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Mystery of the memory engram: History, current knowledge, and unanswered questions

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ABSTRACT

The quest to understand the memory engram has intrigued humans for centuries. Recent technological advances, including genetic labelling, imaging, optogenetic and chemogenetic techniques, have propelled the field of memory research forward. These tools have enabled researchers to create and erase memory components. While these innovative techniques have yielded invaluable insights, they often focus on specific elements of the memory trace. Genetic labelling may rely on a particular immediate early gene as a marker of activity, optogenetics may activate or inhibit one specific type of neuron, and imaging may capture activity snapshots in a given brain region at specific times. Yet, memories are multifaceted, involving diverse arrays of neuronal subpopulations, circuits, and regions that work in concert to create, store, and retrieve information. Consideration of contributions of both excitatory and inhibitory neurons, micro and macro circuits across brain regions, the dynamic nature of active ensembles, and representational drift is crucial for a comprehensive understanding of the complex nature of memory.

In his Nobel lecture, Eli Wiesel recounted the Hasidic legend centered around the revered figure of Rabbi Baal-Shem-Tov, known as the Besht. This legendary Rabbi, deeply affected by the suffering of the Jewish people, embarked on a mission to hasten the Messiah's arrival. However, his audacious attempt to alter history led to a poignant punishment—exile to a distant island alongside his devoted servant. In their isolation, desperation crept in, and the servant implored the Rabbi to use his magical abilities to guide them home. Tragically, the Rabbi had lost these powers, and his own memories had abandoned him. The servant, driven by steadfast loyalty, asked the Rabbi to seek absolution from the heavens, yet the Rabbi's memory lapses hindered his ability to recall prayers or penitent words. In a moment of hopelessness, the servant, who had also lost his memory, recalled a simple but profound tool—the alphabet, a basic framework of language and thought. With this modest yet potent foundation, the servant began reciting the alphabet, softly at first, then with growing fervor. Miraculously, as the rhythm of the alphabet's cadence enveloped them, the Rabbi's lost memories began to return, accompanied by his powers. This allegorical tale embodies memory's indomitable influence, serving as a testament to our very existence. Wiesel eloquently encapsulates this sentiment: "*Without memory, our existence would be barren and opaque, like a prison cell into which no light penetrates; like a tomb which rejects the living. Memory saved the Besht, and if anything can, it is memory that will save humanity. For me, hope without memory is like memory without hope.*"
Elie Wiesel (Wiesel, 1986).

1. Introduction

1.1. Current advances and questions

The narrative featuring the Besht Rabbi emphasizes the concept that memories are constructed from basic components, creating foundational knowledge that acts as a framework for assimilating additional information. However, the gist representation, symbolized by the alphabet, does not fully capture the actual memory of the Rabbi. His prayers and memories come to the forefront only when the alphabet triggers other elements that gradually merge into the recollection. This story implies that while certain fundamental elements may play a crucial role in memory retrieval, and can, in some cases, elicit simple recollections, recalling complex memories necessitates the activation of components that may not be inherent to the fundamental units of memory.

Analogous to how the alphabet offers a foundational structure

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enabling the Rabbi to recapture lost memories, recent animal studies indicate that the activation of specific neurons can recover forgotten memories (Perusini et al., 2017; Roy et al., 2016; Ryan et al., 2015). These neurons, referred to as engram cells, are recognized as the fundamental components of memory (Josselyn and Tonegawa, 2020). These engrams have been identified through technological innovations that enable the tracking of neuronal activity over time. Results from these studies shed critical insights into how specific engram ensembles can modify, create, or erase simple associations, supporting the view that they are the elemental units of memory (Josselyn and Tonegawa, 2020). However, despite the extremely valuable information gained through these studies, their reliance on specific promoters or markers allowing tracking of only subsets of all active neurons, poses some constraints to the identification of all the variables that contribute to memory retrieval. In particular, the contributions of various cell types with distinct patterns of activity or expressing distinct markers remain largely unexplored. Furthermore, the majority of engram animal studies used simple tasks that facilitate the identification of neuronal pathways engaged in learning, disputing whether recalling a simple association mirrors the same processes involved in remembering a complex memory (Ranganath, 2022). Lastly, memory recollections are fluid (Mau et al., 2020), showing changes over time, which raises questions about how engram activity maps memory drift. In this review, we concisely explore the historical journey in pursuit of memory engrams and discuss current discoveries and unanswered questions in this field. Our scrutiny is concentrated on memory engrams within the hippocampus (HC) and medial prefrontal cortex (mPFC), regions recognized for their role in memory consolidation; but our proposition likely extends to other interconnected regions and memory processes.

1.2. *Historical search for the “engram”*

The term “engram” was first coined by Richard Semon, who postulated that experiences activate networks of interconnected elements, producing enduring changes that can be reactivated during recall by appropriate external or internal cues (Schacter, 2001; Schacter et al., 1978; Semon, 1923). Semon outlines four essential characteristics of an engram. Firstly, engrams should produce enduring changes in the brain resulting from experiences. Secondly, the behavioral manifestation of an engram should emerge through interaction with retrieval cues, a process termed ecphory. Thirdly, the content of an engram ought to mirror the events during encoding and accurately reflect what can be retrieved during recall. Finally, an engram could exist in dormant states between the encoding and retrieval phases (Schacter, 2001; Schacter et al., 1978). Although Semon’s view was initially ignored, some of its main elements were discussed in Donald Hebb’s “Theory of Cell Assemblies,” which postulated that memories do not reside in a specific region but are distributed throughout the brain’s interconnected cell networks (Hebb, 1949). In Hebb’s view, neurons could form part of many cell assemblies participating in various functions and memory traces. He further suggested that the efficiency of communication among cell assemblies could be enhanced through the coordinated activity of presynaptic and postsynaptic neurons. A view that became widely known as “cells that fire together, are wired together”. Experimental evidence in support of the structural changes postulated by Hebb emerged with the discovery of long-term potentiation (LTP), a perduring mechanism of synaptic enhancement (Bliss and Lømo, 1973). This finding gave rise to the conceptualization of engrams as neural changes involving the strengthening of synaptic connections among neurons engaged in encoding (Bliss and Collingridge, 1993), a perspective that continues to be supported by several researchers to this day [for review see, (Poo et al., 2016)].

The idea that memories entail lasting structural changes in specific brain networks prompted researchers to investigate the neural substrate responsible for these changes. Pursuing this goal, Karl Lashley conducted experiments with rats trained to navigate a maze for a food reward. He then systematically removed various portions of cortical regions in an attempt to pinpoint the spatial memory engram for this task (Lashley, 1931, 1950). The results revealed a positive correlation between cortex removal and the number of errors made by the rats but failed to pinpoint a specific engram location. These findings led Lashley to conclude that memories were distributed throughout the cortex, a concept known as equipotentiality, indirectly implying that memory did not produce synaptic structural changes only in specific brain circuits (Lashley, 1950). It is essential to note that Lashley’s removal of cortical regions limited the evaluation of subcortical memory substrates. Furthermore, since Lashley overtrained the animals in the maze, it remains possible that the task engaged the striatum, a subcortical area recognized for its role in habitual exploratory behavior (Howe et al., 2011).

While Lashley’s ideas exerted a significant influence for decades (Bruce, 2010), the notion of equipotentiality encountered challenges from both animal and human lesion studies. In studies involving lesions in monkeys, a link was established between the medial temporal lobe-, encompassing the HC and amygdala, and specific memory deficits (Klüver and Bucy, 1938), such as the absence of fear responses to predators. Subsequent research emphasized the role of the amygdala, rather than the HC, in emotional memory (Weiskrantz, 1956). The exploration of engram substrates gained momentum as researchers observed selective memory impairments in patients with brain lesions or neurodegeneration in specific brain regions. These findings emphasized that memory is not a singular phenomenon but rather comprises multiple cognitive processes with varying levels of awareness. The prime illustration of this dissociation is the case study of Henry Molaison, known as HM. In the early ’50s, HM underwent bilateral removal of the medial temporal lobe, including the HC, to treat severe epilepsy. While the surgery left HM’s perceptual abilities and personality intact, it resulted in significant deficits in declarative memories—the conscious recollection of facts and events. Remarkably, his ability to form procedural associations, involving unconscious memories of skills and habits, remained unaffected. This revelation led researchers to posit the existence of distinct memory systems, with the medial temporal lobe being crucial for declarative memories and other brain substrates associated with procedural memories. (Corkin, 1984, 2002; Milner, 2005; Penfield and Milner, 1958; Schacter and Tulving, 1994; Scoville and Milner, 1957; Squire and Zola-Morgan, 1991; White and McDonald, 2002).

Further insights about declarative memory emerged when Endel Tulving proposed dividing this type of memory into semantic and episodic components (Tulving, 1972). Semantic memory represents general knowledge about historical events, people, and places, whereas episodic memory reflects events at specific times in particular contexts. These two forms of memory are not entirely independent since their interaction influences declarative recall (De Brigard et al., 2022; Greenberg and Verfaellie, 2010). A widely accepted notion is that semantic memories arise through the decontextualization of episodic memory over time (Baddeley, 1988), a concept that is supported by some theories of memory consolidation (see below). It is noteworthy that while memory taxonomies didn’t elucidate the neural and molecular mechanisms of engrams, they did emphasize key characteristics that engrams should display. For instance, as engrams reduce reliance on contextual information, their dependence on the HC is anticipated to decrease, supporting the idea that remote consolidation of engrams occurs in other brain regions. Furthermore, dynamic shifts between episodic and semantic recollections suggest that engrams should also be fluid.

1.3. *Theories of consolidation*

To be remembered, learned episodic or semantic information must be stabilized and stored in the long term through a process known as consolidation. Consolidation involves synaptic and system changes occurring over varying time scales. Synaptic consolidation requires RNA production and protein synthesis, molecular changes that lead to more efficient synaptic coupling (Bailey et al., 1996). Conversely, systems consolidation involves reorganization of memory traces across brain regions as the consolidation progress advances (Tonegawa et al., 2018; Wiltgen and Tanaka, 2013). Numerous reviews have extensively detailed the molecular cascades underlying synaptic consolidation (Abel and Kandel, 1998; Alberini and Kandel, 2014; Asok et al., 2019; Josselyn and Nguyen, 2005; Lisman et al., 2018; Morris, 2013; Rogerson et al., 2014; Schoch and Abel, 2014; Silva et al., 1998; Takeuchi et al., 2014). In this review, we will focus on exploring the interplay between synaptic and systems consolidation, as elucidated by several consolidation theories. This emphasis is crucial for gaining insights into the nature of memory engrams.

The Standard Consolidation Theory (SCT) posits that the HC plays a pivotal role in the initial synaptic consolidation phase, but over time, memories progressively emancipate themselves from the HC as information is stored in neocortical networks (Dudai et al., 2015; Squire, 1992; Squire and Alvarez, 1995). Advocates of this perspective propose that once cortical engrams are consolidated, they give rise to stable representations, suggesting that the same ensembles are activated during each recollection (Fig. 1A). This notion finds support across various species, including humans, where hippocampal lesions show minimal impact on the recall of old memories (Dede et al., 2016; Kapur and Brooks, 1999; Kim et al., 1995; Kim and Fanselow, 1992; Manns et al., 2003; Takehara et al., 2003; Zola-Morgan and Squire, 1990). Notably, SCT does not differentiate between context-dependent episodic and semantic memories, assuming that the same reorganization process affects these memory types equally (Winocur and Moscovitch, 2011). Furthermore, it is implied thatthere is a transition towards a more semantic nature in episodic recall with the passage of time .

