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Perspective

Beyond hippocampus: Thalamic and prefrontal contributions to an evolving memory

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SUMMARY

The hippocampus has long been at the center of memory research, and rightfully so. However, with emerging technological capabilities, we can increasingly appreciate memory as a more dynamic and brain-wide process. In this perspective, our goal is to begin developing models to understand the gradual evolution, reorganization, and stabilization of memories across the brain after their initial formation in the hippocampus. By synthesizing studies across the rodent and human literature, we suggest that as memory representations initially form in hippocampus, parallel traces emerge in frontal cortex that cue memory recall, and as they mature, with sustained support initially from limbic then diencephalic then cortical circuits, they become progressively independent of hippocampus and dependent on a mature cortical representation. A key feature of this model is that, as time progresses, memory representations are passed on to distinct circuits with progressively longer time constants, providing the opportunity to filter, forget, update, or reorganize memories in the process of committing to long-term storage.

INTRODUCTION

Humans and other organisms have a remarkable capacity to extract information from the environment into a spatiotemporal framework and store such episodes as distinct memories. However, time and experience have a pivotal role in shaping the subsequent evolution of a memory. For instance, some everyday memories such as seeing pedestrians on the way to work may be quickly forgotten the next day, whereas vivid details of one's graduation ceremony or repeated interactions with a school teacher may acquire importance over time and experience that solidify those memories. Where and how in the brain these memories initially form and gradually reorganize/stabilize over time has been an active area of investigation.[1–6] Early insights came from patients with damage to the hippocampus (HPC) who exhibited a profound inability to form new episodic memories, providing an entry point for scientific inquiry. Indeed, decades of studies have since focused on the HPC and associated medial temporal lobe areas to understand what makes memory possible—what are the inherent molecular, cellular, and physiological properties of hippocampal neurons that enable transient external information to be coded into lasting internal representations. Through this work, we have understood that strong external stimuli can lead to progressively longer lasting internal cellular changes, for instance from enhanced pre-synaptic neuromodulatory release (seconds), to post-synaptic receptor activation and signaling (minutes), to nuclear protein synthesis (hours), and to functional and structural synaptic strengthening (days).[7–10] These events together are thought to lead to stable stimulus-associated activity patterns of cellular ensembles, network-level contextual memory representations in the HPC, and behavioral memory recall.[11–14]

One of the most striking features of the HPC is that it is the first and perhaps primary location in the brain where there is a convergence of "what," "where," and "when" streams of information about the external world.[15–20] This ideally situates the HPC to store "episodes," which through its recurrent circuitry, can bind episodic features into unifying conjunctive memory representations. However, the HPC may primarily be an engine for memory formation but have time-limited roles in memory storage and recall. Indeed, while patients with hippocampal lesions exhibit an almost complete inability to form new memories, and retrieve recent memories, they exhibit an intact ability to retrieve memories as they become more remote in time.[1–4] Thus, these phenomenological observations provided the first hints of an evolving memory trace extending beyond the HPC, and spurred interest to locate the neural substrates.

Without surprise, these memory traces are neither static nor localized to a single brain region, but rather they are constantly evolving. Even as memories are being formed in the HPC, there are parallel representations that facilitate an active reorganization across the brain into cortical structures. Classical models have emphasized the role of the HPC as an "index," which can reactivate and strengthen cortical representations.[21,22] Over time and experience, such cortical stabilization may lead to a gradual decontextualization of the memory into a more semantic form at the expense of detailed episodic representations.[3,23,24] Thus, it is widely agreed upon that memories continuously evolve and that extra-hippocampal structures have significant contribution to the progressive stabilization of memory representations, but the mechanistic details beyond the HPC are still poorly

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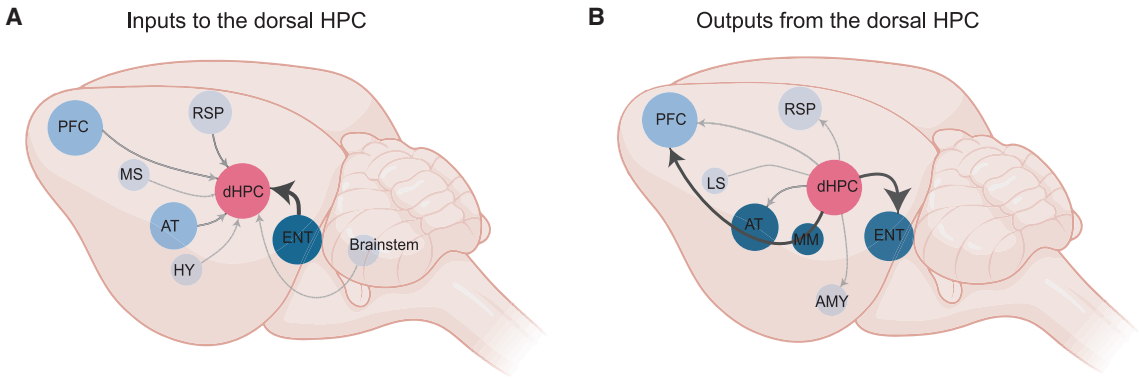

Figure 1. Anatomical connectivity of the dorsal hippocampus

(A) Inputs to the dorsal hippocampus (dHPC) involved in memory processing. Most prominent input to dHPC (depicted in bold) are from the entorhinal cortex (ENT). Other inputs to the dorsal hippocampus include the prefrontal cortex (PFC), anterior thalamus (AT), medial septum (MS), hypothalamus (HY), retrosplenial cortex (RSP), and various neuromodulatory regions. This perspective focuses on regions highlighted by high color opacity.

(B) Outputs from the dHPC involved in memory processing.

