood et al., 1999b). In addition, some authors have suggested that there is a functional distinction along the longitudinal axis of the HPC such that the dorsal HPC (posterior HPC in humans) encodes details about an episode whereas the ventral HPC (anterior HPC in humans) encodes more general information that might be common across events (Poppenk et al., 2013). Recent studies (Dimsdale-Zucker et al., 2018; Molitor et al., 2021) and some computational models (Schapiro et al., 2017) further suggest that different subfields of the HPC can separately encode specific instances or common regularities across related episodes. Together, these properties of the HPC indicate that this brain region is able to simultaneously represent commonalities and differences between related experiences, which might support the formation of mnemonic structures discussed here.

Overall, the HPC and associated parahippocampal regions, are involved in encoding different aspects of episodic memory, with an apparent segregation of streams of information representing *what, where* and *when* components, which might be crucial to separately organize information into percept-, space-, and time-based mnemonic structures, respectively.

The role of PFC in memory

The contribution of the PFC to declarative memory has been shown to be crucial when learned information needs to be distinguished, organized, or reconciled with previous memories (Szczepanski and Knight, 2014). Patients with PFC damage do not present strong memory deficits but are impaired in their ability to correctly identify the context where information was acquired (source memory), to correctly remember the temporal order of multiple events, and suffer from constant interference from previous memories during new learning (Eichenbaum, 2017c). While there is currently no general agreement regarding the similarities between human and rodent PFC, functional studies in rodents suggest parallels with the human findings. For example, as in humans, lesions in PFC produce deficits in source memory, increases in memory interference, and decreases in behavioral flexibility in rule-alternation tasks (Eichenbaum, 2017c). Electrophysiological studies in rodents suggest a bidirectional communication between PFC and HPC during memory retrieval, where PFC appears to dictate which memories are activated in the HPC (Depue, 2012; Place et al., 2016). More recently, several studies have demonstrated the contribution of this brain region to the acquisition of HPC-dependent memories, indicating that the PFC might be involved in controlling both acquisition and retrieval of these memories (reviewed in (Takehara-Nishiuchi, 2020)). Of particular importance for the topic discussed here is the reported involvement of the PFC in updating HPC-dependent memories. For example, in rodents, PFC activity is crucial for updating the valence of a spatial context (Heroux et al., 2017), for memory reconsolidation (Stern et al., 2014), and memory extinction (Giustino and Maren, 2015). Moreover, the PFC has been implicated in the formation of memory schemas, and this suggests that this brain region is able to represent and track commonalities between different memories (Tse et al., 2007, 2011).

In both humans and rodents, the PFC can be divided into different areas, defined by the pattern of connectivity with medio dorsal thalamic nucleus (Dalley et al., 2004; Miller and Cohen, 2001). While different areas have been shown to play a different role in memory, most studies reviewed here suggest that formation of mnemonic structures preferentially involves the medial PFC in both species. The PFC receives direct projections from the ventral part of the HPC (anterior in humans) that are necessary for the development of site-specific representations in the PFC (Hok et al., 2013) and for spatial memory (Barker et al., 2017). Recently, rodent studies demonstrated that the dorsal cornu Ammonis (CA) 1 of the HPC also projects to PFC, and these projections are important for retrieval-mediated enhancement of contextual fear conditioning (CFC) (Ye et al., 2016), as well as for correctly encoding the temporal sequence of events (Barker et al., 2017). In turn, the PFC is thought to indirectly influence HPC activity via projections to parahippocampal regions (Jayachandran et al., 2019) and nucleus reuniens, a thalamic nucleus that has reciprocal connections with both the HPC and the PFC (Dalley et al., 2004; Eichenbaum, 2017c). A

recent study in mice found a direct projection from the anterior cingulate cortex (one area of the PFC) to the dCA1/CA3 that bidirectionally modulated retrieval of a CFC memory, representing yet another route of control from the PFC to the HPC (Rajasethupathy et al., 2015).

One generally accepted view is that the PFC exerts strategic or cognitive control over hippocampal function during memory processes and is crucial to organize and update hippocampal representations (Eichenbaum, 2017a, 2017c; Miller and Cohen, 2001). In addition to its involvement in the formation of memory schemas mentioned above (Gilboa and Marlatte, 2017; Tse et al., 2007, 2011), the PFC has also been implicated in the retrieval/storage of remote memories (Frankland and Bontempi, 2005; Kitamura et al., 2017). This raises the possibility that its role in the formation and maintenance of mnemonic structures might by two-fold: On one hand, this brain region can directly influence HPC function during the formation of mnemonic structures and support the retrieval of appropriate memories at the time of integration (Depue, 2012; Miller and Cohen, 2001; Schlichting and Preston, 2015) while preventing interference between related memories (Guise and Shapiro, 2017; Shimamura et al., 1995). On the other hand, the PFC might itself store abstract relationships between memories (Schlichting and Preston, 2015; Schlichting et al., 2015) that might be important to support inferences at remote time points and to allow for the formation of memory schemas through extraction of regularities between multiple events involving mnemonic structures. Thus, through its interactions with the HPC, the PFC emerges as a crucial brain region for the development and maintenance of the mnemonic structures described here.

Systems-level regulation of memory organization

How might the properties of the PFC and HPC modulate the formation and use of mnemonic structures? In the case of percept-based mnemonic structures, the presence of a common perceptual element during encoding of the second memory may serve as a cue to retrieve related memories that can be integrated with new information during acquisition of a second memory (Zeithamova et al., 2012a). This process requires precise control over which memory ensembles are reactivated to avoid memory interference (Poll et al., 2020). One possibility is that during encoding of related information, the PFC exerts control over which HPC representations are reactivated by directly modulating the perirhinal cortex, the "*what*" pathway (Eichenbaum, 2017c; Preston and Eichenbaum, 2013). In line with this idea, a recent study in rodents used a sensory preconditioning paradigm to demonstrate that the perirhinal cortex is essential for the formation of indirect associations during learning of a second memory. In this study, rats first learned a sound-light association followed by a light-shock association on a subsequent day. Inactivation of the perirhinal cortex during learning of the light-shock association impaired freezing levels to the sound (indirectly associated with shock), but not to the light (directly associated with shock) during a memory test, suggesting that this brain region is essential for the retrieval-mediated formation of a mnemonic structure containing sound-light-shock elements (Wong et al., 2019). It remains to be tested if this effect is dependent on specific PFC inputs to the perirhinal cortex that were recently shown to modulate the correct retrieval of a sequence of odors in rats (Jayachandran et al., 2019). Retrieval-mediated learning has also been demonstrated to

depend on hippocampal synaptic plasticity at the time of encoding, suggesting that HPC representations are directly updated during encoding of related information (Iordanova et al., 2011). The exact mechanisms underlying the concomitant retrieval and encoding of information in this type of learning are not well understood, but recent studies suggest that the mammalian brain uses partially different circuits for memory retrieval and memory encoding (Eldridge et al., 2005; Roy et al., 2017).

In one rodent study, the authors demonstrated that projections from dorsal CA1 to the layer 5 of MEC are necessary for encoding a CFC memory, whereas a circuit involving projections from dorsal CA1 to dorsal subiculum, and from there to layer 5 of MEC, was necessary for memory retrieval (Roy et al., 2017). Using optogenetics and a context preexposure facilitation protocol, the authors further demonstrated that the two circuits are involved in real-time updating of the valence of a spatial context: the activity in the retrieval circuit was necessary during context re-exposure (i.e. cue-elicited retrieval), whereas activity in the encoding circuit was required during context-shock pairing (i.e. memory update). The existence of partially different circuits preferentially recruited for memory retrieval and memory encoding in the MTL might facilitate the formation of percept-based mnemonic structures by accommodating retrieval and learning mechanisms that work in parallel to promote memory integration while minimizing memory interference. The PFC could regulate both encoding and retrieval processes via direct projections to different areas of the parahippocampal regions (Jayachandran et al., 2019; Preston and Eichenbaum, 2013).