The Indexing Theory (IT) shares similar memory temporal dynamics as those postulated by SCT but offers a potential mechanism through which neocortical memory traces become consolidated over time (Teyler and Rudy, 2007). According to this view, experiences activate patterns of activity in neocortical ensembles that project to the HC. The hippocampal cells receiving these inputs consolidate this information in potentiated synapses. During retrieval, a subset of the original inputs activates the strengthened hippocampal ensemble, which in turn, retrieves the cortical representation of the memory. In this view, the HC stores an index of cortical patterns of activity during encoding, but the actual memory traces are stored in cortical networks. Repeated activation of the hippocampal index during recall reinforces connections among neocortical memory traces, gradually making the cortical engrams less reliant on the hippocampal index (Teyler and Rudy, 2007). Therefore, according to this view, episodic memories may progressively transition to semantic as they become independent of the HC (Fig. 1B).

The SCT and IT have faced challenges from accounts suggesting that, although recall remains possible, old memories become less accurate when the HC is compromised (Nadel and Moscovitch, 1997). These observations led researchers to propose the Multiple Trace Theory (MTT). According to this view, during HC-dependent retrieval, new trace elements are added to the original memory, leading to the notion that older memories are more widely distributed in the HC than newer ones. Moreover, MTT suggests that semantic memories initially rely on the HC but progressively shift to neocortical representations, allowing independent retrieval. In contrast, episodic memories continue to rely on the HC as long as they preserve detailed contextual information. Importantly, as episodic memories gradually lose precision, critical elements undergo abstraction, giving rise to a gist representation. This gist is subsequently stored in the neocortex as a semantic recollection. Therefore, according to MTT, retrieval can be episodic or semantic, depending on how much the original memory has been abstracted at the time of recall (Nadel and Moscovitch, 1997; Nadel et al., 2000). This theory raises some interesting predictions for engram research because it suggests that each instance of retrieval will alter the engram and recollection (Fig. 1C). Several animal studies have shown that memories are fluid and engrams undergo modifications (Mau et al., 2020). Yet, it is still unclear if engram representations become less susceptible to change at some point or what factors affect the rate of change.

Given that context inevitably evolves over time, the MTT proposition that contextual episodic memories undergo continuous modification during retrieval aligns with intuition. This notion was initially observed in the late ‘60s (Misanin et al., 1968; Schneider and Sherman, 1968) and subsequently experimentally validated through the pioneering work of Nader and collaborators. These investigators confirmed that consolidated memories exhibited susceptibility to modification during retrieval. Crucially, the retrieved memory traces underwent re-stabilization through a reconsolidation process dependent on protein synthesis (Nader et al., 2000). Since then, reconsolidation has been observed in various species, tasks, and brain regions (Haubrich et al., 2020; Lee et al., 2017; McKenzie and Eichenbaum, 2011; Nader, 2015; Przybyslawski et al., 1999; Przybyslawski and Sara, 1997; Roullet and Sara, 1998; Schiller, 2022). Notably, reconsolidation can strengthen memory if neuro-modulatory signals involved in attention or arousal are active during retrieval (Sara, 2000). However, the effectiveness of the reconsolidation process depends on the age and strength of the original memory (Inda et al., 2011). These data highlight that engram research should acknowledge the effects of time and encoding characteristics when evaluating the stability of ensembles over time (Visser et al., 2018).

Finally, the Complementary Learning Systems Theory (CLST) suggests that the HC is crucial for encoding, consolidating, and transferring memory traces to the neocortex, where this information is structured into schemas—collections of rules and knowledge that can be applied to present situations to steer actions (Fig. 1D). One of the earliest accounts of schema formation suggested that new memories are rapidly encoded in the HC but become intertwined with pre-existing memories in the neocortex during retrieval (McClelland et al., 1995). Hippocampal inputs produce slow neocortical schema updating when new information contradicts prior knowledge, but it can happen fast when it is consistent with previously stored information (McClelland, 2013). Alternative views of schema formation combine elements from IT and MTT by proposing that the HC specifically identifies patterns of regularity across experiences, while the neocortex stores these commonalities and response options within schemas (Kroes and Fernández, 2012). However, it has also been proposed that the HC can encode episodic memory and extract regularities from experience (Schapiro et al., 2017). Importantly, regardless of how schemas are formed, these representations are flexible and capable of continuously assimilating new information, characteristics that could explain the expansion of semantic knowledge .

In summary, there is significant agreement that experiences modify engrams in the HC and neocortex. However, it remains to be established whether the engram representations in these regions are qualitatively distinct and if updating affects them differently. Animal research on engrams has not conclusively shown how engrams facilitate the shift from episodic to semantic memory, the components of an engram that encode the gist of recollection, or how repeated activation of the same neurons contributes to memory fluidity. We propose that a comprehensive understanding of memory can only be achieved by integrating multiple levels of analysis, considering different cell types, and concurrently recording from the HC and cortex during tasks that permit the transition from episodic to semantic knowledge.

2. The hippocampus: cognitive maps, hippocampal neuroanatomy, and engrams

2.1. *Cognitive maps*

A critical feature of episodic memories is their dependence on contextual information. This feature emphasizes the notion that facts and events within our experiences become integrated within a

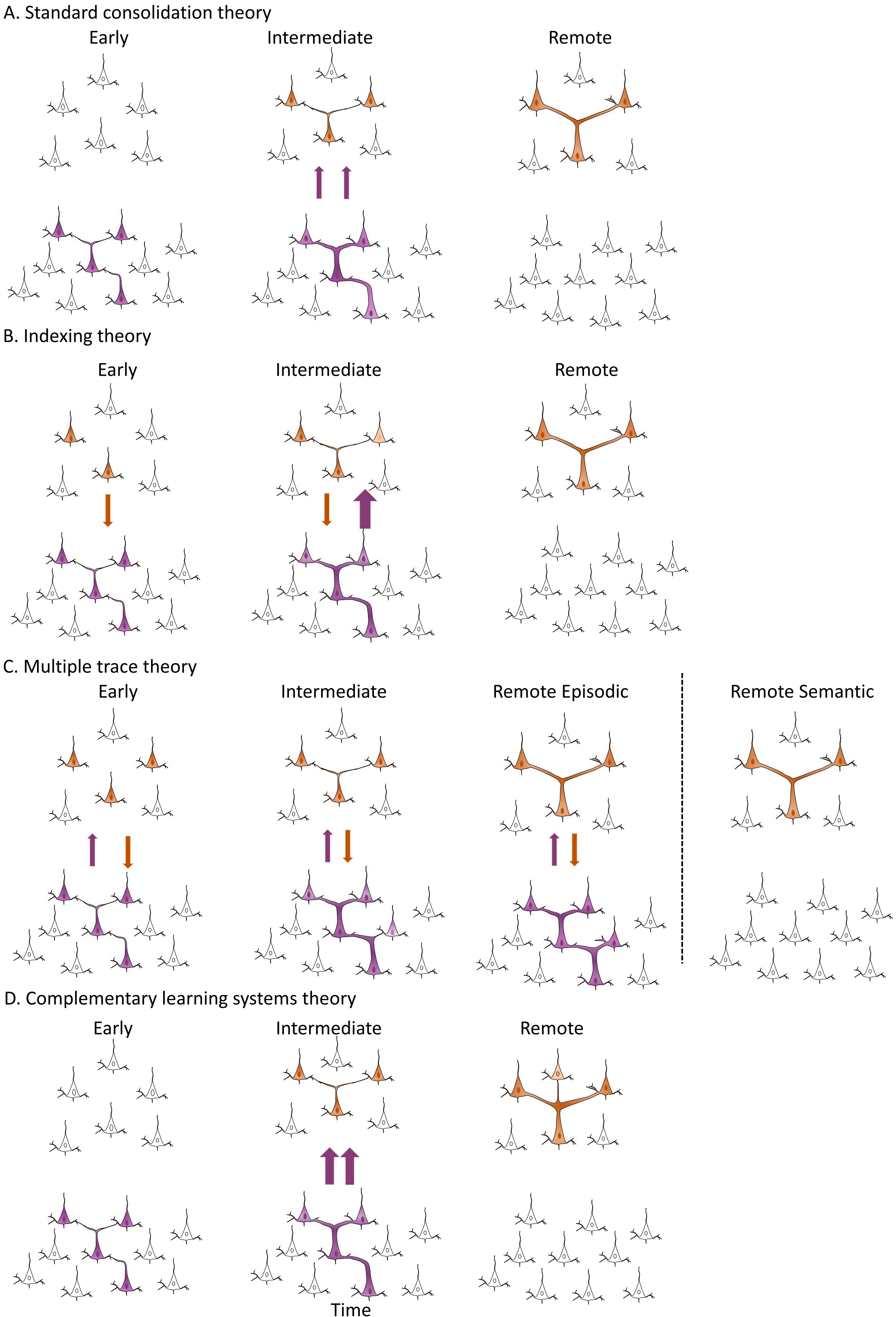

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Fig. 1. Theories of consolidation. A. **Standard Consolidation Theory.** This view proposes that memories are initially encoded in the hippocampus. However, memory traces are gradually transferred over time to neocortical regions, where they consolidate. During remote recall, neocortical networks can retrieve memory independently of the HC. This theory suggests uniform mechanisms for both episodic and semantic memories. B. **Indexing Theory.** This view proposes that the HC encodes cortical activity patterns as an index of experience. Over time, the neurons representing this index consolidate by forming enhanced synaptic connections. These connections allow the HC index to retrieve complete memory representations in the cortex. With time, cortical representations become more semantic and can be retrieved without the HC. C. **Multiple Trace Theory.** This view proposes that memory traces are simultaneously formed in the HC and cortex. During episodic retrieval, HC engrams expand, amplifying the episodic representation. According to this perspective, the HC is always necessary for episodic retrieval. Conversely, cortical semantic memories tend to evolve into more abstract forms as time progreses, allowing for the retrieval of the semantic gist without the direct involvement of the HC. D. **Complementary Learning Systems Theory.** This view suggests that initial encoding and consolidation occur exclusively in the HC. As these HC memory traces stabilize through enhanced synaptic connections, they are transferred to the cortex. Cortical engrams are encoded as schemas, capable of expanding through experience and retrievable without HC engagement.

contextual framework (Eichenbaum, 2017b). Edward Tolman (1943) introduced the concept that memories were organized into mental representations, serving as cognitive maps (Tolman, 1948). In a seminal experiment, Tolman demonstrated that rats trained to navigate a complex maze could discover a shortcut to the goal location when tested in a different enclosure within the same room (Tolman et al., 1946). This showcased the ability of animals to utilize room cues for the formation of cognitive maps of the environment.

Neurophysiological findings implicated the HC as the brain region that generates the cognitive map necesssary for embedding episodic events . This is evidenced by the discovery that pyramidal cells in the HC, known as place cells, display firing activity in distinct locations as an animal navigates through space (O'Keefe and Dostrovsky, 1971). This finding led researchers to propose that the simultaneous activity of place cells generates an internal representation of allocentric space (i.e., cognitive map), which animals utilize for efficient navigation (O''Keefe, 1978). Place cells respond to environmental changes through various forms of remapping. Global remapping reflects a cell's tendency to shift its preferred firing location (Muller and Kubie, 1987), while rate remapping indicates changes in firing rate without altering the cell's firing location. Notably, HC cells frequently display partial remapping wherein only a subset of cells shifts their preferred firing location in response to stimuli (Colgin et al., 2008; Huxter et al., 2003; Leutgeb et al., 2006; Muller and Kubie, 1987). This illustrates that distinct place cell subpopulations represent different facets of an experience. Notably, all types of remapping can be influenced by parameters beyond spatial cues including task contingencies, attention, rewards, motivation, and time (Eichenbaum, 2014; Huxter et al., 2003; Kennedy and Shapiro, 2009; Kentros et al., 2004; MacDonald et al., 2011; Markus et al., 1995; Muzzio et al., 2009; Salz et al., 2016; Smith and Mizumori, 2006; Wood et al., 1999), suggesting that place cells can represent multifaceted episodic experiences. These observations raise an important question for engram research: Are engrams representing episodic events segregated into different hippocampal subpopulations, each carrying distinct types of information, or do these ensembles integrate diverse components of experience through alterations in spatial and rate coding?