The major outputs from the dorsal hippocampus (depicted in bold) target the mammillo-thalamic tract and entorhinal cortex. The former is through the fornix bundle, which targets the anterior thalamus (AT) directly or via the mammillary (MM) bodies, that then further project to PFC, forming the Papez circuit. dHPC also sends strong direct and indirect projections through subiculum to the entorhinal cortex (ENT). Other notable outputs include the retrosplenial cortex (RSP), lateral septal nuclei (LS), amygdala (AMY), and prefrontal cortex (PFC). This perspective focuses on regions highlighted by high color opacity.

understood. Why are some memories selected for further stabilization while others forgotten? Are there a series of anatomically defined circuits extending beyond the HPC that provide sequential or parallel routes of memory reorganization, and does memory stabilization happen as a continuous process, in a stepwise punctuated manner, or in multiple discrete stages? With increasing technological capabilities to observe brain-wide activity patterns longitudinally during behavior, it is becoming more possible to follow the dynamics of an ever-evolving memory trace. The emergence of functional studies at cellular resolution across anatomically connected circuits in the brain is providing an opportunity to build upon previous models and advance our collective understanding of the time-dependent reorganization of memories.

In this perspective, our aim is to provide a mechanistic framework for how memory representations may evolve over time, with emphasis on extra-hippocampal structures, and in particular the progressive involvement of thalamus and prefrontal cortex (PFC) with time. First, we review the connectivity of the HPC, discussing its inputs and outputs, which may provide defined neuro-anatomical pathways for the maturation of memory representations (Figure 1). We then investigate their roles in representing memories of varying durations from (1) newly formed memories (minutes to hours) to (2) recent memories (days) and (3) remote memories (weeks to months in rodents, years in humans). Reviewing work from both animal and human studies, we propose a model where the entorhinal-hippocampal circuit is primarily involved in the initial construction of a memory, but parallel representations emerge in thalamus and PFC that are recruited for subsequent recall and stabilization of the memory. Over time, hippocampal memory representations gradually evolve rostrally and reorganize over frontal cortical circuits but require subcortical interactions, including sustained thalamocortical interactions, for long-term stabilization of cortical representations (Figure 2). A key component of this model is that as time progresses, memory representations are passed on to distinct circuits, each of which have progressively longer time constants. We also discuss alternative solutions. Ultimately, a more mechanistic understanding of memory progression in the brain may inform a search for therapeutic targets aimed at various stages of cognitive rescue.

Anatomical connectivity

Inputs and outputs of dHPC that may provide defined neuroanatomical pathways for the maturation of memory representations

The connectivity patterns of the HPC change gradually across its dorsoventral gradient. Dorsal HPC (dHPC) (posterior in primates) has been shown to be necessary for the formation and storage of episodic memories,[25,26] whereas the ventral (anterior in primates) is more prominently associated with its roles in the regulation of emotional or affective processing.[27] Here, we confine our discussion of the anatomical connectivity to the dHPC.

Inputs to dHPC

Across species, the strongest input to the dHPC is from the entorhinal cortex (ENT)[28,29] (Figure 1A). The lateral and medial entorhinal cortices receive broad sensory input into layer V and in turn convey contextual and spatial information to the HPC via layers II/III. ENT layer II provides the main indirect input to CA1 via the tri-synaptic pathway (DG-CA3-CA1), whereas layer III provides direct input to CA1, through both excitation and long-range feedforward inhibition. Together, these inputs are thought to provide signals related to learning and memory formation.[30,31]

Other inputs to dHPC in rodents and also in humans are from the PFC, anterior thalamus (AT), medial septum (MS), hypothalamus (HY), retrosplenial cortex (RSP), and various neuromodulatory nuclei[32–35] (Figure 1A). Many of these hippocampal inputs have been hard to appreciate and quantify until recently, as advances in tractography and viral tracing methods, in particular the improved sensitivity of retrograde tracers, have helped

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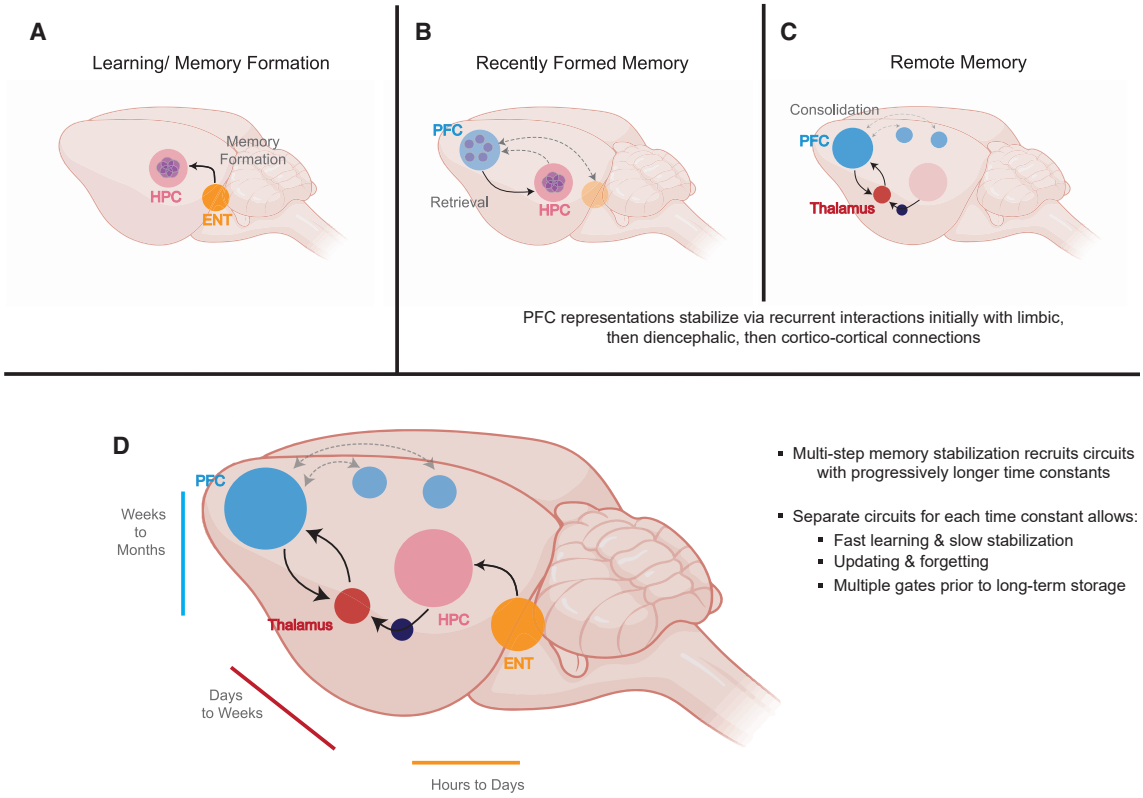

Figure 2. Proposed model of memory reorganization/stabilization over time

(A) Entorhinal cortex (ENT) supports the formation of a conjunctive representation of a contextual memory in the hippocampus (HPC) during learning.