Different circuits might be involved in the formation of time-based mnemonic structures, since in this case there is no obvious common element to trigger memory retrieval during learning of the second event. The representation of time during memory processes is not completely understood, and is thought to involve multiple brain regions, including the HPC, the striatum, the parietal cortex parahippocampal region, and the PFC (reviewed in (Eichenbaum, 2017b)). In rodents, both the HPC and PFC have been shown to be necessary for encoding temporal order (DeVito and Eichenbaum, 2011), and interval duration between events (Jacobs et al., 2013; Kim et al., 2009). In addition to the presence of time cells in the HPC and MEC, recent studies in rodents demonstrated the existence of similar cells in the PFC (Tiganj et al., 2017). The activity of time cells is thought to be involved in tracking time in the scale of seconds to minutes within the context of a specific task or event. In contrast, the encoding of time across larger temporal scales (hours-days), has been hypothesized to be carried out by a slow drift in the population of cells encoding different events. In line with this hypothesis, several studies have identified a constant change in the identity of dorsal CA1 pyramidal cells encoding the same stimulus over time. This has been observed for neural cells encoding spatial contexts (Rubin et al., 2015), for place cells (Ziv et al., 2013), and for time cells (Mau et al., 2018). Another study demonstrated that the LEC also encodes time during experience at both the level of single neuron activity and at the population level (Tsao et al., 2018). Temporal encoding at the population level was observed at multiple time scales raging from seconds to hours, raising the possibility that the LEC might contribute to the general attribution of time tags observed in dorsal CA1(Rolls and Mills, 2019). Overall, these studies demonstrate that the pattern of neural activity representing similar experiences slowly changes over extended periods of time in different brain regions, perhaps providing a

temporal tag for an extended temporal context that could directly influence the organization of memories acquired over long time periods, as proposed in previous sections.

Finally, memory organization according to a spatial dimension might be different from arranging information into percept-based structures, in part due to the processing of this type of information by different circuits (the *where* pathway mentioned above). During memory encoding, information about the spatial context activates the parahippocampus, which feeds information to the MEC, and this in turn projects to the HPC, where the spatial environment is partially encoded (i.e., the *where*). At the same time, information about the content of an event involves the perirhinal cortex-LEC-HPC circuit (*what* and possibly *when*). These two pathways converge into the same cells in the DG and CA3, allowing for a combination of the *what, where,* and *where* information into conjunctive representations (Witter et al., 2000). In contrast, different CA1 neurons receive inputs from each pathway, allowing for segregation between spatial and non-spatial information (Witter et al., 2000). Parallel processing would allow the encoding of the spatial context and items/events encountered in that space into different cells, with multiple events being co-encoded with the same contextual representation. Such parallel encoding could be essential for organizing multiple memories according to a common spatial context while allowing for the flexible use of information in other contexts, an essential characteristic of information acquired during episodic memory. Interestingly, a recent rodent study (Tanaka et al., 2018) demonstrated that neurons potentially encoding episodic memories in the dorsal CA1 of the HPC, the so called engram cells (Josselyn and Tonegawa, 2020), are a distinct population of neurons that displays low spatial information and are activated in parallel with place cells during memory encoding and retrieval, perhaps representing two distinct neural populations receiving information from the two different pathways mentioned above.

It is worth noting that multiple studies have now demonstrated that the spatial encoding of a given context _is not as stable as originally thought, but changes with task requirements, motivational states (Moser et al., 2017), and gradually drifts over time, with different place cells in the dorsal CA1 being recruited on different visits to the same environment (Ziv et al., 2013). The behavioral- and temporal-induced drifts of spatial information observed in CA1 might reflect the influence of time and event features that allow animals to distinguish each visit to the same environment as a unique event. This could allow for the organization of information not only according to spatial similarity but also according to other dimensions, potentially leading to an interaction between space-, percept- and time-based mnemonic structures. Interestingly, the PFC receives information about temporal order of events and the position of items in space from different HPC inputs, with the dorsal CA1 transmitting information about temporal order and the intermediate CA1 transmitting information about the position of objects in space (Barker et al., 2017). Such segregation could allow the PFC to weight the relative contribution of these two dimensions for memory organization, thus influencing the formation of appropriate mnemonic structures.

Cellular mechanisms of memory organization

Human and rodent studies reviewed here suggest that mnemonic structures depend on shared memory ensembles. For example, rodent studies imaging neural representations of two

contexts integrated in a potential time-based mnemonic structure demonstrated that linked contexts shared higher overlapping neuronal representations than independent contexts in the dorsal CA1 (Cai et al., 2016). Importantly, by exploring memory linking in aged-adult mice, this study provided the first evidence that neuronal overlap might be essential for the functional linking of two memories. Aged-adult mice (15-18 months old) presented deficits in memory linking and neuronal overlap with no deficits in single memory. Using a chemogenetic approach, the authors demonstrated that increasing neuronal excitability in the same group of dorsal CA1 cells during exposure to both contexts, so that the memories of both contexts were allocated to overlapping populations of cells, was sufficient to rescue memory linking deficits in these mice, a result consist with the allocate-to-link hypothesis (Rogerson et al., 2014; Silva et al., 2009). Similar results were obtained in a study investigating the overlap of neuronal representations and functional association between two amygdala-dependent memories acquired 5 hours versus 1 day apart, suggesting that overlapping representations are also essential for linking related memories processed in other brain regions (Rashid et al., 2016). In a related study, other authors demonstrated that the overlapping cells between two memory ensembles in the amygdala were necessary for linking those two memories, but they were not essential for the retrieval of each individual memory, suggesting a specific role for this population of cells in supporting links between memories of a mnemonic structure (Yokose et al., 2017). These studies indicate that although the overlapping cells might not directly encode individual memories, they are an integral part of the “memory engram” (in these studies defined as learning-related active cells that express immediate early genes and presumably undergo synaptic plasticity to store a memory (Josselyn and Tonegawa, 2020)). This raises the possibility that during memory encoding there is a specific population of engram cells that is “tuned” to encode general features of an event or even potential relationships between different memories. It will be important to explore the nature of these overlapping cells in terms of their circuit connectivity and genetic profile. An intriguing possibility is that these overlapping cells could be a functionally distinct population of engram cells that encode or allow the retrieval of different aspects of an experience, as recently suggested in a rodent study investigating the heterogeneity of engram cells in the dentate gyrus of the hippocampus (Sun et al., 2020).