2.2. *Hippocampal neuroanatomy*

The neuroanatomy of the HC has been extensively reviewed (Amaral and Witter, 1989; Forster et al., 2006; Sloviter and Lomo, 2012). In this section, we will only address key features that render this region an optimal substrate for episodic memories. The HC proper consists of three subregions: the dentate gyrus, CA3, and CA1. The distinct characteristics and connectivity of these subregions imply that they serve different roles in memory processing. The dentate gyrus contains a greater number of neurons in the pyramidal cell layer compared to the entorhinal cortex, the primary input area for the HC. This attribute facilitates the differentiation of similar stimuli (Marr, 1971). Furthermore, the dentate gyrus is one of the few brain regions generating new neurons throughout the lifespan (Kempermann et al., 2015). This phenomenon, known as neurogenesis, is believed to alleviate memory interference, where specific information hampers the recall of similar material (Becker, 2017; Wojtowicz, 2012). These characteristics suggest that the dentate gyrus is involved in pattern separation—a cognitive process that minimizes interference between related experiences by reducing overlap of similar input patterns (Marr, 1971; McClelland et al., 1995; McNaughton and Nadel, 1990; Yassa and Stark, 2011). Interestingly, newborn dentate cells are integrated into hippocampal circuits by reducing synaptic potentiation of previously enhanced connections (Alam et al., 2018; Frankland et al., 2013; Kitamura et al., 2009), further suggesting that hippocampal engrams have dynamic properties that evolve over time.

Area CA3 is distinguished by the presence of auto-associative recurrent connections among excitatory and inhibitory cells, fostering a configuration that could support pattern completion—where activation of a partial memory trace triggers retrieval of a complete one (Leutgeb and Leutgeb, 2007; Marr, 1971; McClelland et al., 1995). In contrast, Area CA1 receives indirect, pre-processed sensory inputs through the trisynaptic loop, a relay of synaptic connections involving the entorhinal cortex, dentate gyrus, CA3, and CA1. Additionally, CA1 receives direct inputs from the entorhinal cortex via the temporo-ammonic pathway (Brun et al., 2008; Maccaferri and McBain, 1995). This suggests that CA1 neurons have the ability to compare new sensory information with past experiences (Schlichting et al., 2014). Finally, the primary output of CA1 is directed towards the subiculum, which establishes connections with subcortical regions and projects back to the entorhinal cortex (Amaral and Witter, 1989). This arrangement potentially creates a loop for re-processing information that necessitates additional consolidation.

The cytoarchitecture of hippocampal subfields is maintained along the dorsoventral axis (posterior-anterior in humans); however, the dorsal and ventral HC differ in terms of activity patterns and connectivity. Place cells with high spatial information are solely found in the dorsal region, which receives pre-processed spatial information from the mediolateral entorhinal cortex (Amaral and Witter, 1989; Ohara et al., 2023; Zhang et al., 2014). Conversely, the ventral HC, which contains cells that display very large place fields (Keinath et al., 2014; Kjelstrup et al., 2008; Royer et al., 2010), connects extensively with brain regions involved in emotion and anxiety (Kerr et al., 2007; Majak and Pitkänen, 2003; Petrovich et al., 2001), including the basolateral amygdala (Majak and Pitkänen, 2003) and the hypothalamic-pituitary-adrenal axis (Cenquizca and Swanson, 2006, 2007). Moreover, fear and anxiety-associated genes are selectively expressed in the ventral HC (Dong et al., 2009; Fanselow and Dong, 2010; Thompson et al., 2008). Lastly, only the ventral HC sends robust projections to the prelimbic (PL) and infralimbic (IL) cortices (Hoover and Vertes, 2007; Ishikawa and Nakamura, 2006; Jay and Witter, 1991) .

The differences in activity patterns and connectivity between the dorsal and ventral regions led researchers to propose a segregation of function between these areas, with the dorsal HC playing a role in spatial processing and the ventral HC in anxiety (Bannerman et al., 2004). However, an alternative posibility is that the redundancy in spatial information along the longitudinal axis serves to maintain a balance between memory interference and generalization. The discrete dorsal fields may reduce interference, while the overlapping large ventral fields may promote generalization (Keinath et al., 2014). A corollary of these ideas is that dorsal and ventral engrams may exhibit distinct properties. Indeed, a recent study demonstrated that the repeated reactivation of engram ensembles in these regions has differential effects on behavior (Chen et al., 2019).

It is important to note that critical distinctions are also observed along the proximo-distal hippocampal axis (Henriksen et al., 2010; Igarashi et al., 2014; Nakazawa et al., 2016; Ng et al., 2018; Paw Min Thein et al., 2020). For instance, place fields in proximal CA1, the area bordering CA2, are less dispersed than distal ones in the region bordering the subiculum. These differences reflect that proximal CA1 receives spatial inputs from the medial entorhinal cortex, whereas distal CA1 receives projections from less-spatial areas of the lateral entorhinal cortex (Henriksen et al., 2010). Lastly, superficial and deep pyramidal cell layers also display place cell differences (Danielson et al., 2016; Masurkar et al., 2017). Superficial place cells exhibit greater place field stability compared to deep ones. However, deep place fields stabilize during goal-oriented tasks (Danielson et al., 2016), suggesting that distinct sublayers may be associated with different memory roles.

In summary, the neuroanatomical characteristics of the HC suggest that engrams representing episodic events may have multiple components that respond differently depending on the inputs they receive. Additionally, the presence of neurogenesis in the dentate gyrus suggests that engrams are fluid, involving continuous updating. Indeed, neurogenesis has been shown to reduce synaptic potentiation (Alam et al., 2018; Frankland et al., 2013; Kitamura et al., 2009), a mechanism that may serve to maintain memory capacity by eliminating information that interferes with new knowledge (Alam et al., 2018). These complexities illustrate that engram research requires a comprehensive approach that incorporates connectivity patterns and cell properties to disentangle the elements that contribute to memory.

2.3. *Hippocampal memory engrams*

2.3.1. *Correlational findings from hippocampal electrophysiological studies*

Several studies have reported changes in hippocampal cells that correlate with memory recall. Notably, in simple associative tasks, results have demonstrated that different subsets of hippocampal cells represent distinct aspects of the memory trace, with only some neurons responding to learned valence. Moita and collaborators (2003) investigated the immediate and short-term changes in place cell activity during auditory fear conditioning. Prior to conditioning, most place cells showed little or no response to a tone used as the conditioned stimulus (CS); however, after conditioning, half of all recorded cells fired in response to the CS while animals traversed the cells' place fields. (Moita et al., 2003). Expanding on this study, Moita and colleagues examined place cell responses after contextual conditioning. Rats were exposed to a training box where they experienced shock and a control box without shock. Contextual fear conditioning caused only a subset of cells to show location remapping immediately after conditioning (Moita et al., 2004), further demonstrating heterogeneity in HC responses following learning.

To investigate if HC emotional representations stabilize in the long term, Wang et al. (2012) recorded HC activity for several days using a predator odor conditioning task. Most recorded cells, including those that remapped immediately after conditioning, became increasingly stable in the long term, firing in the same spatial locations on repeated trials (Wang et al., 2012). These findings suggested that the representations formed after conditioning created a persistent fear memory of the training environment during HC-dependent consolidation. Interestingly, when fear conditioned mice were exposed to extinction, a process that leads to the formation of a new association between the context and safety, the ensemble of active place cells remapped heterogeneously. Certain CA1 neurons responded to conditioning, some to extinction, and others to both processes (Wang et al., 2015). These findings highlighted that distinct elements of HC engrams can coexist. More recent studies looking at threats present in circumscribed regions of an environment (Wu, Haggerty, Kemere, & Ji, 2017) or moving in certain areas of a context (Kim et al., 2015) corroborated place cell remapping in response to changes in emotional valence. However, the extent of remapping in selective subpopulations varies across studies depending on threat proximity and predictability. These results indicate that activity patterns in engram populations may vary according to the characteristics of the conditioning cues.

Activity changes in different HC subpopulations have also been observed in response to appetitive tasks. Wood et al. (1999) trained rats to dig for a food reward in delayed matching and non-matching odor tasks. Different groups of HC cells responded to odors, trial type (matching vs. non-matching), reward, or location, indicating that HC cells represent various task-relevant cues through the activity of distinct sub-ensembles (Wood et al., 1999). Other studies corroborated that distinct place cell subpopulations respond to various task contingencies (Hampson et al., 1999; Markus et al., 1995), motivational states (Ferbinteanu and Shapiro, 2003), reference frames (Gothard et al., 2001; Gothard et al., 1996; Kelemen and Fenton, 2016; Zinyuk et al., 2000), rewards (Gauthier and Tank, 2018), objects (Yuan et al., 2021), odors (Muzzio et al., 2009), and sound frequencies (Aronov et al., 2017). Lastly, hippocampal cells code temporal information at different time scales (Banquet et al., 2021; Eichenbaum, 2013, 2017a; Howard and Eichenbaum, 2013; Pastalkova et al., 2008), suggesting that place cells possess flexible characteristics to integrate episodic events. It remains to be determined if the distinct components of complex memories are represented by neurons expressing the same or different molecular markers and how these markers correlate with contextual and temporal components in the HC.

Further support for the idea that memory engrams involve diverse contributions from distinct cell types is illustrated in studies looking at the role of inhibitory neurons (Cattaneo and Mainardi, 2022; Giorgi and Marinelli, 2021). GABAergic neurons constitute 15–20% of the total neurons in the HC (Klausberger and Somogyi, 2008; Pelkey et al., 2017; Topolnik and Tamboli, 2022; Tremblay et al., 2016) and are categorized based on anatomical targets, morphology, and expression of molecular markers (Booker and Vida, 2018; Lourenco et al., 2020; Pelkey et al., 2017). Inhibitory cells comprise perisomatic cells inhibiting the soma [e.g., parvalbumin (PV)-positive basket cells], axo-axonic cells inhibiting the axon initial segment (e.g., chandelier cells), and dendritic cells inhibiting the dendrites of principal cells [e.g., somatostatin (Som)--positive neurons]. Additionally, there are interneuron-specific inhibitory cells that target other GABAergic cells (Topolnik and Tamboli, 2022). Lastly, GABAergic cells also form long-range projections across brain regions (Basu et al., 2016; Cho et al., 2023; Mazo et al., 2022; Rock and Apicella, 2015; Rock et al., 2018; Rock et al., 2016; Urrutia-Pinones et al., 2022; Zurita et al., 2018), a feature that gives inhibitory cells the potential to synchronize and modulate information across brain areas.

Hippocampal GABAergic cells exhibit spatial information (Wilent and Nitz, 2007), a characteristic shared by all GABAergic cell types (Geiller et al., 2020). For instance, the activity of presynaptic inhibitory neurons influences the spatial tuning of place cells, implying that spatial information integrates activity in both inhibitory and excitatory circuits (Geiller et al., 2022). This conclusion has been supported by the observation that inhibition of chandelier neurons results in place field remapping in CA1 (Dudok et al., 2021). Interestingly, inhibitory neurons also exhibit retrospective coding—a phenomenon believed to contribute to memory consolidation, wherein firing activity is reactivated to represent past spatial trajectories (Frank et al., 2001).