(B) Limbic areas (HPC and ENT) support the emergence of prefrontal cortex (PFC) representations, which initially are constituent features of contextual memory. This also enables prefrontal feature representations to exert top-down control over HPC in providing cues, goals, and context that guide recall of recently formed memories.

(C) With passage of time, there are increased diencephalic (thalamic) and cortical-cortical interactions that enable memories to become independent of hippocampus and progressively stabilized across distributed cortical circuits.

(D) Memory reorganization and stabilization across the brain over time, with passage onto circuits with progressively longer time constants.

illuminate their density and functional importance. For instance, multiple studies have now reported direct long-range projections from the PFC to the dHPC[20,32,36–38] that were traditionally suspected to interact via solely intermediary structures. Retrograde labeling of even just a few starter cells in the HPC CA1 reveals prefrontal inputs,[39] and by accessing a more complete population of starter cells (tracing protocols detailed in Yadav et al.,[20] Methods, ED Figures 5 and 7, and Note S1), the prefrontal projections to dHPC are substantial, can be optimized for tracing in the anterograde direction, and are found to be functionally important, as now characterized by several studies.[20,32,36–38] The real value of these anatomical advances, especially when convergent across species,[34,40,41] is that it allows for targeted neurophysiological investigation in rodents of long-standing prefrontal-hippocampal theoretical frameworks developed in humans.[42–44]

Both excitatory[20,32,37,38] and inhibitory[36] projections from the anterior cingulate (AC) and prelimbic/infralimbic (PL/IL) regions of the PFC, respectively, have mono-synaptic inputs onto dHPC including at its superficial and deep layers. Interestingly, the prefrontal inputs appear to target a largely non-overlapping population of neurons in dHPC-CA1 compared with the entorhinal inputs.[20] Functionally, the direct prefrontal excitatory and inhibitory inputs allows PFC to exert top-down control of HPC during goal-directed behaviors and memory recall, via changes in excitation—inhibition balance, signal-to-noise, and recruitment of associated memory ensembles.[20,32,36–38] PFC also exerts indirect influence over the dHPC through extra-cortical pathways, via MS, midline thalamus, amygdala (AMY), and ENT, with dense projections particularly to layer V of lateral entorhinal cortex (LEC) (Figure 1A). Together, prefrontal inputs are positioned to provide top-down context-dependent signals during learning and recall. Throughout the manuscript, for comparison across species, we define PFC as the cortical region with recurrent connections to the medial dorsal nucleus of the thalamus. Where appropriate, we will define the sub-region of the PFC that we are referring to, either in rodents or primates.

Within the thalamus, it is components of the association thalamus (areas of thalamus that do not receive primary sensory innervation nor project to primary sensory/motor cortices), and

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in particular the AT, specifically the anterodorsal (AD) and anteroventral (AV) nuclei, that send dense projections to the parahippocampal regions including the postsubicular, presubicular, and parasubicular cortices, with AD terminating in layers I, II/III, and V, and AV terminating in I and V[45] (Figure 1A). The nucleus reuniens also provides input to dHPC,[46] though this may be species specific.[47–49] The anterior thalamic nuclei provide head-direction signals and contribute to spatial encoding in the HPC and may be an area that is actively disengaged during memory consolidation.[50] However, beyond these roles, other functions of AT, and of association thalamic nuclei in general, are poorly understood.

Outputs from dHPC

Across species, the major output of the dHPC is the fornix fiber bundle tract—the anterior portion of which targets the AT directly or via the mammillo-thalamic tract while the posterior portion targets septal nuclei and ventral striatum (Figure 1B).[33,51,52] Notably, in humans, the single largest output of the HPC (20% of all output) is direct connection to AT,[51] which in turn has strong recurrent projections to frontal cortex, forming the core component of the hippocampal-thalamo-cortical Papez circuit. The other main outputs of the dHPC are to the entorhinal and retrosplenial cortices, which in turn project to PL and IL areas of PFC in rodents and AC regions of PFC in humans.[53,54] Other hippocampal outputs include to AMY and lateral septum, as well as direct connections from dHPC to PFC.[37,55]

LEARNING AND MEMORY FORMATION (MINUTES TO HOURS)

The entorhinal-hippocampal system in learning and memory formation, with extra-hippocampal representations emerging in parallel

Memory formation in the HPC has been extensively reviewed.[11,30,56] The ENT, being a major gateway into the HPC, has been well studied for its role in memory formation (Figure 2A). In brief, it is composed of medial and lateral subdivisions, where the medial entorhinal cortex (MEC) conveys spatial maps and the LEC conveys temporal and multi-sensory integration, thus together providing the elements of an episodic memory. Accordingly, MEC cells have defined spatial firing fields, called grid cells, and related navigational and self-motion signals that provide a reference orientation of the organisms' position with respect to the environment, contributing to the formation of place fields in the HPC.[57–61] LEC cells, on the other hand, encode for multi-sensory and object-context associations that are then conveyed to HPC via direct and indirect pathways to CA1,[62–65] with important contributions of long-range and local inhibition in selecting and refining the precision of these representations.[65–69] Recent studies have also shown combined spatial and contextual information relayed by each of the entorhinal cortices to the HPC.[70,71] Thus, during learning, EC enables the creation of an episodic memory representation in HPC, and moreover, can sculpt the overrepresentation of behaviorally relevant aspects of an episodic experience, for instance, spatial locations or sensory experiences tied to reward.[72,73]