The allocate-to-link hypothesis proposes that mechanisms that regulate which cells and synapses of a given ensemble store a memory have a key role in linking that memory to other memories within a given temporal context (Rogerson et al., 2014; Silva, 2017; Silva et al., 2009). This hypothesis proposed that the increased overlap of neuronal representations of linked memories reviewed above is due to increases in intrinsic neuronal excitability triggered by activation of the transcription factor CREB following encoding on the first memory (see next section) (Rogerson et al., 2014; Silva, 2017; Silva et al., 2009). This increase in neuronal excitability observed following the encoding of the first memory (Cai et al., 2016) increases the probability that the second memory is allocated to some of the same cells encoding the first memory. Over time (a day or more) this increase in neuronal excitability is thought to dissipate, and therefore subsequent memories are no longer allocated to the neuronal ensembles that encoded the first memory. This hypothesis proposes that time-dependent changes in excitability are an efficient way to tag neuronal ensembles and prepare them for recruitment into time-based mnemonic structures, since

these excitability changes are sufficient to modulate the co-allocation of related memories without the need for more complex mechanisms, such as the sequential activity of time cells over hours or even days. Moreover, the increases in neuronal excitability observed following encoding could also be an integral part of the formation of mnemonic structures involving retrieval-mediated mechanisms that are independent of a common temporal context. For example, during the formation of percept-based mnemonic structures, encoding of a novel association “B-C” can trigger the retrieval of a related association “A-B” that shares the common element “B”. This may lead to a situation where neural populations encoding the newly acquired association (B-C) and the previous retrieved association (A-B) both have relatively higher excitability after learning (Pignatelli et al., 2019). Consequently, these two populations would have a higher likelihood of being co-activated during subsequent hippocampal sharp-wave ripples that have been implicated in consolidation of long-term memories (e.g. of review (Skelin et al., 2019)) and formation of links between related events not observed together (Barron et al., 2020). The co-activation of both memories during this consolidation period could therefore potentiate the emergence of an overlapping population of cells that is necessary to link both memories. In fact, it has been shown that co-retrieval of independent memories can lead to memory linking via overlapping ensembles (Yokose et al., 2017) and that post learning optogenetic-reactivation of the memory ensembles of two different memories in the HPC is sufficient to induce memory linking (Oishi et al., 2019). Thus, increases in neural excitability could be an effective way to ensure the formation of links between two memories that share common features but are encoded in a different temporal/spatial context.

Other studies suggest that independently of their identity, items sharing a common spatial context also share more of the same encoding neurons than items encountered in different contexts. In a rodent study, single unit activity was recorded in CA1 and CA3 while rats learned a behavioral task involving a conditional discrimination between 2 contexts and 2 objects (object A or B) (McKenzie et al., 2014). In one context, object A was rewarded, and object B was not, while in the other context this contingency was reversed. The authors found individual neural responses that were specific to different aspects of the task, including the identity of the context, the spatial location of the objects, their identity and valence on each trial. An analysis of representational similarity of the entire population of recorded neurons demonstrated that the spatial context seems to function as a primary cue to determine how each of the other features is encoded, with different items encountered in the same context sharing higher representational similarity than the same item encountered in different contexts. These results suggest that spatial contexts can have a direct impact on memory encoding and allocation, and this might be essential for the formation of space-based mnemonic structures.

When two or more memories share a larger than normal overlapping population of neurons, these neurons may serve as a bridge between memories, so that reactivation of one memory leads to the reactivation of other memories with overlapping neuronal ensembles (Figure 2b) (Rogerson et al., 2014; Silva, 2017; Silva et al., 2009). This process might employ pattern completion mechanisms similar to the ones reported for memories involving the visual cortex, where artificial reactivation of as few as two neurons belonging to a behavioral-related neural ensemble in this brain region was sufficient to reactivate the

entire ensemble and trigger memory retrieval (Carrillo-Reid et al., 2019). This effect might also induce the simultaneous reactivation of multiple brain regions relevant for memory processes, as recently demonstrated when engram cells in the HPC or PFC were artificially reactivated using chemogenetic methods (Chowdhury and Caroni, 2018). Thus, it is likely that mnemonic structures involve overlapping populations of neurons in multiple brain regions, and that activation of one memory in one or more of these regions can lead to system-wide reactivation of memories in the same mnemonic structure.

One outstanding question is how these overlapping populations in mnemonic structures might influence the long-term consolidation of memories across multiple brain regions. Memory consolidation is thought to involve the spontaneous reactivation of encoding neural ensembles across the brain following learning (reviewed in (Skelin et al., 2019)), and recent studies have shown that engram cells in different brain regions are directly involved in the process (Kitamura et al., 2017; de Sousa et al., 2019). It is possible that memories sharing a high number of overlapping cells are co-reactivated during the consolidation process, which might be essential for the formation of links between indirectly related events within the same mnemonic structure, as recently proposed in a study in mice (Barron et al., 2020). Given the known participation of the HPC and PFC in memory consolidation (Skelin et al., 2019) and in the formation of mnemonic structures reviewed here, it is likely that crosstalk between these two brain regions will be important for the consolidation and long-term maintenance of mnemonic structures. By ensuring the simultaneous reactivation of related memories in the HPC during memory consolidation, overlapping ensembles might facilitate the extraction of regularities by the PFC for long-term memory storage and formation of memory schemas (Tompary and Davachi, 2017). In addition, this dialogue between the two structures during “offline” periods, might provide an opportunity to further increase or decrease the strength of associations present in a given structure based on previous information stored in neocortical areas.

It is reasonable to assume that mechanisms underlying the formation of mnemonic structures must involve multiple levels of regulation since a simple association of memories sharing common elements might not always be beneficial (Carpenter and Schacter, 2017; Chowdhury and Caroni, 2018; Rogerson et al., 2014; Silva, 2017; Silva et al., 2009). Neurogenesis (Aimone et al., 2006) as well as cellular and synaptic allocation mechanisms in the HPC (and other encoding regions) (Rogerson et al., 2014; Silva et al., 2009), are likely to be a crucial component of organizational processes that allow the maintenance of the detailed information in each memory despite overlapping neurons with other memories (Abdou et al., 2018; Lisman et al., 2018). Future studies will explore the nature of overlapping ensembles and clarify whether the cellular mechanisms leading to increased overlap in memory representations are similar for all types of mnemonic structures (e.g. increases in neural excitability), or if organization of information according to different dimensions of experience results in the same cellular phenotype albeit through different biological mechanisms.

Molecular mechanisms of memory organization

Very few studies have specifically investigated the molecular mechanisms involved in the organization of multiple memories; however, some insights can be drawn from studies that explored the encoding of two experiences related by either temporal proximity or conceptual similarity.

Following learning, neuronal circuits undergo a cellular consolidation period that is necessary for the formation of long-term memories (in this context, memories that last more than 24 hours). This initial consolidation phase lasts around 2-3 hours and requires the synthesis of new proteins involved in stabilizing synaptic changes that took place during learning (Davis and Squire, 1984). Acquisition of a second memory during this consolidation period can lead to interference (Robertson, 2012). However, in some cases a “weak memory” (i.e. a learning event that would not generate a long-term memory) can be strengthened if a second “strong memory” is acquired within the consolidation period. These results have been interpreted in light of the behavioral/synaptic tagging and capture hypothesis, which postulates that weak learning that does not initiate new protein synthesis can be strengthen if another learning event occurring shortly before or after (usually no longer than 2 hours apart) is co-allocated to the same cells and induces new protein-synthesis that can be used to stabilize the weak memory (Frey and Morris, 1997; Moncada et al., 2015; Nomoto et al., 2016; Redondo and Morris, 2011; Rogerson et al., 2014). The idea is that weak learning leaves a “tag” on activated synapses that then can capture plasticity-related proteins induced by the other learning event. Multiple molecular events, such as dopaminergic modulation, protein synthesis and activity, have been shown to be necessary for this process (Moncada et al., 2015; Navakkode et al., 2010), demonstrating that there are specific molecular mechanisms necessary to modulate and stabilize information co-allocated to the same neurons. It is possible that these mechanisms are involved in the creation of mnemonic structures composed of strong and weak memories acquired over multiple time scales.

Additionally, rodent studies of memory linking across time proposed that the transcription factor CREB is essential for this process (Cai et al., 2016; Rashid et al., 2016). CREB is thought to play a key role in triggering changes in neural excitability underlying the co-allocation of memories to neuronal ensembles with an overlapping population of neurons (Rogerson et al., 2014; Silva et al., 2009). Interestingly, the effects of synaptic tagging and capture mechanisms described above are limited to memories acquired within an interval of approximately two hours, while the mechanisms of memory linking seem to apply to memories acquired within 5-24 hours. Coordination of both mechanisms might be essential to organize memories related by different time scales and contribute not only for the encoding of the order of sequential events but also for encoding the relative temporal distance between memories of the same mnemonic structure.