Different kinds of inhibitory neurons have also been shown to have specific roles in distinct forms of memory (Giorgi and Marinelli, 2021). For example, Som interneurons have been implicated in emotional learning. Inactivation of Som neurons targeting CA1 place cells during the presentation of aversive stimuli increases pyramidal cell activity and inhibitesfear learning (Lovett-Barron et al., 2014). Conversely, PV basket cells respond to expected contextual changes during a working memory odor/place task (Forro and Klausberger, 2023). Inhibitory neurons also regulate information flow in the HC. Som interneurons facilitate the processing of CA3 to CA1 inputs while constraining direct entorhinal projections (Leao et al., 2012). Lastly, engram neurons in the dentate gyrus activate Som interneurons that inhibit surrounding granule cells dendrites. This mechanism constrains engram size and the stability of fear memory (Stefanelli et al., 2016). These findings demonstrate that both excitatory and inhibitory neurons contribute to memory processes. They also underscore the need for a comprehensive approach that considers cell types and functional heterogeneity within subpopulations to discern the essence of memory engrams.

2.4. *Immediate early gene studies*

2.4.1. *Creating or modifying memory*

Immediate early genes (IEG) are rapidly and transiently activated in response to external stimuli, and memory encoding is modulated by the regulation of these genes (Kubik et al., 2007). Therefore, researchers interested in studying the neural ensembles active during learning and memory have used various IEG tagging techniques to track these populations. These techniques have been described in detail in some reviews (DeNardo and Luo, 2017; Ortega-de San Luis and Ryan, 2022; Sakaguchi and Hayashi, 2012). The following paragraphs summarize some crucial findings obtained from these methods as well as the molecular strategies employed to address engram populations.

Garner et al. (2012) employed a combination of genetic and chemogenetic tools to manipulate active neurons during learning and assess whether reactivating these networks led to memory modifications (Fig. 2). They utilized a transgenic mouse to tag active neurons with the hM3Dq receptor during a specific time window (Reijmers et al., 2007). In this system, the Fos promoter, which responds to neuronal activity, drives expression of the tetracycline transactivator (tTA). In the presence of Doxycycline (Dox), tTA binds to the tetracycline response element (TRE), leading to the expression of the hM3Dq receptor in active neurons. This receptor induces strong neuronal depolarization in the presence of clozapine-N-oxide (CNO). Neurons expressing cFos were tagged when mice explored a novel context and were reactivated during contextual fear conditioning the following day in a different context. Exposure to the conditioning context alone or CNO-induced reactivation of the tagged neurons outside the conditioning context failed to produce fear expression after conditioning. However, when CNO was administered in the conditioning context, animals showed strong fear expression, suggesting that artificially induced activity during acquisition had been incorporated into the fear memory trace creating a hybrid memory (Garner et al., 2012).

In the last two decades, the Tonegawa lab conducted several elegant experiments to manipulate cells that are part of an engram using the cFos-tTA system described above along with optogenetic tools. To label and reactivate engram neurons in the dentate gyrus, Liu et al. (2012) injected cFos-tTA transgenic mice with a viral construct containing channelrhodopsin 2 (ChR2), a light-gated channel that depolarizes neurons when activated with blue light, tagged with TRE . In the absence of Dox, experience-induced neuronal activity labels active cFos-expressing dentate gyrus neurons with ChR2, which can then be reactivated by light stimulation during testing (Fig. 3). Light activation of the tagged-engram neurons in a chamber distinct from the training context resulted in animals displaying freezing behavior, showing that artificial activation of an engram could lead to fear expression in a context that was never paired with shock (Liu et al., 2012). In a follow-up study, Ramirez et al. (2013) labelled dentate gyrus cells activated in a novel context with ChR2. These neurons were later activated by light during fear conditioning in a different context. During testing, the experimental animals displayed fear in the original context, where they never experienced a fearful shock, showing recall of a false memory (Ramirez et al., 2013).

Lastly, a recent study evaluated whether a memory could be created in the complete absence of natural experience. Optogenetic stimulation of a specific glomerulus in the olfactory bulb was paired with either activation of an appetitive or aversive pathway. Following the manipulations, animals displayed attraction or aversion to the real olfactory cue activated by the stimulated glomerulus, respectively. This indicated

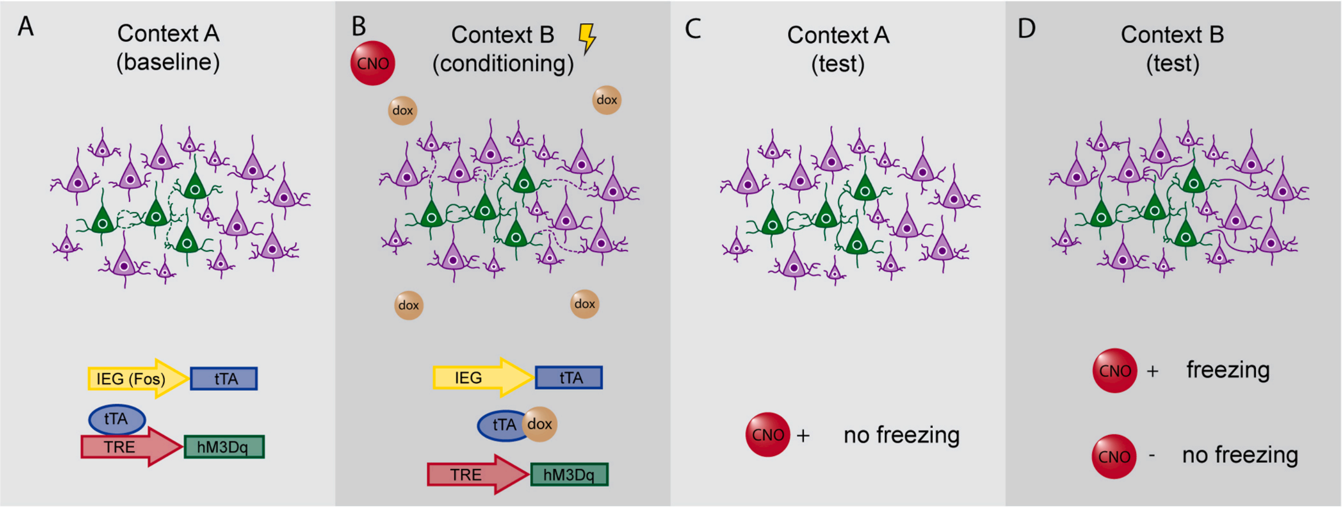

Fig. 2. IEG promoters driving tTA: Chemogenetic approach. Fos-tTA mice, in which the Fos promoter drives expression tetracycline transactivator (tTA) have been used to investigate the properties of neurons activated during learning (Reijmers et al., 2007). In the absence of doxycycline (Dox), tTA binds the tetracycline response element (TRE), leading to the expression of the effector gene of interest through recombination. Gardner et al. (2012) used a double transgenic mouse line expressing Fos-tTA and the G-protein coupled receptor (hM3Dq) under tetracycline response element (TRE). **A.** Mice were exposed to a novel context (A), to induce tagging of active neurons in this environment. In the absence of Dox, expression of hM3Dq is driven by cFos tagging the active engram. **B.** Dox was administered to the diet again, and the mice were exposed to another novel context (B) where foot shock (US) and clozapine-N-oxide (CNO) injection were administered. The hM3Dq receptor produces depolarization in response to the exogenous ligand CNO. This manipulation led to the formation of a memory that included the engram associated with the conditioning context (B) and the engram of the artificially activated context (A) (i.e., neurons responding to CNO). **C-D.** During testing in the presence of Dox to prevent further tagging, mice showed freezing only when both CNO injection (activating the Context A engram) and exposure to Context B occurred together (panel D, CNO+). The tagging conditioning context B or CNO alone in context A did not generate freezing. These results indicated that activation of an artificial engram during conditioning created a hybrid memory.
Adapted from Garner et al. (2012).

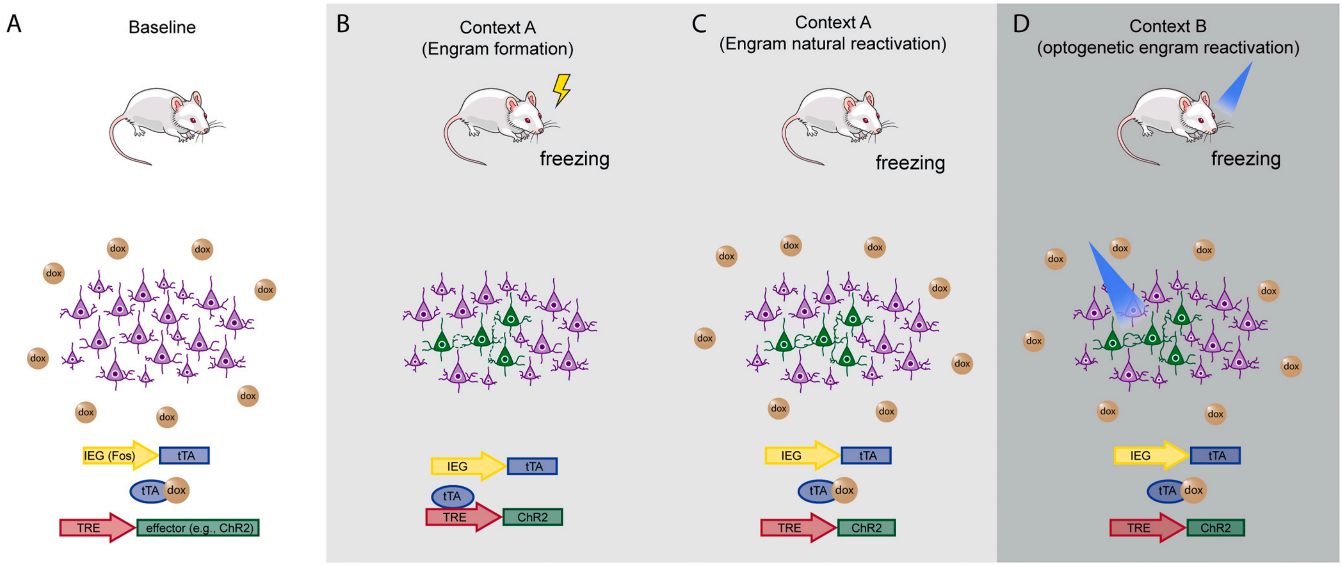

Fig. 3. IEG promoters driving tTA: Optogenetic approach. The Fos-tTA system has been widely used to express opsins (e.g., channel rhodopsin 2, ChR2). In this case, the Fos promoter drives expression of tTA, which, in the absence of Dox, drives expression of the effector opsin. **A.** In Liu et al. (2012), tTA did not interact with the tetracycline response element (TRE) in the presence of Dox (baseline). **B.** Dox was removed from the animal's diet, and mice were subjected to fear conditioning in Context A. In the absence of Dox, Fos drove expression of ChR2 in active neurons. **C.** Dox was reintroduced into the diet to prevent further neuronal tagging and animals were exposed to the conditioning Context A, where they exhibited freezing. **D.** In the absence of Dox, mice were introduced to a novel context B in the presence of blue light, activating ChR2. The mice exhibited freezing behavior in a context where they have never encountered a shock.
Adapted from Liu et al. (2012).

that an artificial memory could be created through manipulation of engram circuits (Vetere et al., 2019). These data support the idea that the reactivation of artificial ensembles is sufficient to produce recall or create memories.