Moving beyond the entorhinal-hippocampal system, recent studies have pointed toward the emergence of parallel memory representations in the PFC and the thalamus during learning (Figure 2B). For instance, immediate early gene studies and neural recordings reveal episodic representations, i.e., contextual and/or spatial responses, in PFC during learning.[20,48,74–78] Interestingly, while these representations emerge concurrently with the HPC during learning, it is not clear the extent to which they are in fact required for learning and rather may support subsequent memory reorganization and stabilization. Upon PFC inactivation during learning, some studies show impairment in task performance in both spatial and non-spatial learning, whereas others show little to no effect during learning with stronger deficits in memory retrieval.[79–85] A parsimonious explanation can be derived from observing PFC activity across tasks with different cognitive loads. For instance, in rodents, behavioral tasks requiring a higher cognitive load such as new learning that conflicts with or has spatiotemporal overlap with prior memories recruit more prefrontal activity and require PFC for learning and memory formation. In these cases, PFC actively interacts with and informs ongoing hippocampal representations, for instance by signaling a rule or goal change or relaying the context of novel information.[74,86,87] Further underscoring the importance of these top-down interactions during learning, inhibition of PFC results in suppressed hippocampal activation of immediate early genes, reduced stability of place cells, remodeling across the LEC-CA1 network, and an impairment in memory expression.[88,89]

Similarly, in humans, patients with frontal lobe dysfunction exhibit deficits in tasks such as novel word learning, contextual encoding, temporal ordering, semantic organization, and associative memory encoding, all supporting the involvement of PFC in learning and memory formation, particularly when organizing newly learned information with respect to prior memory architecture in the brain. Notably, such continuous learning processes likely recruit multiple prior memories into working memory[90] at the time of new learning, further underscoring the progressive involvement of the PFC in memory formation with increasing cognitive load. Collectively, studies spanning animal models to humans support active involvement of PFC at the time of learning, to support ongoing memory formation, but also to support future memory reorganization and updating.

What supports the formation of these contextual representations in the PFC? PFC is well positioned to receive sensory information directly from sensory and association cortices as well as more processed contextual information from the hippocampal-entorhinal circuit. For instance, entorhinal inputs to PFC have been shown to be necessary for acquisition of learned information,[91] inhibition of which can destabilize prefrontal network assemblies and increase cortical representational drift.[92] Furthermore, it has been shown that hippocampal- and entorhinal-prefrontal synchrony increases learning and memory retention[93–96] and also that the hippocampal activity leads prefrontal activity during learning,[20,97] suggesting that bottom-up inputs from HPC-EC engages and stabilizes the prefrontal cortical network during learning.

In the thalamus, learning related representations of context have primarily been shown to emerge in the AT, which is composed of three sub-nuclei (anteromedial [AM], AV, and AD) with overlapping functions spanning both contextual memory and spatial processing.[45] The most prominent learning related

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signals are observed in AD, where neurons are strongly tuned to spatial features, including head-direction[98] and lesions of the AD dramatically impair spatial memory formation.[99–101] AM on the other hand has strongly tuned contextual representations that emerge during learning; however, silencing of AM during learning has no effect on memory formation but does lead to long-term deficits in memory stabilization and consolidation.[52] Thus, while AD and AV thalamic nuclei have active roles in ongoing learning and memory formation, AM representations during learning support future memory reorganization and stabilization.

An incredible amount of collective progress has been made in understanding how memories are formed in the HPC. There is increasing mechanistic clarity on how bottom-up stimulus driven inputs (i.e., from entorhinal) shape learned associations in HPC, and at the same time, how top-down processed, goal-directed information (i.e., from prefrontal, association thalamus, and other areas) can also shape ongoing hippocampal memory representations. Future work will benefit from an increased understanding of how these bottom and top-down processes work together and continuously inform each other, especially as task complexity, cognitive control, and anticipation of future events become important components of memory formation.[69,102–105]

RECENT MEMORIES (HOURS TO DAYS)

Early prefrontal memory representations participate in a recall circuit and may mature to represent the eventual consolidated memory

While the role of the entorhinal-hippocampal circuit as the major gateway for memory formation has been well studied, comparatively less is known about the process of memory recall, and whether it uses the same or different pathways. Many studies, over a variety of model organisms and behavioral tasks have cemented the notion that the HPC, and in particular the CA1 region, is essential for recall of recently formed memories. However, during recall, it is not well understood how externally or internally cued stimuli are routed to HPC, how a specific memory representation is accessed, and how it drives appropriate recall-related conditioned responses and behavioral output. The classical model has suggested that the same pathway used for memory formation, i.e., the entorhinal-hippocampal circuit, is likely to be used for memory recall.[106] This is especially attractive since many of the original cues, i.e., sensory and spatial features of the original memory, may remain stably represented in the ENT, providing cues for future retrieval of episodic representations in HPC. However, there has been a sparsity of evidence of strong memory recall deficits with silencing or lesion of the ENT. In many cases, inhibition of ENT after the initial formation of a memory results in preserved spatial and contextual representations in HPC and intact memory recall.[73,107–109] This suggests that the ENT may refresh its representations rapidly to support new learning and that alternate inputs to HPC may take over functions of memory recall. In support of this, several studies in rodents have demonstrated that perturbations of PFC can lead to substantial memory retrieval deficits, especially as expectation guides memory retrieval in a "top-down" manner as is often the case in daily life; for instance, during memory retrieval with partial cues or goal-directed spatial navigation .[48,75,110–112] Furthermore, simultaneous paired LFP recordings have shown that the activity of HPC leads PFC during memory formation, for instance, as rodents enter a spatial context, but this information flow reverses and PFC leads HPC during recall as objects are sampled and context-appropriate features are retrieved.[97] Finally, a direct mono-synaptic projection from PFC (AC cortex) to HPC was identified and it was found that activation of this projection was sufficient to recruit memory-associated ensembles in HPC, representing a previously experienced context, as well as behavioral recall of the associated conditioned response.[32] These studies together suggested an important role for PFC in memory recall, but the mechanistic details of this process remained poorly understood. What do neurons in PFC encode during learning and how do they route cues to the HPC to access memory representations and enable memory recall?