Studies investigating the encoding of two or more memories in sequence, found that the molecular mechanisms required for the acquisition of the first memory can be different from those engaged during the acquisition of subsequent memories in that sequence. For example, several studies have demonstrated that although HPC NMDA receptors are required for the

acquisition of CFC memories, acquisition of a second CFC memory in a sequence does not require the activation of HPC NMDA receptors [e.g. (Crestani et al., 2019; Tayler et al., 2011)]. Instead, formation of the second memory involves many of the same neurons that were engaged by the first memory, and requires activity of metabotropic glutamate receptors in the HPC at the time of learning (Crestani et al., 2019). Interestingly, this effect was shown to be dependent on the contingencies of the task and not on temporal, spatial, or valence components (Crestani et al., 2019; Finnie et al., 2018; Tayler et al., 2011), suggesting the formation of a concept-based mnemonic structure. Together, these studies suggest that learning of conceptually-related information might engage unique molecular mechanisms that are usually not used to encode and consolidate single memories. By relying on different molecular mechanisms, the HPC might be able to encode related memories into the same neurons without risking memory interference or reconsolidation of previous memories. This process might be essential for the formation of mnemonic structures that allow for the establishment of functional relations amongst memories while maintaining the details of each individual memory.

Conclusion

Here, we reviewed multiple studies of mnemonic structures in humans and rodents. These structures are an essential feature of the mammalian brain that allow for the establishment of indirect associations between items or events not experienced together. The formation of mnemonic structures involves biological mechanisms operating at multiple levels and in different brain regions. These structures are organized according to different dimensions of experience involving, for example, a common percept/concept, or a common temporal or spatial context, and we propose that neuronal allocation mechanisms, including the ones reviewed here, are key for linking memories within these structures. The study of the biological mechanisms of mnemonic structures at multiple levels of analyses, including studies in animal models, will be crucial to advance our knowledge of how cognitive processes optimize the storage and usage of large amounts of information in changing environments.

Acknowledgments

We thank Francisco Mata for designing the figures. We thank Daniel G. Almeida-Filho and Megha Sehgal for discussions and comments on initial drafts of the manuscript. We thank all members of the Silva lab for comments on the manuscript. This work was supported by grants from the National Institutes of Health R01 MH113071 and R01AG013622 as well as by the Dr. Miriam and Sheldon G. Adelson Medical Research Foundation to AJS.

References

Abdou K, Shehata M, Choko K, Nishizono H, Matsuo M, Muramatsu S, and Inokuchi K (2018). Synapse-specific representation of the identity of overlapping memory engrams. Science. 360, 1227–1231. [PubMed: 29903972]

Aimone JB, Wiles J, and Gage FH (2006). Potential role for adult neurogenesis in the encoding of time in new memories. Nat. Neurosci 9, 723–727. [PubMed: 16732202]

Backus AR, Schoffelen JM, Szebényi S, Hanslmayr S, and Doeller CF (2016). Hippocampal-prefrontal theta oscillations support memory integration. Curr. Biol 26, 450–457. [PubMed: 26832442]

Barker GRI, Banks PJ, Scott H, Ralph GS, Mitrophanous KA, Wong L, Bashir ZI, Uney JB, and Warburton EC (2017). Separate elements of episodic memory subserved by distinct hippocampal-prefrontal connections. Nat. Neurosci 20, 242–250. [PubMed: 28067902]

Barron HC, Reeve HM, Koolschijn RS, Perestenko PV, Shpektor A, Nili H, Rothaermel R, Campo-Urriza N, O'Reilly JX, Bannerman DM, et al. (2020). Neuronal Computation Underlying Inferential Reasoning in Humans and Mice. Cell 183, 228–243. [PubMed: 32946810]

Barsalou LW (1988). The content and organization of autobiographical memories. In Remembering Reconsidered, (Cambridge University Press), pp. 193–243.

Bartlett FC, and Kintsch W (1932). Remembering : a study in experimental and social psychology (Cambridge University Press).

Brown NR, and Schopflocher D (1998). Event Cueing, Event Clusters, and the Temporal Distribution of Autobiographical Memories. Appl. Cogn. Psychol 12, 305–319.

Brunec IK, Chadwick MJ, Javadi AH, Guo L, Malcolm CP, and Spiers HJ (2015). Chronologically organized structure in autobiographical memory search. Front. Psychol 6, 1–9. [PubMed: 25688217]

Brunec IK, Robin J, Olsen RK, Moscovitch M, and Barense MD (2020). Integration and differentiation of hippocampal memory traces. Neurosci. Biobehav. Rev 116544.

Bunsey M, and Eichenbaum H (1996). Conservation of hippocampal memory function in rats and humans. Nature 379, 255–257. [PubMed: 8538790]

Buzsáki G, and Llinás R (2017). Space and time in the brain. Science . 358, 482–485. [PubMed: 29074768]

Cai DJ, Aharoni D, Shuman T, Shobe J, Biane J, Lou J, Kim I, Baumgaertel K, Levenstain A, Tuszynski M, et al. (2016). A shared neural ensemble links distinct contextual memories encoded close in time. Nature 1–16.

Carpenter AC, and Schacter DL (2017). Flexible retrieval: When true inferences produce false memories. J. Exp. Psychol. Learn. Mem. Cogn 43, 335–349. [PubMed: 27918169]

Carrillo-Reid L, Han S, Yang W, Akrouh A, and Yuste R (2019). Controlling Visually Guided Behavior by Holographic Recalling of Cortical Ensembles. Cell 1–11.

Chowdhury A, and Caroni P (2018). Time units for learning involving maintenance of system-wide cFos expression in neuronal assemblies. Nat. Commun 9, 4122. [PubMed: 30297716]

Clayton NS, Griffiths DP, Emery NJ, and Dickinson A (2001). Elements of episodic-like memory in animals. Philos. Trans. R. Soc. B Biol. Sci 356, 1483–1491.

Coutureau E, Killcross AS, Good M, Marshall VJ, Ward-Robinson J, and Honey RC (2002). Acquired equivalence and distinctiveness of cues: II. Neural manipulations and their implications. J. Exp. Psychol. Anim. Behav. Process 28, 388–396. [PubMed: 12395496]

Crestani AP, Krueger JN, Barragan EV, Nakazawa Y, Nemes SE, Quillfeldt JA, Gray JA, and Wiltgen BJ (2019). Metaplasticity contributes to memory formation in the hippocampus. Neuropsychopharmacology 44, 408–414. [PubMed: 29849054]

Dalley JW, Cardinal RN, and Robbins TW (2004). Prefrontal executive and cognitive functions in rodents: Neural and neurochemical substrates. Neurosci. Biobehav. Rev 28, 771–784. [PubMed: 15555683]

Davis HP, and Squire LR (1984). Protein synthesis and memory: A review. Psychol. Bull 96, 518–559. [PubMed: 6096908]

Depue BE (2012). A neuroanatomical model of prefrontal inhibitory modulation of memory retrieval. Neurosci. Biobehav. Rev 36, 1382–1399. [PubMed: 22374224]

Deuker L, Bellmund JL, Navarro Schröder T, and Doeller CF (2016). An event map of memory space in the hippocampus. Elife 5, 1–26.

DeVito LM, and Eichenbaum H (2011). Memory for the order of events in specific sequences: Contributions of the hippocampus and medial prefrontal cortex. J. Neurosci 31, 3169–3175. [PubMed: 21368028]

DeVito LM, Lykken C, Kanter BR, and Eichenbaum H (2010). Prefrontal cortex: Role in acquisition of overlapping associations and transitive inference. Learn. Mem 17, 161–167. [PubMed: 20189961]

Dimsdale-Zucker HR, Ritchey M, Ekstrom AD, Yonelinas AP, and Ranganath C (2018). CA1 and CA3 differentially support spontaneous retrieval of episodic contexts within human hippocampal subfields. Nat. Commun 9.