2.4.2. *Erasing memories*

The previous section described optogenetic tools used to create or modify memories. Josselyn and colleagues performed the first manipulation of IEG-tagged neurons leading to loss of function. Although this study was conducted in the lateral amygdala, we mention it here because it introduced the idea that ablating specific neurons could lead to memory erasure. The authors relied on a previous finding from their lab showing that LA neurons with increased cyclic adenosine monophosphate response element-binding protein (CREB) were preferentially activated by fear memory (Han et al., 2007). The authors then used an inducible diphtheria-toxin approach to selectively ablate these CREB overexpressing neurons. The results showed that deleting these neurons after learning blocked fear expression, suggesting that CREB

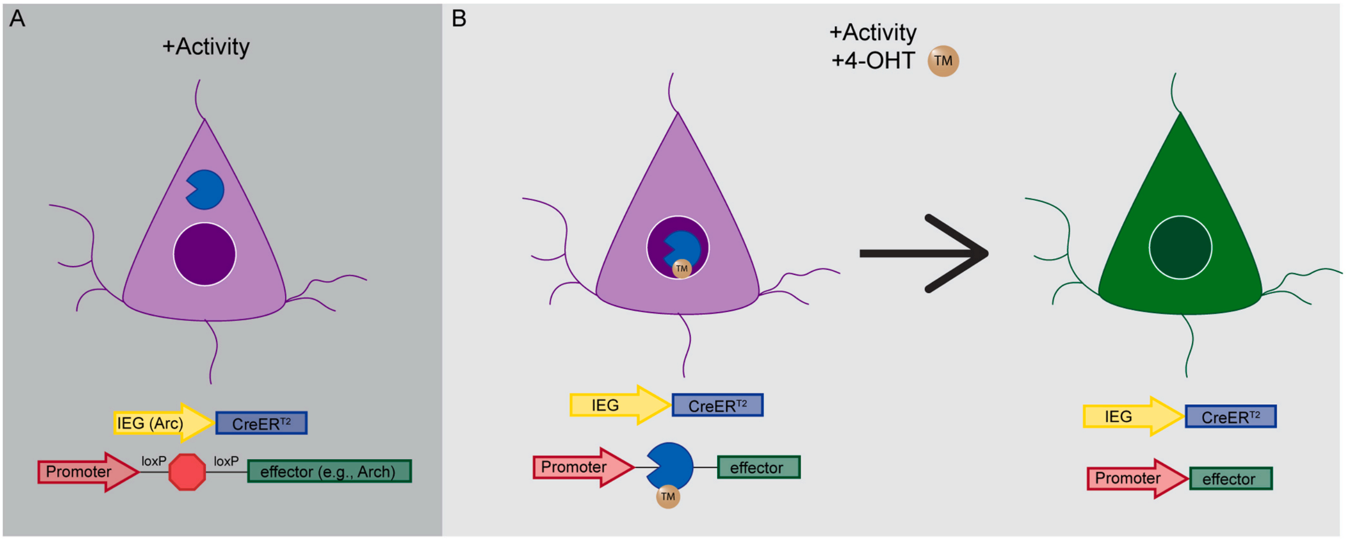

Fig. 4. Targeted Recombination in Active Populations (TRAP). In TRAP transgenic lines, CreER is knocked-in to a promoter (usually Fos or Arc). **A.** In the absence of Tamoxifen, CreER remains in the cytoplasm . **B.** Conversely, in the presence of Tamoxifen (+4-OHT), CreER translocates to the nucleus and produces recombination of the effector gene, leading to its permanent expression . Denny et al. (2014) used an ArcCreER bacterial artificial chromosome (BAC) transgenic line. The advantage of BAC lines is that the IEG of interest remains functional. CreER replaces the IEG coding and regulatory sequences, creating null alleles in other lines. (DeNardo and Luo, 2017). The ArcCreER line was crossed with a Floxed-Archaerhodopsin-GFP line. Archaerhodopsin (Arch) is an inhibitory opsin. During fear learning, active neurons in the presence of Tamoxifen allowed translocation of CreER to the nucleus, where recombination occurred in the floxed alleles, resulting in permanent expression of Arch.

overexpressing neurons encoded the fear memory. Subsequent studies using various techniques to delete engram cells in different tasks and brain regions found similar results reflecting loss of function [HC: (Denny et al., 2014; Lacagnina et al., 2019; Park et al., 2016; Tanaka et al., 2014); amygdala: (Zhou et al., 2009); nucleus accumbens: (Koya et al., 2009); prefrontal cortex: (Matos et al., 2019)]. Here, we will discuss in more depth hippocampal studies that illustrate the use of distinct IEG markers.

Denny et al. (2014) labelled neurons using targeted recombination in active populations (TRAP) in BAC transgenic mice to mark active neurons (Fig. 4). The transgenic mice expressed tamoxifen-regulated Cre recombinase, known as CreER^{T2}, where the immediate early gene Arc served as the activity marker. These mice were crossed with a floxed Archaerhodopsin-green fluorescent protein (Arch-GFP) line, leading to the expression of Arch in the same neurons labelled with Arc. Arch is a light-gated channel that pumps protons out when activated by yellow light, producing hyperpolarization. Using this approach, the authors labelled active ensembles in the dentate gyrus or CA3 during contextual fear conditioning. Optogenetic inactivation of labelled neurons in either region prior to retrieval impaired expression of contextual fear (Denny et al., 2014). Similar impairments were obtained when engram cells were inactivated in CA1 using the cFos-tTA system (Tanaka et al., 2014). Moreover, this latter study also demonstrated that distinct fear conditioning memory engrams could be stored in non-overlapping CA1 ensembles since inactivation of the initial engram cells during retrieval did not inhibit the ability of mice to acquire new fear memories. These results suggest that similar memories can potentially recruit multiple ensembles.

2.4.3. *Altering the valence of memories*

Engram cells can switch valence in some regions (Redondo et al., 2014). Cells in the dentate gyrus or basolateral amygdala were tagged with ChR2. Reactivation of the labelled cells in each region, while animals were trained in fear conditioning or appetitive conditioning tasks, led to place aversion or place preference, respectively. The original contingencies were subsequently switched to change the valence of the engram cells. The cells labelled during fear or appetitive conditioning were reactivated while animals underwent conditioning of the opposite valence (e.g., light-activated fear cells were paired with an appetitive reward and vice versa), and animals were tested in a place preference task. Light-activated cells in the dentate gyrus switched their valence. However, light-activated cells in the amygdala did not. These results demonstrate that engram cells in the dentate gyrus can show plasticity, whereas engram cells in the amygdala have rigid properties.

Recent studies also demonstrated that IEG engram cells in different subregions display specific properties. Shpokayte et al. (2022) showed that ventral HC cells responding to positive or negative valence displayed distinct transcriptional profiles and DNA methylation patterns. Interestingly, although optogenetic manipulation of these distinct ventral subpopulations could not induce appetitive or fear behavior, selective activation of ventral projections to the amygdala or nucleus accumbens elicited place preference or avoidance, respectively. These results suggested that expression of distinct emotional memories in ventral HC involves the circuits controlling these memories, rather than the local engrams. Notably, a follow-up study showed that engram-labelled cells along the dorsoventral hippocampal axis produce distinct effects after repeated reactivation. In the dorsal HC, chronic reactivation of IEG engram cells led to a reduction of fear, whereas in the ventral region, the same manipulation led to an enhancement of fear behavior (Chen et al., 2019). These results illustrate the complexity of interpreting memory engrams in different brain subregions having unique connectivity patterns which likely influence how active neurons respond to various experiences.

2.4.4. *Recovering lost memories*

An exciting prospect emerging from engram studies is that memory impairment could reflect a failure to activate specific memory representations. This idea was tested in an experiment where mice were administered anisomycin, a protein synthesis inhibitor, following contextual conditioning. This intervention, known to impede synaptic consolidation and induce amnesia (Bourtchouladze et al., 1998; Schafe and LeDoux, 2000), led to impaired fear memory. Optogenetic activation of tagged fear engrams in anisomycin-treated mice reinstated normal fear memory, which persisted several days post-conditioning (Ryan et al., 2015). Notably, engram cells from these mice displayed weaker synaptic connections compared to engram cells from control mice. These intriguing findings prompted the same research team to explore whether artificial stimulation of silent engram cells (i.e., engram cells that do not diaplay potentiated synapses) could alleviate amnesia in an animal model of Alzheimer's disease (Roy et al., 2016). Optogenetic stimulation of fear engram neurons in transgenic mice resulted in increased fear following conditioning compared to control mice, suggesting that certain unretrievable memories can be rescued under some conditions. Based on these findings, Ryan and Frankland (2022) proposed that forgetting results from a process of circuit remodeling, where engrams are transformed from a state responsive to external reminders to an unresponsive state .

Reactivating silent engrams has proven effective in rescuing memory even under normal conditions. A recent study demonstrated that the reactivation of brain-wide engrams associated with contextual fear conditioning following extinction training successfully reinstated the fear response. Using a chemogenetic approach to manipulate distributed fear engrams (same method described in Fig. 2), researchers tagged engrams in dorsal CA1, subiculum, cerebral cortex, and basolateral amygdala during conditioning. Although extinction training suppressed fear expression, reactivating the distributed fear engram returned the fear response. These findings suggested that the original fear memory persisted in a dormant state rather than being erased (Yoshii, Hosokawa, Matsuo, 2017). Another study corroborated that safe or fearful memories could be reversed through engram manipulations. Optogenetic inhibition of fear engrams post-conditioning reduced fear, while inhibition of extinction engrams after extinction increased fear. Conversely, optogenetic activation of these distinct engrams produced the opposite effects. These results reinforced the idea that fear associations and extinction ensembles coexist in different states, and the expression of fear or safety depends on which ensemble is active and which is dormant (Lacagnina et al., 2019).

Activation of engram cells also served to recover object location memories following sleep deprivation, a procedure that impairs memory. Bolsius et al. (2023) trained animals in an object-place memory task. During the exploration of two objects, engram cells were labelled in mice. Following this encoding phase, the animals underwent sleep deprivation. During testing, one of the objects was placed in a novel location, a procedure that normally leads to more exploration due to novelty. Sleep deprivation reduced exploration of the displaced object in control animals, indicating memory impairment. However, reactivation of engram cells led to more exploration of the moved object in experimental mice, rescuing the adverse effects of sleep deprivation. Furthermore, the negative effects of sleep deprivation were ameliorated by increasing the levels of cAMP, a second messenger involved in synaptic consolidation (Bolsius et al., 2023). These results suggest that sleep deprivation may bring synapses to a silent state that can be rescued under some circumstances.

These findings collectively suggest that the artificial activation of silent engrams could serve to restore some lost memories. Investigating whether such manipulations can effectively revive memory when synaptic connections are compromised by disease shows promise for therapeutic interventions. However, several questions remain unanswered. For example, is there a specific time window during disease progression in which the reactivation of dormant engrams proves beneficial? Are artificially reactivated memories similar to those retreieved with real reminders? While mouse behavior is typically assessed using basic measures like freezing or exploratory time, evaluating behavior through a diverse set of measures would be essential to determine if the quality of artificial recollection aligns with normal memory. Lastly, it would be critical to explore if reactivation of silent engrams successfully recovers more intricate episodic experiences.

2.4.5. Limitations of single IEG markers

In an important study, McHugh and collaborators examined cells expressing cFos (engram cells) from other active place cells during spatial exploration. The authors conducted single-unit recordings from CA1 in cFos-tTA transgenic mice using the same labelling system described in Fig. 2. Dox was removed from the diet when animals were exposed to a novel context, which labelled cFos-expressing neurons with ChR2 during exploration of an environment. The following day, animals were placed in the same context and cells expressing ChR2 were activated with light to identify the cFos-positive neurons (engram cells) while the entire ensemble of active place cells was recorded. Most of the recorded neurons were cFos-negative cells. These neurons displayed typical place cell activity, showing high stability in a familiar context and remapping in a novel one. Conversely, engram cells displayed shifts in the cells' preferred firing locations within a familiar context and did not remap in a novel environment. The authors interpreted these findings in the context of the indexing theory of consolidation and suggested that cFos-positive cells provide a hippocampal memory index by binding activity patterns with current experience. Conversely, the cFos negative cells code spatial components of the memory trace, such as the stable characteristics of the context (Tanaka et al., 2018). This study highlights that episodic experience is much more complex than noted in previous engram studies and that relying on a single marker may not be sufficient to capture all the components of a memory trace.