A recent study provided a first in-depth exploration into the mechanistic details underlying the process of contextual memory recall.[20] The authors began by developing a behavioral task in which memory formation and recall can be studied separately. To do so, they took advantage of the fact that during memory formation animals typically experience all aspects of a context (sight, sound, tone, and smell) that are bound together into a single contextual representation, whereas during recall animals can experience just a subset of the original cues (a scent) to bring back the full memory. Therefore, they developed a behavioral task where mice learn to associate entry into multi-modal contexts or "rooms" with either rewards or punishments and then later are exposed to partial features of these rooms to elicit memory recall. By interleaving recall trials cued by one, two, or three partial features, delivered at precise times or locations in virtual reality, the authors were able to vary the cognitive load on memory retrieval. The authors also developed methods to perturb and image multiple brain areas while mice performed this task. Through these approaches they found that mice do not use the canonical storage pathway (entorhinal-to-hippocampal circuit) when performing recall. Rather, as mice form a memory, the HPC encodes a low-dimensional representation of global context, whereas the individual contextual features are parsed and stored in high-dimensional orthogonal neural populations in frontal cortex (Figure 2B). These parallel encoding approaches are consistent with the notion that PFC tends to encode information in a high-dimensional manifold via non-linear embeddings, whereas the HPC tends to compress this vast dimensionality into a global context of experience.[113–117] They subsequently found that during behavioral recall, presentation of any individual feature was sufficient to activate the corresponding feature ensemble in PFC, which led to recruitment of corresponding contextual ensembles in HPC that were necessary to enable behavioral recall. They thus identified and characterized a memory recall pathway where previously stored features in PFC act as pointers to recall the associated contextual memory in HPC. More broadly, their work supports a model where even as memories are being formed via the entorhinal-hippocampal pathway, a parallel prefrontal-to-hippocampal retrieval circuit is being trained and established to support future externally—or internally—cued memory recall (Figure 2B). This early prefrontal feature-code may eventually mature and

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constitute a core component of the long-term cortical repository of the memory (Figure 2C), akin to previously proposed molecular[118] and cellular[74] cortical tags.

The dichotomy of separable storage and retrieval pathways emerging in the rodent literature is indeed well supported by the human literature. Advances in human brain imaging in the 1990s and 2000s revealed multiple reports of neural activation of entorhinal cortices during memory formation[119,120] but of prefrontal cortices during memory recall.[121–130] The PFC was strongly and specifically recruited for recall tasks including for verbal and non-verbal recall[126] and prominently during voluntary recall[124] of detailed source memories beyond simply recognition memory.[129] For instance, both PET and fMRI imaging methods in humans and electrophysiological studies in primates detected prefrontal correlates for memory recall of cued associations, object-item pairs, and verbal recall of previously learned passages.[123,125,130] Furthermore, patients with frontal lobe damage exhibited striking deficits in the accuracy of memory recall and a significantly weaker release from proactive interference.[121,122,127,128] Continued mechanistic studies spanning rodent, primate, and human across a range of behavioral tasks will further clarify whether and how continuous reorganization in the brain supports separable circuits for memory formation and recall.

As we work toward building a model that integrates these findings, an important area of focus will be to understand the evolution of these ''early'' prefrontal memory representations over time—its progressive stabilization and gradual transformation across multiple experiences (Figure 2C). An interesting element of our memories is the ability to remember salient contextual details and yet also abstract out semantic knowledge from multiple experiences. Given that the PFC is thought to be heavily involved in continual learning as well as the generalization and abstraction of knowledge (recently investigated in Bernardi et al.,[131] Reinert et al.,[132] and Samborska et al.[133]) are the feature representations observed in PFC schema-like and therefore regularized across similar experiences? Or are these representations gradually transformed and stabilized with bottom-up inputs from the HPC/ENT as memories become consolidated? Future studies will thus benefit from understanding how memory representations evolve over time, and in particular, how bottom-up pathways integrate with top-down pathways to balance new learning with the assimilation of prior memories.

REMOTE MEMORIES (WEEKS TO MONTHS IN RODENTS; YEARS IN HUMANS)

Early prefrontal memory representations may require continuous stabilization, initially via limbic input followed by diencephalic input and then cortical-cortical input

Recently formed memories critically rely on the HPC, however, over time these memory representations are thought to reorganize and distribute across the brain, becoming gradually hippocampal independent. This process of memory stabilization, or consolidation, was first articulated by Brenda Milner and colleagues and subsequently by many others through a series of observations from patient studies.[1,134,135] They found that patients having damage to the HPC and medial temporal lobe exhibited a profound inability to form new memories, and amnesia for recently formed memories, but preserved recall of remote memories from several years ago and including childhood and autobiographical memories. Decades of study in animal models, including in primates and rodents, have reproduced these findings.[6,25,136–142] For instance, hippocampal lesions have resulted in a predominant recent memory deficit whereas frontal cortical lesions have resulted in a stronger remote memory deficit when testing on a variety of behavioral tasks such as contextual fear conditioning, spatial and non-spatial episodic memory tasks, spatial discrimination tasks, and novel object recognition. Furthermore, metabolic labeling, immediate early gene analysis, or neural recordings predominantly identified decreased activity in HPC over the lifetime of a memory with a concomitant increase in frontal cortical activity, thus providing a potential neural substrate in cortex for remote, stabilized, memories. These studies led to a formal ''standard model of systems consolidation''[143] in which the HPC transiently stores new memories, and over time, trains cortex, in particular frontal cortex, to create and store more enduring representations. However, the mechanistic details of this process have remained elusive.

Meanwhile, parallel case studies emerged where patients with hippocampal damage exhibited a flat retrograde amnesia, i.e., a loss of both recent and remote recall leading to the development of the multiple trace theory,[4] and indexing theories,[22,144] suggesting more continued involvement of the HPC over the lifetime of a memory. In particular, multiple trace theory posits a continued role of HPC for episodic information with semantic information being extracted and maintained in cortex. Whenever the HPC maintains involvement, index theory posits that the HPC forms an index of neocortical activity encoding a memory, and that this index can reactivate cortical patterns during recall. Accordingly, subsequent studies in rodents with hippocampal lesions also found a flat retrograde amnesia, particularly so for spatial memories.[145–148] These studies have led to alternate models of memory consolidation[4,149,150] that describe varying levels of continued involvement of the HPC over time.