Eichenbaum H (2017a). Memory: Organization and Control. Annu. Rev. Psychol 68, 19–45. [PubMed: 27687117]

Eichenbaum H (2017b). On the Integration of Space, Time, and Memory. Neuron 95, 1007–1018. [PubMed: 28858612]

Eichenbaum H (2017c). Prefrontal-hippocampal interactions in episodic memory. Nat. Rev. Neurosci 18, 547–558. [PubMed: 28655882]

Eichenbaum H, Dudchenko P, Wood E, Shapiro M, and Tanila H (1999). The Hippocampus, Memory, and Place Cells. Neuron 23, 209–226. [PubMed: 10399928]

Eichenbaum H, Sauvage M, Fortin N, Komorowski R, and Lipton P (2012). Towards a functional organization of episodic memory in the medial temporal lobe. Neurosci. Biobehav. Rev 36, 1597–1608. [PubMed: 21810443]

Eldridge LL, Engel SA, Zeineh MM, Bookheimer SY, and Knowlton BJ (2005). A dissociation of encoding and retrieval processes in the human hippocampus. J. Neurosci 25, 3280–3286. [PubMed: 15800182]

Finnie PSB, Gamache K, Protopoulos M, Sinclair E, Baker AG, Wang S-H, and Nader K (2018). Cortico-hippocampal Schemas Enable NMDAR-Independent Fear Conditioning in Rats. Curr. Biol 28, 2900–2909.e5. [PubMed: 30197087]

Frankland PW, and Bontempi B (2005). The organization of recent and remote memories. Nat Rev Neurosci 6, 119–130. [PubMed: 15685217]

Frey U, and Morris RGM (1997). Synaptic tagging and LTP. Nature 385, 533–536. [PubMed: 9020359]

Ghosh VE, and Gilboa A (2014). What is a memory schema? A historical perspective on current neuroscience literature. Neuropsychologia 53, 104–114. [PubMed: 24280650]

Gilboa A, and Marlatte H (2017). Neurobiology of Schemas and Schema-Mediated Memory. Trends Cogn. Sci 21, 618–631. [PubMed: 28551107]

Giustino TF, and Maren S (2015). The role of the medial prefrontal cortex in the conditioning and extinction of fear. Front. Behav. Neurosci 9, 1–20. [PubMed: 25653603]

Guise KG, and Shapiro ML (2017). Medial Prefrontal Cortex Reduces Memory Interference by Modifying Hippocampal Encoding. Neuron 94, 183–192.e8. [PubMed: 28343868]

Hall G (1996). Learning about associatively activated stimulus representations: Implications for acquired equivalence and perceptual learning. Anim. Learn. Behav 24, 233–255.

Heroux NA, Robinson-Drummer PA, Sanders HR, Rosen JB, and Stanton ME (2017). Differential involvement of the medial prefrontal cortex across variants of contextual fear conditioning. Learn. Mem 24, 322–330. [PubMed: 28716952]

Hok V, Chah E, Save E, and Poucet B (2013). Prefrontal cortex focally modulates hippocampal place cell firing patterns. J. Neurosci 33, 3443–3451. [PubMed: 23426672]

Holland PC (1981). Acquisition of representation-mediated conditioned food aversions. Learn. Motiv 12, 1–18.

Honey RC, and Watt A (1998). Acquired relational equivalence: Implications for the nature of associative structures. J. Exp. Psychol. Anim. Behav. Process 24, 325–334. [PubMed: 9679308]

Howard MW, and Eichenbaum H (2015). Time and space in the hippocampus. Brain Res. 1621, 345–354. [PubMed: 25449892]

Howard MW, and Kahana MJ (2002). A distributed representation of temporal context. J. Math. Psychol 46, 269–299.

Hupbach A, Gomez R, and Nadel L (2011). Episodic memory updating: The role of context familiarity. Psychon. Bull. Rev 18, 787–797. [PubMed: 21647786]

Iordanova MD, Killcross AS, and Honey RC (2007). Role of the Medial Prefrontal Cortex in Acquired Distinctiveness and Equivalence of Cues. Behav. Neurosci 121, 1431–1436. [PubMed: 18085898]

Iordanova MD, Good M, and Honey RC (2011). Retrieval-mediated learning involving episodes requires synaptic plasticity in the hippocampus. J. Neurosci 31, 7156–7162. [PubMed: 21562278]

Jacobs NS, Allen TA, Nguyen N, and Fortin NJ (2013). Critical role of the hippocampus in memory for elapsed time. J. Neurosci 33, 13888–13893. [PubMed: 23966708]

Jayachandran M, Linley SB, Schlecht M, Mahler SV, Vertes RP, and Allen TA (2019). Prefrontal Pathways Provide Top-Down Control of Memory for Sequences of Events. Cell Rep. 28, 640–654.e6. [PubMed: 31315044]

Josselyn SA, and Tonegawa S (2020). Memory engrams: Recalling the past and imagining the future. Science . 367, eaaw4325. [PubMed: 31896692]

Kahana MJ (1996). Associative retrieval processes in free recall. Mem. Cogn 24, 103–109.

Kim J, Jung AH, Byun J, Jo S, and Jung MW (2009). Inactivation of medial prefrontal cortex impairs time interval discrimination in rats. Front. Behav. Neurosci 3, 1–9. [PubMed: 19194528]

Kitamura T, Ogawa SK, Roy DS, Okuyama T, and Tonegawa S (2017). Engrams and circuits crucial for systems consolidation of a memory. Science. 78, 73–78.

Komorowski RW, Manns JR, and Eichenbaum H (2009). Robust conjunctive item - Place coding by hippocampal neurons parallels learning what happens where. J. Neurosci 29, 9918–9929. [PubMed: 19657042]

Koster R, Chadwick MJ, Chen Y, Berron D, Banino A, Düzel E, Hassabis D, and Kumaran D (2018). Big-Loop Recurrence within the Hippocampal System Supports Integration of Information across Episodes. Neuron 99, 1342–1354.e6. [PubMed: 30236285]

Kumaran D, and McClelland JL (2012). Generalization through the recurrent interaction of episodic memories: A model of the hippocampal system. Psychol. Rev 119, 573–616. [PubMed: 22775499]

Lisman J, Cooper K, Sehgal M, and Silva AJ (2018). Memory formation depends on both synapse-specific modifications of synaptic strength and cell-specific increases in excitability. Nat. Neurosci 21, 309–314. [PubMed: 29434376]

Long NM, Danoff MS, and Kahana MJ (2015). Recall dynamics reveal the retrieval of emotional context. Psychon. Bull. Rev 22, 1328–1333. [PubMed: 25604771]

Mace JH (2014). Involuntary Autobiographical Memory Chains: Implications for Autobiographical Memory Organization . Front. Psychiatry 5, 183. [PubMed: 25566102]

Mace J, and Clevinger A (2019). The Associative Nature of Episodic Memory: The Primacy of Conceptual Associations. In Organization and Structure of Autobiographical Memory, (Oxford University Press), pp. 183–200.