In a more recent study, Pettit et al. (2022) used a dual labelling approach and recorded CA1 calcium signals during a virtual reality goal-oriented task. The authors employed a cFos-transgenic reporter mouse line in which a short half-life green fluorescent protein (GFP) was expressed under the control of the cFos promoter. The authors also expressed a red-shifted calcium indicator in cFos-GFP reporter mice. This approach allowed simultaneous monitoring of neurons expressing different levels of cFos. Cells showing high levels of cFos had greater stability and spatial information content than cells that did not (Pettit et al., 2022). The differences between the results from Tanaka et al. and Pettit et al. could be due to the use of different tasks, recording techniques (calcium imaging vs. electrophysiological recordings), and/or experimental settings (freely moving vs. virtual reality tasks). However, despite the differences, the most important observation in both studies is that engrams are comprised of cells that express distinct levels of IEGs, with each subpopulation coding unique aspects of the episodic experience.

A recent study investigated the potential limitation of relying on a single IEG marker to study memory engrams. The researchers used two IEG markers, cFos and Npas4, known for triggering distinct synaptic changes during learning and memory to evaluate their involvement in fear conditioning (Flavell and Greenberg, 2008; Sun and Lin, 2016). cFos has been associated with potentiation of synapses (Fleischmann et al., 2003), while Npas4 exhibits a preference for recruiting inhibitory neurons (Weng et al., 2018). The results revealed that these distinct IEG activated different engram ensembles. The cFos ensemble received inputs from the medial entorhinal cortex and promoted fear generalization, whereas the Npas4 ensemble received inputs from cholecystokinin-inhibitory interneurons and promoted fear discrimination (Sun et al., 2020). This pivotal study highlighted that even in a seemingly straightforward associative task, engrams exhibit heterogeneity. Moreover, these results underscore the significance of considering both excitatory and inhibitory contributions to engrams.

To conclude, hippocampal engram research suggests potential ways to manipulate, recover, or erase memories. However, the validity of these observations should be confirmed through more intricate tasks that encompass a comprehensive examination of the various cell types contributing to recollections. Such endeavors are vital for advancing our understanding of memory and pushing the boundaries of research in this field.

3. Medial prefrontal cortex (mPFC) and memory

3.1. mPFC neuroanatomy

There is currently no consensus regarding the neuroanatomical subdivisions of the prefrontal cortex in rodents (Carlén, 2017; Myers-Schulz and Koenigs, 2012), which has led to incongruencies among studies (for review see, Dixsaut and Gräff, 2021). Despite these challenges, three major subdivisions are generally accepted in rodents: anterior cingulate (ACC), prelimbic (PL), and infralimbic (IL) cortices. Some studies suggest that the human dorsolateral (DL-PFC) and ventromedial (VM-PFC) prefrontal cortices share functional resemblance with the rodent PL and IL, respectively (Heilbronner et al., 2016; Quirk and Beer, 2006). However, recent neuroanatomical comparisons indicate the following homologies with Brodmann areas: PL corresponds to 32 (dorsal-anterior cingulate), IL to 25 (subgenual cingulate region), and anterior cingulate to 24 (cingulate cortex), all of which are components of the human VM-PFC (Laubach et al., 2018). Considering the ongoing debates regarding homology, predictions about memory from rodent studies should be taken with caution.

The entire rodent mPFC receives projections from motor, sensory, emotional, and visceral areas (Euston et al., 2012), with all subregions sharing strong reciprocal connections (Hoover and Vertes, 2007; Voorn et al., 2004). The dorsal PL and ACC receive dense projections from sensory and motor regions, whereas the ventral PL and IL receive strong projections from limbic areas, particularly the HC and amygdala (Hoover and Vertes, 2007). These distinctions are not exclusive since less robust limbic projections to the dorsal PL and ACC have been identified and implicated in recent (Ye et al., 2017) and remote memory (Kitamura et al., 2017; Kol et al., 2020).

Regarding outputs, the rodent mPFC sends projections to the amygdala, nucleus accumbens, dorsal striatum, and ventral pallidum, granting this region the ability to modulate emotional and motor behavior (Gabbott et al., 2005; Hoover and Vertes, 2007). The dorsal area of the mPFC, including the dorsal PL and ACC, projects to motor and premotor areas, while the ventral portions of the mPFC, including the ventral PL and IL, project to autonomic and limbic structures (Gabbott et al., 2005). Interestingly, the mPFC sends topographically organized projections to the striatum (Voorn et al., 2004). The PL projects to the nucleus accumbens core, an area involved in goal-directed behavior (Peak et al., 2020), whereas IL sends projections to the nucleus accumbens shell, a region involved in habitual behavior (Barker et al., 2014). This organization likely allows mPFC to modulate distinct behaviors and engrams.

The PL and IL also connect to the HC via an indirect route that involves the nucleus reuniens (Varela et al., 2014; Vertes, 2004), a ventral midline thalamic region that has been shown to synchronize oscillations between HC and mPFC (Hallock et al., 2016), modulate the firing of hippocampal cells during goal-oriented tasks (Ito et al., 2015), and play a role in memory (Ramanathan, Jin et al., 2018; Ramanathan and Maren, 2019; Ramanathan, Ressler et al., 2018). This connectivity suggests that the nucleus reuniens may also act as a hub that controls distinct types of memories, which has been corroborated in a study looking at brain-wide engrams (Vetere et al., 2017). Finally, the mPFC has heavy reciprocal projections with the ventral tegmental area (Hui and Beier, 2022), a pathway that likely involves evaluation and processing of rewards. In summary, the connectivity of the rodent mPFC places this region in a unique position to integrate, modulate, and retrieve intricate memories.

3.2. Role of mPFC in memory

3.2.1. Human studies

Human lesion studies of patients with mPFC damage have revealed that this region is involved in various functions; however, in this review, we will only discuss deficits related to declarative and episodic memory. Deficits differ depending on whether the lesions affected the DL-PFC or VM-PFC regions. Memory deficits observed after DL-PFC damage are not as pronounced as those observed after medial temporal lobe damage. However, DL-PFC lesion patients are confused about when and where events have taken place, which has implicated this area in episodic memory recall (Chapados & Pedrides, 2015; Janowsky et al., 1989; Magels et al., 1996). Conversely, the VM-PFC is involved in more complex mnemonic functions. This area is recruited when contextual situations require disambiguation (Chapados and Petrides, 2015). Additionally, patients with VL-PFC damage tend to confabulate false recollections without the intention of deceiving (Benson et al., 1996; Moscovitch and Melo, 1997). This tendency to believe false memories appears to be related to an inability to suppress irrelevant information (Burgess and Shallice, 1996) and schemas (Ghosh et al., 2014; Hebscher and Gilboa, 2016). In summary, human lesion studies suggest that the DL- and VM-PFC play distinct roles in memory, with the DL-PFC being more involved in episodic recall and the VM-PFC controlling memory suppression and selecting the appropriate rules to guide behavior.

3.3. Non-human animal studies

Studies conducted several decades ago showed that mPFC neurons display heterogeneous responses during memory tasks. In experiments where monkeys were trained to execute motor actions following a cue and a subsequent delay, distinct subgroups of prefrontal neurons were observed, each responding to specific aspects of the task and motor responses. (Fuster, 1990; Fuster and Alexander, 1971). Moreover, stimulation and lesion studies implicated the mPFC in distinct memory stages (Kesner et al., 1987; Kesner and Holbrook, 1987; Santos-Anderson and Routtenberg, 1976).

Follow-up studies identified the specific contributions of different mPFC subregions to learning and memory, particularly remote recall. In a seminal study, Bruno Bontempi and colleagues measured the uptake of (^{14}C)2-deoxyglucose, an indicator of neuronal activity, to determine the involvement of the HC and cortex during memory retrieval. Rats trained to find rewards in a radial arm maze were administered (^{14}C)2-deoxyglucose before early or remote retrieval. Histological examination of the brains revealed heightened hippocampal activity during early, but not remote recall. Conversely, increased metabolic activity in the ACC and frontal cortex was evident only during remote recall (Bontempi et al., 1999). Subsequent research corroborated the involvement of the ACC in remote memory. This confirmation was established through studies investigating changes in IEGs (Frankland et al., 2004; Maviel et al., 2004), alterations in spine density (Aceti et al., 2015; Restivo et al., 2009), and the effects of inhibition (Goshen et al., 2011).

Studies have also implicated the mPFC in early stages of memory consolidation. The ACC is involved in contextual associative learning using predatory threats (de Lima et al., 2022), innate fear responses (Jhang et al., 2018), and trace fear conditioning (Han et al., 2003). The PL cortex contributes to recent and remote fear expression (Blum, Hebert, & Dash, 2006; Do-Monte et al., 2015; Vidal-Gonzalez, Vidal-Gonzalez, Rauch, & Quirk, 2006), while the IL cortex has been implicated in the acquisition and consolidation of extinction (Laurent and Westbrook, 2009; Quirk and Mueller, 2008). Although functional dissociations between PL and IL have found considerable support, recent evidence challenges the assumption that these regions play opposite roles. For instance, an excitatory projection from PL to IL enhances fear extinction (Marek et al., 2018), suggesting a more complex interaction between these areas than previously thought. Since the majority of tasks employed to evaluate the memory-related roles of mPFC subregions also implicate the HC, these findings indirectly lend support to the MTT. Furthermore, these results emphasize the importance of considering the neuroanatomical intricacies of the mPFC.

3.4. Engrams in mPFC: rodent studies

The characterization of neocortical engrams in rodents has gained significant attention in the last decades. Morris and collaborators first showed that memory traces could be simultaneously encoded in the HC and neocortex when new learning required prior learned rules (schemas). Rats were trained to form pair associates between different odors and locations. After rats were overtrained in this task, the authors tested acquisition of new pair associates (e.g., hippocampal-dependent learning of novel odors and locations). The results demonstrated that when new learning could be assimilated into prior schemas, there was an immediate upregulation of IEG in the PL cortex, providing support for the formation of simultaneous memory traces in both the HC and cortex (Tse et al., 2011). The idea that neocortical engrams may rapidly encode rules of knowledge was further supported by a study looking at contingency representations in the HC and mPFC in a task involving rule switches. Patterns of hippocampal activity could be anticipated based on preceding mPFC activity in trials following rule changes, corroborating simultaneous and interactive encoding of information in these regions (Guise and Shapiro, 2017).

In an elegant study, Kitamura et al. (2017) provided evidence for the idea that hippocampal and neocortical engrams are formed simultaneously, even in the absence of prior knowledge. The authors showed that neocortical engrams formed rapidly during contextual conditioning through hippocampal/entorhinal and amygdala inputs. Although the neocortical engrams were initially immature, they gradually consolidated over time. Conversely, the initially strong hippocampal engrams became progressively silent. Notably, calcium imaging of PL neurons revealed that a subset of shock-responsive cells recorded during conditioning became silent during early retrieval, but reactivated during remote recall. Therefore, these results not only illustrated the existence of multiple engrams, but also their dynamic quality (Kitamura et al., 2017). Although these results provided strong experimental support for the MTT, they also showed that hippocampal engrams became silent 2 weeks after conditioning. It is possible that for very simple associations, such as contextual fear conditioning, neocortical spatial information is sufficient for retrieval (Burke et al., 2005). This implies that basic learning processes result in accelerated semantic transitions, prompting inquiries about the adequacy of simple associative tasks as models for studying the intricacies of episodic memory.