There are several lines of thought that may integrate these alternate findings with the historically overwhelming support for the standard model of gradual hippocampal-to-cortical memory consolidation. Perhaps the most parsimonious explanation is that hippocampal dependent memories become ''semanticized'' or more ''generalized'' as they reorganize to cortex, i.e., competitive trace theory and trace transformation theory.[23,24,151] Since most remote memories that we recollect in our everyday lives are not detail oriented, the cortical representation is sufficient, even adaptive, for serving the purpose of remote memory recall. For the rare memories that we continue to recollect in a detailed manner, these may continue to require hippocampal access. In the case of contextual-spatial memory in rodents with high navigational demands, the HPC may initially store detailed spatial locations, whereas over time this continuous space may be discretized and generalized as broad features of a memory, i.e., reward locations or object-place associations stored across cortical networks. This framework aligns with classical work that makes an important distinction between memory recall due to recognition vs. that due to detailed

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recollection.[30,150,152] Another parsimonious model involves formulating the role of the HPC as one of scene construction—the HPC is known to be able to construct and anticipate representations based on information from cortical substrates, which aligns with its roles in prospective coding.[153–156] Thus, while the HPC in most cases may not maintain a long-standing active memory representation, under novel circumstances, it might receive information from cortical and subcortical inputs to link and anticipate spatial or contextual scenes, i.e., "scene construction theory."[149]

In both of the above cases, such a model allows the HPC to offload most memory representations over time in order to support rapid and continuous new learning and memory formation. More importantly, it enables multiple layers of filtering, gating, and brain-reorganization before committing a memory into longer-term storage. The gradual hippocampal-to cortical reorganization also supports adaptive memory processes including forgetting, updating, and progressive stabilization. Accordingly, while some memories may involve the HPC to varying degrees over its lifetime based on the nature of the memory, that all memories eventually become cortically represented remains uncontroversial.

Despite this, since the initial studies of Brenda Milner in the 1950s describing hippocampal-to-cortical consolidation, still today there is limited to no mechanistic understanding of this brain-wide reorganization; why some memories are consolidated, while others are forgotten, and how. Toward mechanistic insight, two recent studies aimed to understand how an initial memory-associated cortical ensemble matures with time.[77,91] To do so, they permanently labeled cortical ensembles that are active at the time of memory encoding, in this case the memory of a context that is associated with shock. They then reactivated this same labeled population weeks later to assess whether it would be sufficient to drive memory recall of the original encoded memory, i.e., a fear response associated with the original context. In both studies, the results suggested that while a small subset of the initial encoding population still functionally contributes to memory recall weeks later, the majority of the initial ensemble functions to support the maturation of other ensembles that constitute a more stable memory representation supporting remote memory recall. These studies thus suggested continuous functional reorganization occurring in cortex throughout memory consolidation.

These efforts thus begged the question, can we follow the maturation of cortical ensembles in real-time with longitudinal neural recordings? Even better can we capture simultaneous neural activity patterns in HPC, cortex, and intervening brain circuits during behavioral memory consolidation to understand the mechanistic details of this weeks-to-months-long HPC to cortex brain-reorganization process? A recent study aimed to address these challenges.[52] They began by developing a behavioral task where mice formed multiple memories, i.e., room-outcome associations in a virtual linear corridor, but over time, due to variation in the salience of the room or value of the outcome, mice consolidated some memories while forgetting others. This allowed isolation of brain dynamics that uniquely support the process of memory stabilization. By recording bulk neural activity from circuits that link HPC and cortex, i.e., AMY, ENT, RSP, AT, as mice performed this task, the authors identified a sustained weeks-long neural correlate of memory in the AT, suggesting roles in hippocampal-to-cortical memory consolidation. Indeed, inhibition of the AT to PFC thalamo-cortical projection, while having no effect on memory formation, or early retrieval, severely disrupted memory consolidation over several weeks. More strikingly, activation of this circuit was sufficient to drive consolidation of otherwise unconsolidated memories. To develop mechanistic insights into the computations occurring in AT that enable cortical consolidation, the group developed a technology for simultaneous high-resolution cellular imaging of HPC, AT, and PFC for many weeks throughout consolidation. They found that while HPC encodes multiple memories equally, the AT preferentially encodes strong memories (i.e., rooms associated with higher reward value) and gradually establishes long-range functional interactions with PFC for stabilization. Thus, it supports a model where HPC and PFC initially form parallel memory representations, but cortex requires sustained thalamo-cortical interactions for long-term stabilization. Overall, these findings identify a memory consolidation pathway, via HPC to AT to cortex, and reveal a function of the AT in selecting and stabilizing memories for long-term cortical storage (Figure 2C). Notably, in humans, the AT has roles in directing and prioritizing the selection of preferred cortical ensembles during memory-guided behaviors.[157] More importantly, these findings in rodents resonate with clinical observations where Korsakoff syndrome patients bearing lesions of the same HPC (mammillary [MM])—AT—cortex circuit present with graded retrograde amnesia,that, importantly, is increasing in retrograde severity with increasing thalamo-cortex pathology[158–161] (Box 1).

The development of a new behavioral model and an approach for high-resolution longitudinal multi-area brain imaging has helped to begin offering insights into how memory representations gradually reorganize and stabilize across the brain over time. Still, many questions remain. How is selection of salient experiences performed at the level of the AT? Why does it take so long to stabilize these representations to cortex (given that the thalamic representation emerges during training, but the cortical representation is not stabilized and required for behavioral recall until weeks later)? And how do sleep and "offline" processing contribute to this slow but robust process? More in-depth study of the thalamus in memory processing, which due to technical and conceptual barriers has been largely neglected, will help facilitate answers to these questions.