Mace J, Clevinger A, and Martin C (2010). Involuntary memory chaining versus event cueing: Which is a better indicator of autobiographical memory organisation? Memory 18, 845–854. [PubMed: 20924946]

Marr D (1971). Simple memory: a theory for archicortex. Philos. Trans. R. Soc. Lond. B. Biol. Sci 262, 23–81. [PubMed: 4399412]

Mau W, Sullivan DW, Kinsky NR, Hasselmo ME, Howard MW, and Eichenbaum H (2018). The Same Hippocampal CA1 Population Simultaneously Codes Temporal Information over Multiple Timescales. Curr. Biol 28, 1499–1508.e4. [PubMed: 29706516]

McClelland JL, McNaughton BL, and O'Reilly RC (1995). Why there are complementary learning systems in the hippocampus and neocortex: insights from the successes and failures of connectionist models of learning and memory. Psychol. Rev 102, 419–457. [PubMed: 7624455]

McKenzie S, Frank AJ, Kinsky NR, Porter B, Rivière PD, and Eichenbaum H (2014). Hippocampal representation of related and opposing memories develop within distinct, hierarchically organized neural schemas. Neuron 83, 202–215. [PubMed: 24910078]

Metzger M (2014). Context Dependent Memory: The Role of Environmental Cues.

Miller EK, and Cohen JD (2001). An integrative theory of prefrontal cortex function. Annu. Rev. Neurosci 24, 167–202. [PubMed: 11283309]

Miller JF, Neufang M, Solway A, Brandt A, Trippel M, Mader I, Hefft S, Merkow M, Polyn SM, Jacobs J, et al. (2013a). Neural Activity in Human Hippocampal Formation Reveals the Spatial Context of Retrieved Memories. Science . 342, 1111–1114. [PubMed: 24288336]

Miller JF, Lazarus EM, Polyn SM, and Kahana MJ (2013b). Spatial clustering during memory search. J. Exp. Psychol. Learn. Mem. Cogn 39, 773–781. [PubMed: 22905933]

Molet M, Miller HC, and Zentall TR (2011). Acquired equivalence between stimuli trained in the same context. Psychon. Bull. Rev 18, 618–623. [PubMed: 21465302]

Molet M, Miller H, and Zentall TR (2012). Acquired equivalence of cues by presentation in a common context in rats. Anim. Cogn 15, 143–147. [PubMed: 21688023]

Molitor RJ, Sherrill KR, Morton NW, Miller AA, and Preston AR (2021). Memory Reactivation during Learning Simultaneously Promotes Dentate Gyrus/CA2,3 Pattern Differentiation and CA1 Memory Integration. J. Neurosci 41, 726–738. [PubMed: 33239402]

Moncada D, Ballarini F, and Viola H (2015). Behavioral Tagging: A Translation of the Synaptic Tagging and Capture Hypothesis. Neural Plast. 2015, 1–21.

Morton NW, Sherrill KR, and Preston AR (2017). Memory integration constructs maps of space, time, and concepts. Curr. Opin. Behav. Sci 17, 161–168. [PubMed: 28924579]

Moser EI, Moser MB, and McNaughton BL (2017). Spatial representation in the hippocampal formation: A history. Nat. Neurosci 20, 1448–1464. [PubMed: 29073644]

Navakkode S, Sajikumar S, Sacktor TC, and Frey JU (2010). Protein kinase Mζ is essential for the induction and maintenance of dopamine-induced long-term potentiation in apical CA1 dendrites. Learn. Mem 17, 605–611. [PubMed: 21084457]

Nielson DM, Smith TA, Sreekumar V, Dennis S, and Sederberg PB (2015). Human hippocampus represents space and time during retrieval of real-world memories. Proc. Natl. Acad. Sci. U. S. A 112, 11078–11083. [PubMed: 26283350]

Nomoto M, Ohkawa N, Nishizono H, Yokose J, Suzuki A, Matsuo M, Tsujimura S, Takahashi Y, Nagase M, Watabe AM, et al. (2016). Cellular tagging as a neural network mechanism for behavioural tagging. Nat. Commun 7, 12319. [PubMed: 27477539]

O'Keefe J (1976). Place units in the hippocampus of the freely moving rat. Exp. Neurol 51, 78–109. [PubMed: 1261644]

O'Reilly RC, and McClelland JL (1994). Hippocampal conjunctive encoding, storage, and recall: Avoiding a trade-off. Hippocampus 4, 661–682. [PubMed: 7704110]

Oishi N, Nomoto M, Ohkawa N, Saitoh Y, Sano Y, Tsujimura S, Nishizono H, Matsuo M, Muramatsu SI, and Inokuchi K (2019). Artificial association of memory events by optogenetic stimulation of hippocampal CA3 cell ensembles. Mol. Brain 12, 1–10. [PubMed: 30606245]

Pacheco D, and Verschure PFMJ (2018). Long-term spatial clustering in free recall. Memory 26, 798–806. [PubMed: 29185381]

Pastalkova E, Itskov V, Amarasingham A, and Buzsaki G (2008). Internally Generated Cell Assembly Sequences in the Rat Hippocampus. Science . 321, 1322–1327. [PubMed: 18772431]

Piaget J (1928). Judgement and Reasoning in the Child (Routledge).

Pignatelli M, Ryan TJ, Roy DS, Lovett C, Smith LM, Muralidhar S, and Tonegawa S (2019). Engram Cell Excitability State Determines the Efficacy of Memory Retrieval. Neuron 1–11.

Place R, Farovik A, Brockmann M, and Eichenbaum H (2016). Bidirectional prefrontal-hippocampal interactions support context-guided memory. Nat. Neurosci 19, 992–994. [PubMed: 27322417]

Poll S, Mittag M, Musacchio F, Justus LC, Giovannetti EA, Steffen J, Wagner J, Zohren L, Schoch S, Schmidt B, et al. (2020). Memory trace interference impairs recall in a mouse model of Alzheimer's disease. Nat. Neurosci 6, 535–541.

Polyn SM, Norman KA, and Kahana MJ (2009a). A context maintenance and retrieval model of organizational processes in free recall. Psychol. Rev 116, 129–156. [PubMed: 19159151]

Polyn SM, Norman KA, and Kahana MJ (2009b). Task context and organization in free recall. Neuropsychologia 47, 2158–2163. [PubMed: 19524086]

Poppenk J, Evensmoen HR, Moscovitch M, and Nadel L (2013). Long-axis specialization of the human hippocampus. Trends Cogn. Sci 17, 230–240. [PubMed: 23597720]

Preston AR, and Eichenbaum H (2013). Interplay of hippocampus and prefrontal cortex in memory. Curr. Biol 23, R764–R773. [PubMed: 24028960]

Preston AR, Shrager Y, Dudukovic NM, and Gabrieli JDE (2004). Hippocampal contribution to the novel use of relational information in declarative memory. Hippocampus 14, 148–152. [PubMed: 15098720]

Radvansky GA, and Zacks JM (2011). Event perception. Wiley Interdiscip. Rev. Cogn. Sci 2, 608–620. [PubMed: 23082236]

Rajasethupathy P, Sankaran S, Marshel JH, Kim CK, Ferenczi E, Lee SY, Berndt A, Ramakrishnan C, Jaffe A, Lo M, et al. (2015). Projections from neocortex mediate top-down control of memory retrieval. Nature 526, 653–659. [PubMed: 26436451]

Rashid AJ, Yan C, Mercaldo V, Hsiang HL, Park S, Cole CJ, De Cristofaro AYu J, Ramakrishnan C, Lee SY, et al. (2016). Competition between engrams influences fear memory formation and recall. Science . 353, 383–388. [PubMed: 27463673]

Redondo RL, and Morris RGM (2011). Making memories last: The synaptic tagging and capture hypothesis. Nat. Rev. Neurosci 12, 17–30. [PubMed: 21170072]

Ritvo VJH, Turk-Browne NB, and Norman KA (2019). Nonmonotonic Plasticity: How Memory Retrieval Drives Learning. Trends Cogn. Sci 23, 726–742. [PubMed: 31358438]

Robertson EM (2012). New insights in human memory interference and consolidation. Curr. Biol 22.