The dynamic nature of neocortical engrams was corroborated by a study using viral-based TRAP (general approach illustrated in Fig. 4). PL neurons active during late retrieval had a higher likelihood of being reactivated during remote recall than those labelled during early retrieval. Brain mapping of PL engram cells across regions showed that late-tagged neurons displayed more robust intercortical connectivity than early-tagged ones (DeNardo et al., 2019). These results indicated that while neocortical engrams were initially dynamic, they stabilized over time through enhanced intercortical connections during consolidation. Although this possibility is intriguing, alternative evidence proposes that engrams remain inherently dynamic, showing fluctuations in excitability and synaptic strength. These properties could be beneficial for memory updating processes (Mau et al., 2020).

Substantial evidence points to the pivotal involvement of synaptic plasticity in stabilizing neocortical engrams and memory, mirroring its role in the stability of subcortical engrams. For instance, impairment of remote memory retrieval was observed when the cAMP response element-binding protein (CREB), a crucial transcription factor involved in memory, was disrupted in mPFC following mild conditioning (Matos et al., 2019). Moreover, the strength of synaptic connections among engram neurons has been shown to determine what memories are retrieved. Remote consolidation of fear memory correlated with progressive strengthening of excitatory interconnections among mPFC engram cells, whereas extinction of remote fear memory involved weakening of these synapses (Lee et al., 2023). Finally, the prevention of spontaneous recovery, characterized by a resurgence of fear in a context different from the extinction context, was accomplished by inducing LTP on mPFC engram synapses formed by projections from the amygdala and ventral HC (Gu et al., 2022). Together these data indicate that alterations in synaptic strength on engram networks can affect what memories are retrieved. It is likely that subtle changes in synaptic strength occur with the passage of time, allowing memory updating as experience evolves.

Finally, inhibitory neurons play pivotal roles in shaping and maintaining memory in the mPFC. Roger Clem and collaborators demonstrated that Som GABAergic cells in the mPFC control memory encoding and expression (Cummings and Clem, 2020). A follow-up study by the same group revealed that one subset of Som interneurons in the mPFC played a role in fear expression, while a separate Som subpopulation exerted opposite effects on fear memory. This latter Som subpopulation was sensitive to morphine and promoted reward-related responses (Cummings et al., 2022). These findings highlight that cortical engrams likely involve excitatory and inhibitory contributions, with distinct subsets of neurons producing unique effects on memory.

In summary, strong evidence supports initial cortical engram dynamism. Although certain uncertainties persist regarding the enduring stability of cortical engrams at remote stages, Synaptic strength among engram cells appears to be a critical variable influencing the retrieval of remote memories. A more comprehensive understanding of memory engrams necessitates the mapping of circuits governing specific behaviors, the detailed interconnectivity of active ensembles, and the contributions of various cell types, including both excitatory and inhibitory cells.

4. Hippocampal-mPFC interactions

4.1. *Interactions during learning and memory*

Numerous studies have showcased the interplay between the HC and mPFC in the intricate process of memory formation. These investigations underscore the need to co-activate these areas to form new memories and solidify remote ones (Chao et al., 2020; Eichenbaum, 2017b; Euston et al., 2012; Kitamura et al., 2017; Preston and Eichenbaum, 2013). Learning of HC-dependent paired associates coincides with an upsurge in IEG expression in the PL (Tse et al., 2011). Moreover, early tagging of cortical synapses, reliant on α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) and N-methyl-D-aspartate (NMDA) receptors, necessitates HC activity and is vital for the consolidation of remote memories (Lesburguères et al., 2011). Additionally, disruption of interactions between the mPFC and HC impairs associative memory (Bero et al., 2014). These examples vividly illustrate the pivotal role of bidirectional crosstalk between the HC and mPFC in the intricate process of memory consolidation.

A substantial portion of interactions between the HC and mPFC occurs through the nucleus reuniens of the ventral midline thalamus (Hoover and Vertes, 2012; Varela et al., 2014). Troyner et al. (2018) found that inactivation of the nucleus reuniens negatively affected the intensity, specificity, and stability of long-term fear memory. Mice injected with muscimol, a GABA agonist, in the nucleus reuniens exhibited alterations in the expression of Arc, a proteinlinked to synaptic consolidation and memory, in both the HC and mPFC. Moreover, a study employing simultaneous local field potential and single-unit recordings demonstrated that the nucleus reuniens coordinates and stabilizes neuronal sequences in the HC and mPFC during slow oscillations (Angulo-Garcia et al., 2020). This coordination was further substantiated by a study mapping brain-wide expression of cFos to identify engrams co-activated by contextual fear conditioning. In this study, certain hubs, including hippocampal area CA1 and the nucleus reuniens, exhibited higher connectivity than others. Chemogenetic silencing of highly connected nodes, including CA1 and reuniens , produced the most pronounced impairments in memory consolidation (Vetere et al., 2017). The importance of the HC, reuniens, and cortex, in addition to other brain regions, was further corroborated in a recent brain-wide mapping engram study (Roy et al., 2022).

The mPFC-hippocampal interactions during memory consolidation have been further demonstrated in studies investigating oscillatory synchrony between these regions. A substantial portion of mPFC cells exhibit phase locking to hippocampal theta oscillations (4–10 Hz) in freely moving rats (Siapas et al., 2005), a coupling that intensifies during spatial working memory (Jones and Wilson, 2005). Moreover, the proportion of mPFC cells phase-locked to hippocampal theta oscillations during a delayed matching task is higher during retrieval of correct trials compared to error trials (Hyman et al., 2010). Lastly, synchronization between these regions is crucial for various learning facets and behaviors (Hyman et al., 2005; Morici et al., 2022; Myroshnychenko et al., 2017; O'Neill et al., 2013; Tamura et al., 2017). Interestingly, a recent study analyzing simultaneous activity from mPFC and CA1 during a delayed non-matching task in rats showed that information about the sample is maintained in the mPFC at the population level, even though individual neurons only fired transiently. Moreover, during sample encoding the activity of small ensembles in the mPFC and CA1 was hallmarked by a low oscillation (4–5 Hz) that was not present in the local field potential. These ensembles re-emerged during the choice phase of the task but were not modulated by the low oscillations. Lastly, the mPFC and CA1 ensembles present during encoding and maintenance of the memory trace were not the same, suggesting that during learning there are heterogeneous groups of neurons representing distinct aspects of the task contingencies (Domanski et al., 2023). These results are very significant because oscillations have not only been linked to memory processes but are also considered an integral part of recollections (Buzsaki, 2005; Hanslmayr et al., 2019). Since oscillations are generated by population activity; it remains to be elucidated how engram neurons interact with population rhythmic patterns.

4.2. *Hippocampal-cortical interactions during sleep*

During sleep, the brain undergoes reorganization of neuronal activity, closely linked to memory consolidation. A considerable body of literature supports the idea that interactions between the HC and mPFC occur during sleep, a phenomenon extensively discussed in several reviews (Born and Wilhelm, 2012; Brodt et al., 2023; Girardeau and Lopes-Dos-Santos, 2021; Klinzing et al., 2019; Poe, 2017; Tononi and Cirelli, 2020; Westermann et al., 2015). Here, we will provide a brief overview of potential mechanisms through which sleep could facilitate memory consolidation and the potential contributions of distinct subpopulations to this process.

Sleep has two primary states: Slow wave sleep (SWS) and rapid eye movement (REM). SWS is characterized by high-amplitude, slow (<1 Hz) and delta (1–4 Hz) oscillations in the electroencephalogram (EEG). In contrast, REM is marked by low-amplitude, fast oscillations, predominantly theta (4–8 Hz) in rodents, and a combination of beta (15–35 Hz) and theta in humans (Vijayan et al., 2017). REM sleep is also known as paradoxical sleep due to its characteristic oscillatory patterns resembling wakeful EEG states (Girardeau and Lopes-Dos-Santos, 2021; Feld & Born, 2017). During SWS, spindle, and sharp-wave ripple events are often observed. Spindles are 11–16 Hz oscillations lasting 0.5–3 s, originating in thalamic networks and spreading to cortical regions (Fernandez and Luthi, 2020). Sharp waves are large-amplitude oscillations lasting approximately 70–100 ms. Originating from the excitatory recurrent connections in CA3, sharp waves give rise to synchronized and transient network oscillations in CA1, known as ripples (Buzsaki, 1986, 2015; O''Keefe, 1978). Sharp wave-ripples complexes occur during SWS, consummatory behaviors, and resting states, standing out as recognized biomarkers of memory (Buzsaki, 2015). Supporting evidence for ripple involvement in memory stems from the fact that their oscillatory frequency could promote LTP induction, suggesting a potential role in facilitating synaptic potentiation during sleep (Axmacher et al., 2006). Furthermore, spike activity occurring during wake periods is replayed during ripples at compressed timescales, a process thought to facilitate memory consolidation (Findlay et al., 2020; Lee and Wilson, 2002; Peyrache, 2022; Pfeiffer, 2020; Wilson and McNaughton, 1994).

Although replay of neural activity has been extensively observed in the HC (Chen and Wilson, 2023; Foster, 2017; Ji and Wilson, 2007; Pfeiffer, 2020), it is not limited to this region. Replay phenomena have been observed in various brain areas during different tasks (Brodt et al., 2023). Since extrahippocampal replay aligns with slow oscillations, spindles, and hippocampal ripples during sleep, it is likely that coordinated oscillatory synchronization is crucial in facilitating information transfer and memory consolidation across different brain areas (Inostroza and Born, 2013; Peyrache et al., 2009; Siapas and Wilson, 1998; Sirota et al., 2003; Staresina et al., 2015).

Reactivation of neuronal activity is not exclusive to SWS; also occurring during REM sleep. In a groundbreaking study, Louie and Wilson (2001) illustrated that ensemble firing patterns observed during wake exploratory periods were reactivated during REM sleep. Notably, while reactivations during SWS happen at compressed timescales, those during REM occur at timescales resembling wake periods (Louie and Wilson, 2001). The intriguing aspect of this reactivation is its potential role in facilitating both the encoding and forgetting of information. Poe and collaborators found that during REM sleep, cells active during exploration of a track exhibited a theta phase reversal that varied depending on familiarity with the environment (Poe et al., 2000). Place cells associated with familiar parts of a track showed activity during the theta trough, while those engaged in novel parts were active at the theta peak. Given that these entrainment patterns have been associated with depotentiation and potentiation, respectively (Holscher et al., 1997; Huerta and Lisman, 1995; Pavlides et al., 1988), these data suggest that REM promotes the encoding of new information while inhibiting processing of familiar knowledge (Poe et al., 2000; Poe, 2017). In agreement with these observations, reducing theta power during REM impairs formation of HC-dependent spatial memory (Boyce et al., 2016).

The reactivation of neuronal activity during REM and SWS raises the question of whether IEG engram ensembles are preferentially replayed during sleep. A study using calcium imaging and the cFos-tTA tagging system investigated this question in CA1 during learning of a novel context. cFos-positive engram cells displayed higher repetitive activity than cFos-negative cells during learning. Interestingly, the cFos-positive engram population was heterogeneous, integrated by sub-ensembles with different activity patterns. The sub-ensembles reactivated during sleep were more likely to be active during retrieval, implying that only specific components of the IEG engram required reactivation to consolidate episodic memory (Ghandour et al., 2019). It remains to be investigated what information is carried by the replayed sub-ensembles and how consistent their reactivation is during repeated retrieval.