While the thalamus has been historically viewed as a simple relay for sensory-motor functions, its ability for rich computational processing, and contributions to higher-order cognitive functions are becoming well appreciated.[52,166–169] Indeed the thalamus is a central brain structure that is very heterogeneous, in which the sensory and motor nuclei are well suited to relay and propagate information between brainstem and cortex, whereas higher-order association nuclei receive rich neuromodulatory and other value-assigning input from diverse regions of the brain,[170–174] thus providing capabilities for selecting and stabilizing salient information.[52] Furthermore, given the multiple, parallel, and recurrent loops between the various thalamic nuclei and cortical regions, it is attractive to consider that diverse types of memories, whether it be contextual, motor, perceptual,

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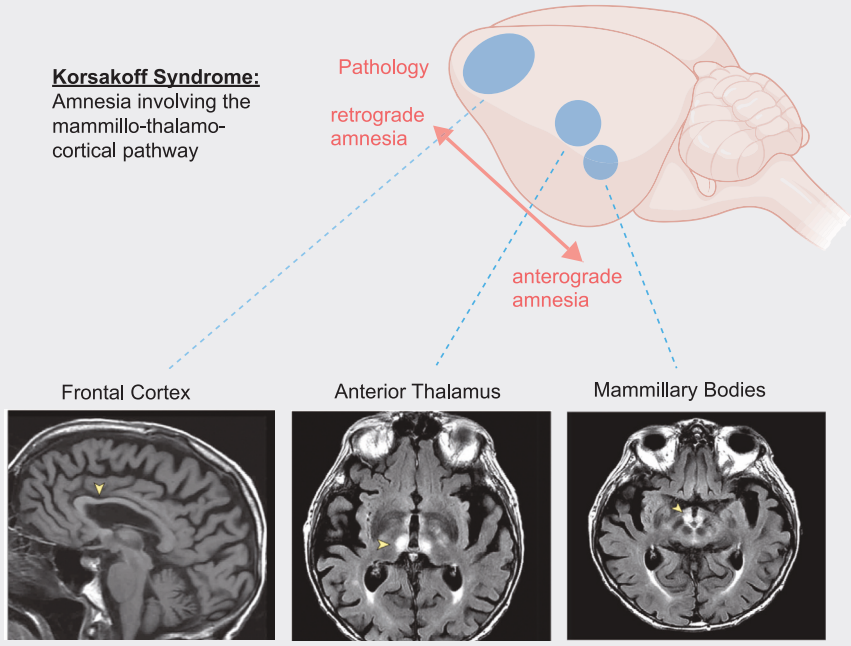
Box 1. Korsakoff syndrome: Amnesia from pathology of the mammillo-thalamo-cortical tract

Etiology: Korsakoff syndrome is a brain disorder characterized by severe lack of thiamine (vitamin B1), most commonly due to chronic alcoholism, which leads to digestive tract damage and vitamin malabsorption. However, any condition that affects vitamin reabsorption can cause Korsakoff syndrome, including for instance irritable bowel syndrome, bariatric surgery, dialysis, cancer, chronic infections, or poor nutrition. In the acute stages of thiamine deficiency, the condition is referred to as Wernicke's encephalopathy, which, if left untreated, progresses to a chronic memory disorder termed Korsakoff syndrome.

Prevalence: approximately 2% of people worldwide are affected with Korsakoff syndrome, the majority of whom are men between the ages of 30 and 70.

Symptoms: most prominently, patients with Korsakoff syndrome exhibit severe and chronic amnesia that is both anterograde and extensively retrograde (see below). The memory impairments are restricted to declarative memories, whereas implicit, spatial, verbal, and procedural memories are relatively intact. Notably, there is no change in IQ. Patients also sometimes show confabulation, delirium and disorientation, attention deficit, anger/agitation, visual changes, and unsteady gait.

Affected brain areas: structural imaging in patients with Korsakoff syndrome has identified prominent midline diencephalic lesions (including mammillary bodies of the hypothalamus and anterior nuclei of the thalamus) and cortical atrophy. In all cases, there are specific and bilateral lesions of the main hippocampal output pathway—the mammillo-thalamo-cortical tract (Papez circuit) (see image below, adapted from Segal et al.[162]). Because patients can exhibit either anterograde or retrograde forms of amnesia, or both, to disambiguate the etiologies driving these diverse conditions, several studies attempted a systematic correlation of brain pathology with the temporal nature of the patient's amnesia. They found that while anterograde amnesia was often associated with lesions of the mammillary bodies, progressively increasing retrograde amnesia was associated with increasing pathology of the AT and cortex (see image below, based on Kopelman,[158] Kopelman et al.,[159] Verfaellie et al.,[160] and Fama et al.[161]). Notably, patient studies involving bilateral thalamic lesions, including those from not only Korsakoff syndrome[158] but also infection, stroke, or TBI[43,163–165] have identified a resulting retrograde amnesia, which can occur without anterograde amnesia, extending back several decades, with cortical atrophy further extending this time frame. These patient studies, together with emerging mechanistic studies in rodents, support a model where memory representations are continuously reorganized across brain circuits endowed with progressively longer time constants for long-term stabilization (Figure 2).



emotional, etc., use the thalamo-cortical highway as a general pathway for subcortical-to-cortical memory stabilization. More broadly, cross-talk between thalamic[50,175] and limbic[91,176,177] circuits will be a requisite area of investigation which may offer convergent, redundant, or sequential routes of memory consolidation, to enhance the integration or robustness of long-term memory representations, respectively.

As thalamo-cortical interactions stabilize cortical representations, there are concurrent reorganization of cortical-cortical networks[37,52,77,91] that require further study. Furthermore, it is still

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unclear why cortical reorganization is such a slow process, but clues may come from observing brain activity patterns during sleep and offline periods, which are likely to contribute importantly to memory stabilization.[178–182] For instance, do sharp-wave ripples[183] pass through the thalamus, and if so, might they reinforce learned associations and support hippocampal-to-cortical interactions during sleep?[184] In particular, sleep spindles in the thalamic reticular nuclei have been suggested to stabilize cortical learning by coupling hippocampal ripples with slow oscillations in cortex during sleep.[180,184] Additionally, homeostatic processes during sleep[185] may also help to explain why the process of cortical consolidation and stabilization is so slow. Under this scenario, cortical synaptic weights that are initially strengthened from learned experiences during waking hours are weakened during sleep, in order to achieve homeostatic balance in the excitability of networks. If so, cortical learning is constantly working against itself in a competitive fashion and only those learned associations that are salient enough (or reactivated frequently) will resist overnight synaptic pruning.[186] Thus, as AT works to stabilize cortical representations, marginal differences in the strengths of thalamo-cortical and cortical-cortical synapses may eventually become magnified over repeated bouts of sleep to sculpt stable ensembles representing longer-term memories. Ultimately, a more comprehensive understanding of the brain-wide process of memory reorganization and consolidation will require continued innovation in behavioral models, large-scale multi-area brain recordings paired with perturbations during both online and offline periods, and theoretical frameworks that bridge multiple time constants toward information stabilization in the brain.