Rogerson T, Cai DJ, Frank A, Sano Y, Shobe J, Lopez-Aranda MF, and Silva AJ (2014). Synaptic tagging during memory allocation. Nat. Rev. Neurosci 15, 157–169. [PubMed: 24496410]

Rolls ET, and Mills P (2019). The Generation of Time in the Hippocampal Memory System. Cell Rep. 28, 1649–1658.e6. [PubMed: 31412236]

Roy DS, Kitamura T, Okuyama T, Ogawa SK, Sun C, Obata Y, Yoshiki A, and Tonegawa S (2017). Distinct Neural Circuits for the Formation and Retrieval of Episodic Memories. Cell 170, 1000–1012.e19. [PubMed: 28823555]

Rubin A, Geva N, Sheintuch L, and Ziv Y (2015). Hippocampal ensemble dynamics timestamp events in long-term memory. Elife 4, 1–16.

Save E, and Sargolini F (2017). Disentangling the role of the MEC and LEC in the processing of spatial and non-spatial information: Contribution of lesion studies. Front. Syst. Neurosci 11, 1–9. [PubMed: 28154528]

Schapiro AC, Turk-Browne NB, Botvinick MM, and Norman KA (2017). Complementary learning systems within the hippocampus: A neural network modelling approach to reconciling episodic memory with statistical learning. Philos. Trans. R. Soc. B Biol. Sci 372.

Schlichting ML, and Frankland PW (2017). Memory allocation and integration in rodents and humans. Curr. Opin. Behav. Sci 17, 90–98.

Schlichting ML, and Preston AR (2015). Memory integration: Neural mechanisms and implications for behavior. Curr. Opin. Behav. Sci 1, 1–8. [PubMed: 25750931]

Schlichting ML, and Preston AR (2016). Hippocampal–medial prefrontal circuit supports memory updating during learning and post-encoding rest. Neurobiol. Learn. Mem 134, 91–106. [PubMed: 26608407]

Schlichting ML, Mumford JA, and Preston AR (2015). Learning-related representational changes reveal dissociable integration and separation signatures in the hippocampus and prefrontal cortex. Nat. Commun 6, 1–10.

Shimamura AP, Jurica PJ, Mangels JA, Gershberg FB, and Knight RT (1995). Susceptibility to memory interference effects following frontal lobe damage: Findings from tests of paired-associate learning. J. Cogn. Neurosci 7, 144–152. [PubMed: 23961820]

Shohamy D, and Wagner AD (2008). Integrating Memories in the Human Brain: Hippocampal-Midbrain Encoding of Overlapping Events. Neuron 60, 378–389. [PubMed: 18957228]

Shuell TJ (1969). Clustering and organization in free recall. Psychol. Bull 72, 353–374.

Silva AJ (2017). Memory's Intricate Web. Sci. Am 317, 30–37.

Silva AJ, Zhou Y, Rogerson T, Shobe J, and Balaji J (2009). Molecular and cellular approaches to memory allocation in neural circuits. Science . 326, 391–395. [PubMed: 19833959]

Skelin I, Kilianski S, and McNaughton BL (2019). Hippocampal coupling with cortical and subcortical structures in the context of memory consolidation. Neurobiol. Learn. Mem 160, 21–31. [PubMed: 29660400]

de Sousa AF, Cowansage KK, Zutshi I, Cardozo LM, Yoo EJ, Leutgeb S, and Mayford M (2019). Optogenetic reactivation of memory ensembles in the retrosplenial cortex induces systems consolidation. Proc. Natl. Acad. Sci 116, 8576–8581. [PubMed: 30877252]

Squire LR, Knowlton B, and Musen G (1993). The Structure and Organization of Memory. Annu. Rev. Psychol 44, 453–495. [PubMed: 8434894]

Staresina BP, and Davachi L (2008). Selective and Shared Contributions of the Hippocampus and Perirhina Cortex to Episodic Item and Associative Encoding. J. Cogn. Neurosci 20, 1478–1489. [PubMed: 18303974]

Stern CAJ, Gazarini L, Vanvossen AC, Hames MS, and Bertoglio LJ (2014). Activity in prelimbic cortex subserves fear memory reconsolidation over time. Learn. Mem 21, 14–20.

Sugar J, and Moser MB (2019). Episodic memory: Neuronal codes for what, where, and when. Hippocampus 29, 1190–1205. [PubMed: 31334573]

Sun X, Bernstein MJ, Meng M, Zhang X, Anikeeva PO, Lin Y, Sun X, Bernstein MJ, Meng M, Rao S, et al. (2020). Functionally Distinct Neuronal Ensembles within the Memory Engram Article Functionally Distinct Neuronal Ensembles within the Memory Engram. Cell 1–14.

Szczepanski SM, and Knight RT (2014). Insights into Human Behavior from Lesions to the Prefrontal Cortex. Neuron 83, 1002–1018. [PubMed: 25175878]

Takehara-Nishiuchi K (2020). Prefrontal–hippocampal interaction during the encoding of new memories. Brain Neurosci. Adv 4, 1–10.

Tanaka KZ, He H, Tomar A, Niisato K, Huang AJY, and McHugh TJ (2018). The hippocampal engram maps experience but not place. Science . 361, 392–397. [PubMed: 30049878]

Tayler KK, Lowry E, Tanaka K, Levy B, Reijmers L, Mayford M, and Wiltgen BJ (2011). Characterization of NMDAR-Independent Learning in the Hippocampus. Front. Behav. Neurosci 5, 28. [PubMed: 21629769]

Tiganj Z, Jung MW, Kim J, and Howard MW (2017). Sequential firing codes for time in rodent medial prefrontal cortex. Cereb. Cortex 27, 5663–5671. [PubMed: 29145670]

Tompary A, and Davachi L (2017). Consolidation Promotes the Emergence of Representational Overlap in the Hippocampus and Medial Prefrontal Cortex. Neuron 96, 228–241.e5. [PubMed: 28957671]

Tsao A, Sugar J, Lu L, Wang C, Knierim JJ, Moser MB, and Moser EI (2018). Integrating time from experience in the lateral entorhinal cortex. Nature 561, 57–62. [PubMed: 30158699]

Tse D, Langston RF, Kakeyama M, Bethus I, Spooner P. a, Wood ER, Witter MP, and Morris RGM (2007). Schemas and memory consolidation. Science 316, 76–82. [PubMed: 17412951]

Tse D, Takeuchi T, Kakeyama M, Kajii Y, Okuno H, Tohyama C, Bito H, and Morris RGM (2011). Schema-dependent gene activation and memory encoding in neocortex. Science 333, 891–895. [PubMed: 21737703]

Witter MP, Wouterlood FG, Naber PA, and Van Haeften T (2000). Anatomical organization of the parahippocampal-hippocampal network. Ann. N. Y. Acad. Sci 911, 1–24. [PubMed: 10911864]

Wong FS, Westbrook RF, and Holmes NM (2019). 'Online' Integration of Sensory and Fear Memories in the Rat Medial Temporal Lobe. Elife 8, 1–18.