DISCUSSION

The HPC has long been at the center of memory research, and perhaps rightfully so. However, with increasing methodological capabilities to observe and manipulate brain-wide neural activity, our appreciation for memory as a dynamic and distributed process is also evolving. Here, reviewing historical and emerging work in the field, we propose a model in which memories are initially formed in HPC, but progressively reorganize and stabilize via thalamus to cortical circuits (Figure 2). We suggest that as initial memory representations form in HPC, parallel traces emerge in frontal cortex to provide routes of access for memory recall, and as they mature further, they require active and continuous stabilization, initially via limbic circuits (entorhinal-hippocampal input) then via diencephalic circuits (thalamic input), and perhaps still others, as eventually memories become independent of HPC and dependent on a mature cortical representation (Figures 2A–2C). A key feature of this model is that, as time progresses, memory representations are passed on to distinct circuits (entorhinal-hippocampal; hippocampal-thalamic; thalamo-cortical; cortical-cortical), each of which have progressively longer time constants (Figure 2D). While multiple time constants can be embedded in the same circuit, the adaptive value of reorganizing memory representations across distinct, progressively slower, and more robust, circuits is the opportunity to filter, forget, update, or reorganize in the process of committing to long-term storage. Such subcortical-to-thalamo-cortical loops may be common motifs for consolidation of not just episodic memories, but also of perceptual, emotional, or motor (i.e., striatal-thalamo-cortical) memories.

Separable brain circuits with progressively longer timescales of information storage also offers the opportunity to explore the underlying molecular and cellular properties that endow these circuits with diverse and extended time constants. For instance, decades of pioneering molecular work across species has established the importance of protein synthesis in extending synaptic time constants from hours to days.[187,188] More specifically, activation of the transcription factor CREB is sufficient to convert a short-term memory, i.e., only 1 h of synaptic facilitation, to a long-term memory, i.e., with synaptic facilitation persisting for at least 72 h.[189–191] Therefore, similar to how transcriptional programs scale synaptic time constants in HPC, the recruitment of still additional molecular programs operating on longer time constants may dictate the progressively longer timescales of information storage across thalamic and cortical networks. Such studies may offer pressing mechanistic insights into long-held assumptions about why the entorhinal-hippocampal system is a rapid but transient learning and memory circuit, while the cortical network may be a slower but more robust and longer lasting repository.[3]

As we further our understanding of the continuously evolving nature of memory representations in the brain, there may be opportunities for targeted cell-type and circuit-specific therapeutic interventions. For instance, in the case of Alzheimer's disease, regardless of the cause of the symptoms or site of pathology, it may be more therapeutically promising to boost access to memories (recall pathways via frontal cortex) or to help make existing memories more robust (consolidation pathways via mammillo-thalamic tract), than to enhance memory formation pathways (entorhinal-hippocampal circuits). Moreover, while existing brain stimulation methods (DBS, TMS, ECT, and TUS) may appear too crude to lack the specificity required to enhance memory recall, the hope is that broad excitation in the correct circuit can leverage learned differences in synaptic strengths, albeit weakened or degenerating, to boost information flow along specified synapses. Indeed, DBS in patients have been most successful in improving memory when targeting the fornix (hippocamus-to-mammillo-thalamic tract),[192–195] with more variable success rates when targeting the ENT or HPC[196–198] though much of the observed variability may also be due to differences in stimulation protocols, time of intervention, advanced stage of disease, or other patient-specific attributes. Thus, there remains much to be understood about the underlying mechanisms of DBS, but continued research spanning rodent and human populations offers promise in refining targeted patient-specific interventions for memory and cognitive improvement in disease.

In this perspective, our goal was to begin developing models to understand the gradual evolution, reorganization and stabilization of memories after their initial formation in the HPC. In doing so, we chose to highlight the contributions of the AT and PFC to this evolution, given their prominent contributions to memory processing over progressive timescales as observed in the rodent and human literature. However, we do not mean to suggest that these circuits are acting in isolation, which is certainly not the case, but rather to spotlight potential outsized contributions of

these circuits to an evolving memory representation. Indeed, other brain regions, including non-neuronal cell types and the role of newborn neurons,[199–201] have functional contributions, which will add to our understanding of a broadly distributed memory representation that requires coherent interaction for successful processing. There may also be different anatomical routes of consolidation for different types of memories, i.e., spatial vs. contextual vs. perceptual vs. motor.

As we explore the complexities of redundant and highly interconnected functional pathways for memory, it will be important to proceed cautiously—large-scale brain recordings can provide the impression that memory-related signals appear everywhere in the brain, while strong perturbations involving whole gene or whole circuit knockout may lead to unusually strong phenotypes, precluding subtle but important differences between circuits and the identification of critical nodes in a complex network. While these are challenges ubiquitous in neuroscience and biology, one approach may be to systematically titrate the strength of brain perturbations and assess their effects on downstream brain circuits and behavior to build confidence in their specificity and effect size. Another solution is to leverage the diversity of natural and outbred rodent and human populations to systematically link variation in circuit physiology with variation in behavior, at scale. These approaches can thus circumvent all-or-none investigations while harnessing the subtle titrations and network dependencies that exist in natural populations to disentangle critical nodes of a complex network. This will help identify key circuits with specific and outsized contributions to memory processing at various stages in the evolution of a memory and also reveal a ''range of solutions'' and thus core principles, for memory processing across timescales. The coming decade promises to be bright.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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