Wood ER, Dudchenko PA, and Eichenbaum H (1999a). The global record of memory in hippocampal neuronal activity. Nature 397, 613–616. [PubMed: 10050854]

Wood ER, Dudchenko PA, and Eichenbaum H (1999b). The global record of memory in hippocampal neuronal activity. Nature 397, 613–616. [PubMed: 10050854]

Ye X, Kapeller-Libermann D, Travaglia A, Inda MC, and Alberini CM (2016). Direct dorsal hippocampal–prelimbic cortex connections strengthen fear memories. Nat. Neurosci 20, 52–61. [PubMed: 27869801]

Yetton BD, Cai DJ, Spoormaker VI, Silva AJ, and Mednick SC (2019). Human Memories Can Be Linked by Temporal Proximity. Front. Hum. Neurosci 13, 1–13. [PubMed: 30774588]

Yokose J, Okubo-Suzuki R, Nomoto M, Ohkawa N, Nishizono H, Suzuki A, Matsuo M, Tsujimura S, Takahashi Y, Nagase M, et al. (2017). Overlapping memory trace indispensable for linking, but not recalling, individual memories. Science 355, 398–403. [PubMed: 28126819]

Zeithamova D, and Preston AR (2017). Temporal Proximity Promotes Integration of Overlapping Events. J. Cogn. Neurosci 29, 1311–1323. [PubMed: 28253077]

Zeithamova D, Schlichting ML, and Preston AR (2012a). The hippocampus and inferential reasoning: Building memories to navigate future decisions. Front. Hum. Neurosci

Zeithamova D, Dominick AL, and Preston AR (2012b). Hippocampal and ventral medial prefrontal activation during retrieval-mediated learning supports novel inference. Neuron 75, 168–179. [PubMed: 22794270]

Ziv Y, Burns LD, Cocker ED, Hamel EO, Ghosh KK, Kitch LJ, Gamal A. El, and Schnitzer MJ (2013). Long-term dynamics of CA1 hippocampal place codes. Nat. Neurosci 16, 264–266. [PubMed: 23396101]

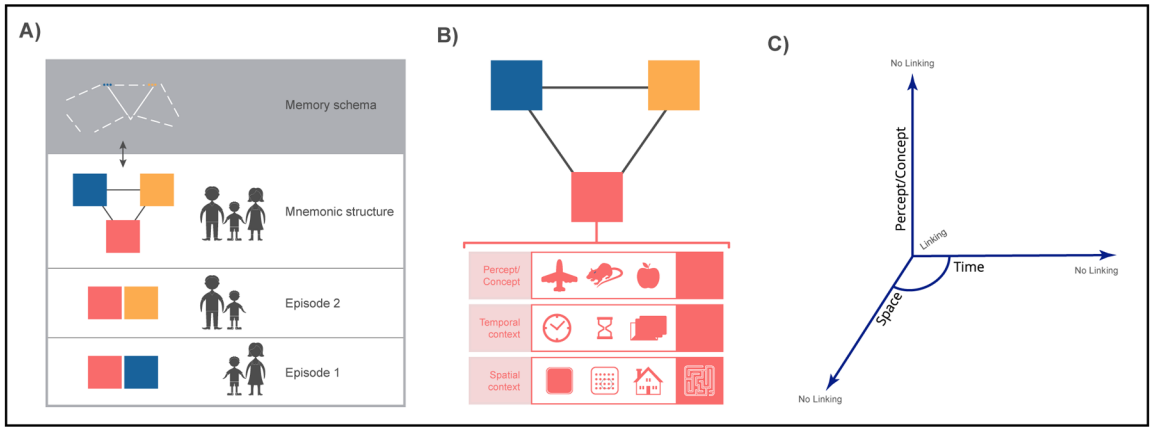

Figure 1. Dimensions of mnemonic structures.

A) Relative organization of Single memories, Mnemonic Structures and Memory Schemas. Memory Schemas are high-level cognitive structures that represent the abstract relation between different memories and can serve as a scaffold for the formation of other structures. Mnemonic structures represent specific relations between specific memories. Schemas and Mnemonic structures may interact. **B)** Example of a mnemonic structure composed of 3 elements. Common element “A” serves as a link to element “B and C”. The linking element can belong to different dimensions of experience. **C)** Theoretical representational space where temporal, spatial and perceptual/conceptual dimensions interact to determine linking and integration of memories into the same mnemonic structure. Note that Time and Space are not necessarily orthogonal.

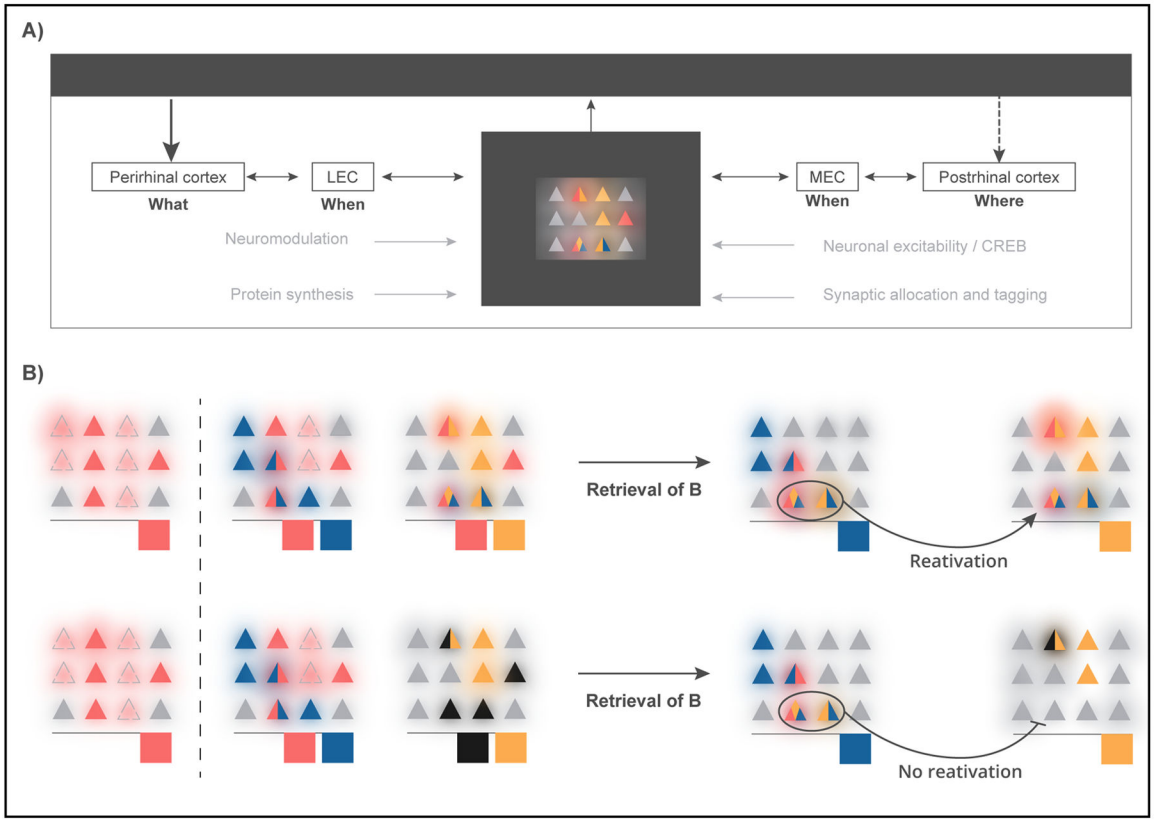

Figure 2. Systems and cellular mechanisms of mnemonic structures.

A) Schematic representation of the potential circuits involved in the formation of mnemonic structures. Different pathways convey information about *what, where,* and *when* to the hippocampus. These different pathways are involved in the formation of item-, space-, and time-bases mnemonic structures, respectively. The PFC, together with additional factors, determine how memories are co-allocated in the HPC and integrated into mnemonic structures. **B)** Cellular mechanisms of HPC mnemonic structures. Cells encoding a common element A (▲) restrict which cells are available for memory allocation (▵) and are co-encoded with different elements B (▲) and C (▲). This leads to the overlap between some cells representing B and C (◭). Upon retrieval of B, overlapping cells can indirectly reactivate memory C. The same effect is not observed when the two memories B and C do not share a common element (bottom panel). Grey triangles (▲) represent cells that are not available for encoding.

Table 1.

Comparison between Memory Schemas and Mnemonic Structures

	Memory Schemas	Mnemonic Structures
Associative network	✓	✓
Multiple episodes	✓	✗
Detailed units	✗	✓
Adaptability	✓	?