Lastly, inhibitory neurons also play a crucial role in modulating sleep and information transfer between the HC and mPFC. PV inhibitory cells, promote wakefulness and REM sleep, while Som inhibitory neurons promote SWS (Xu et al., 2015). PV interneurons modulate oscillations and ripples in the HC, affecting memory expression (Ognjanovski et al., 2017). Interestingly, Som interneuron activity increases in the HC following sleep deprivation, producing impairments in contextual fear conditioning (Delorme et al., 2021). Furthermore, inhibitory interneurons in the superficial layers of mPFC synchronize during spindles, controlling hippocampal information transfer and promoting cortical consolidation (Peyrache et al., 2011). These findings underscore the diversity of cell types influencing memory consolidation during sleep and emphasize the heterogeneity within specific ensembles. Given the critical role of sleep oscillations, particularly the replay of neuronal activity in memory consolidation, further evaluations of how these processes interact with engrams would be crucial.

5. Representational drift in hippocampal and cortical representations

In this review, we present compelling evidence indicating that memories exhibit significant diversity in their composition and dynamic characteristics. These features align with the notion that memories are built upon core concepts, capturing the essence of a recollection. However, these concepts only acquire meaning when intricate details, imbuing significance to the memory, are integrated during retrieval. To illustrate this, we revisit the allegorical tale of Rabbi Besht. The servant remembers being in exile and implores the Rabbi to pray for forgiveness. However, the Rabbi struggles to recall the prayers. A crucial question arises: why do the elements that lend meaning to a recollection diminish over time? Did the memory of the Rabbi fade due to a build-up of experiences post-exile, interfering with the memory of the prayers? Alternatively, was it simply the passage of time in exile that led to forgetfulness? These pivotal questions find answers in two recent rodent studies examining drift in HC representations.

The traditional belief was that hippocampal spatial representations underlying the cognitive map remained constant over time (Thompson and Best, 1989). However, this perspective was challenged by studies demonstrating that mice exhibited different maps of the same environment upon re-exposure to the same context (Kentros et al., 2004; Muzzio et al., 2009). Subsequent landmark studies revealed the high instability of place cell ensembles in CA1, exhibiting drift over periods ranging from hours to days (Keinath et al., 2022; Mankin et al., 2012). Despite these observations, the underlying causes of this drift remained unexplored. It is crucial to highlight that the representational drift discussed in this context does not result from cells being in an active or inactive state, as previously explored in relation to the dynamic properties of ensembles (Ziv et al., 2013). Instead, it involves a shift in the activity of cells that remain persistently active over time.

Representational drift was investigated in a recent study demonstrating that ongoing experiences with a context produce gradual remapping in CA1 at the single cell and population level. This representational shift correlated with the time spent exploring and traversing an environment, rather than the passage of time, suggesting that actual experience in a context influences remapping (Khatib et al., 2023). A complementary study further disentangled the contribution of experience and time by imaging CA1 neurons over several weeks in familiar contexts. Experience with the context produced drift in the spatial map by shifting the spatial tuning of the neurons, whereas the passage of time correlated with rate changes (Geva et al., 2023). These findings raise several questions: How does episodic recall preserve the gist or index of a memory considering the continuous drift in contextual representations? How do IEG manipulations bring back memories considering the context in which they are embedded is systematically altered? One possibility is that despite the representational drift, contextual information is preserved at the population level, a possibility that was elegantly demonstrated in a recent study (Keinath et al., 2022). Another possibility is that consistent features about the spatial context are primarily encoded in CA3, an area that displays more representational stability than CA1 (Sheintuch et al., 2023), whereas dynamic experiences are encoded through representational drift in CA1.

Representational drift has also been observed in various cortical regions including visual (Roth and Merriam, 2023), olfactory (Schoonover et al., 2021), and prefrontal areas (Domanski et al., 2023; Murray et al., 2017). Akin to the HC, persistence of cortical representations was observed at the population level (Domanski et al., 2023; Murray et al., 2017; Roth and Merriam, 2023). In this context, it would be crucial to examine if IEG-engram neurons show evidence of representational drift and how it manifests.

6. Conclusion

Studying memory engrams and their underlying mechanisms is a complex and multifaceted endeavor. Advanced techniques involving time-controlled genetic labelling optogenetics, chemogenetics, and imaging approaches have significantly expanded the capacity to identify, track, and manipulate specific memory components. Nevertheless, numerous questions remain to fully comprehend the nature of memory engrams.

Firstly, it is crucial to reconsider the definition of the term "engram" to encompass all elements that facilitate recall. While Semon's groundbreaking proposal that engrams are enduring changes resulting from experience has significantly influenced memory research (Josselyn et al., 2015; Josselyn and Tonegawa, 2020; Schacter, 2001; Schacter et al., 1978), recent experimental findings indicate a need to broaden the current focus to include additional components. Prominent figures in the memory field have proposed definitions that incorporate more nuanced observations of the "perduring changes" suggested by Semon. These encompass heightened connectivity strength among engram cells in active networks, epigenetic alterations in specific neurons, changes in spines and synapses within selective circuits, and alterations in oscillatory activity within and across regions(for review see Poo et al., 2016). While it is likely that all these phenomena contribute to memory, engram definitions should also consider their functional characteritics-. In this context, Robins emphasized that understanding the explanatory role of the engram might provide a more comprehensive view of memory. According to her, "The engram explains the retention of information from particular past events" [(Robins, 2023), pg. 9]. Building on this perspective, we advocate for conceptualizations of engrams that scrutinize the specific phenomena each approach can explain and acknowledge the limitations inherent in each method or task.

Secondly, it is crucial to ascertain the content of IEG-tagged engram cells. These cells may serve as fundamental units for integrating episodic information, akin to how the alphabet functioned as a mnemonic aid for the Besht. Thus, engrams could prove indispensable for retrieving forgotten memories by providing the essence of recollections. However, just as the alphabet did not encapsulate the complete memory of the Besht's prayers, recalling intricate memories may necessitate more than just the essence of the experience. Within this framework, the concept that complete memories may arise from the amalgamation of multiple active engrams, each contributing distinct elements to a memory, is highly appealing. (Ghandour et al., 2019; Josselyn and Tonegawa, 2020; Kitamura et al., 2017; Terranova et al., 2023; Tonegawa et al., 2018). However, it remains imperative to determine the precise information carried by neurons expressing a specific IEG and understand how this information differs in active ensembles not expressing the same activity marker. For instance, McHugh and collaborators demonstrated that engram cells, constituting only a small subset of the active ensemble, lacked precise spatial information. While it is likely that these neurons encode some critical aspects of episodic events (Tanaka et al., 2018), the context in which these experiences are embedded may necessitate the activity of cells with high spatial tuning, which, in this study, did not express IEG.

Thirdly, it is vital to elucidate the mechanisms by which episodic memories transition into semantic memories. A deeper understanding of this process could offer insights into the involvement of hippocampal engrams and whether these engrams exhibit constant dynamism or stabilize over time. MTT has received experimental support (Kitamura et al., 2017; Tse et al., 2011); however, it is plausible that the brain employs multiple consolidation mechanisms contingent upon the task and circumstances. For instance, simple contextual associations might limit the time window of hippocampal engagement-, whereas more intricate episodic memories may necessitate prolonged hippocampal involvement (Winocur and Moscovitch, 2011). It will also be necessary to establish how patterns of engram activity differ when encoding episodic versus semantic components. Moreover, if semantic components evolve into a gist or schema representation, there must be some stable attributes, even if they can expand over time. This possibility raises questions about how engram representations cope with representational drift. One intriguing prospect is that the essence of a memory could be collectively encoded at the population level, while distinct attributes are encoded through the firing patterns of individual cells. This potential scenario could provide stability to the fundamental abstract components of a recollection, resisting dynamic changes and representational drift.

Fourthly, it is crucial to undertake engram studies across a spectrum of tasks, incorporating some that involve more naturalistic environments. It has been argued that simple associations may not fully capture the intricacies of human episodic recall. In a recent viewpoint, Ranganath (2022) contended that complex memories, such as holiday parties, weddings, or specific childhood recollections, exhibit a hierarchical organization that evolves over time, which is not reflected in simple associations. The core question underlying this perspective is whether understanding the neuronal substrates of these elementary forms of learning can provide insights into the processes involved in the complex phenomenon of human episodic recall. The molecular field of memory has undoubtedly gleaned significant insights through reductionist approaches relying on simple model systems and behavior (Abel and Kandel, 1998; Bank et al., 1988; Kandel, 2001; Tully et al., 1990). Similarly, the insights gained from engram research in simple tasks are likely to be fundamental in uncovering the basic mechanisms that underlie complex memories. Nevertheless, it is imperative that emerging principles are tested in more naturalistic and complex scenarios. Indeed, certain fields of animal research are already moving in that direction (Liberti et al., 2022).

In conclusion, a thorough exploration of engram diversity is indispensable. This entails considering both the inputs and outputs of all interconnected engram neurons, including both excitatory and inhibitory cell types. Additionally, examining the dynamic properties of engram ensembles across distinct brain regions and delineating variations in reactivation patterns of specific sub-ensembles during sleep can contribute to identifying the crucial elements consolidated in a memory trace. The intriguing concept that memories arise from the integration of multiple active ensembles, each contributing distinctive elements to a memory trace, holds promise within this framework (Josselyn and Tonegawa, 2020; Sun et al., 2020). It is anticipated that future conceptualizations will incorporate more diverse definitions of the cell types involved in these active ensembles. In summary, unraveling the intricacies of memory formation and consolidation requires a multidisciplinary and comprehensive approach. By systematically assembling the various components of the memory consolidation puzzle, researchers have the potential to gain valuable insights into how these processes can be harnessed for therapeutic purposes.

Declaration of Generative (AI) and AI-assisted Technologies in the Writing Process

During the preparation of this work the authors used Grammarly in order to check the grammar of sections. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Declaration of Competing Interest

The authors do not have conflicts of interest.

Data Availability

Data will be made available on request.

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References

Abel, T., Kandel, E., 1998. Positive and negative regulatory mechanisms that mediate long-term memory storage. Brain Res. Rev. 26 (2-3), 360–378. https://doi.org/10.1016/s0165-0173(97)00050-7.

Aceti, M., Vetere, G., Novembre, G., Restivo, L., Ammassari-Teule, M., 2015. Progression of activity and structural changes in the anterior cingulate cortex during remote memory formation. Neurobiol. Learn. Mem. 123, 67–71. https://doi.org/10.1016/j.nlm.2015.05.003.

Alam, M.J., Kitamura, T., Saitoh, Y., Ohkawa, N., Kondo, T., Inokuchi, K., 2018. Adult neurogenesis conserves hippocampal memory capacity. J. Neurosci. 38 (31), 6854–6863. https://doi.org/10.1523/JNEUROSCI.2976-17.2018.

Alberini, C.M., Kandel, E.R., 2014. The regulation of transcription in memory consolidation. Cold Spring Harb. Perspect. Biol. 7 (1), a021741. https://doi.org/10.1101/cshperspect.a021741.

Amaral, D.G., Witter, M.P., 1989. The three-dimensional organization of the hippocampal formation: a review of anatomical data. Neuroscience 31 (3), 571–591. https://doi.org/10.1016/0306-4522(89)90424-7.

Angulo-Garcia, D., Ferraris, M., Ghestem, A., Nallet-Khosrofian, L., Bernard, C., Quilichini, P.P., 2020. Cell assemblies in the cortico-hippocampal-reuniens network during slow oscillations. J. Neurosci. 40 (43), 8343–8354. https://doi.org/10.1523/JNEUROSCI.0571-20.2020.

Aronov, D., Nevers, R., Tank, D.W., 2017. Mapping of a non-spatial dimension by the hippocampal-entorhinal circuit. Nature 543 (7647), 719–722. https://doi.org/10.1038/nature21692.

Asok, A., Kandel, E.R., Rayman, J.B., 2019. The neurobiology of fear generalization. Front. Behav. Neurosci. 12 https://doi.org/10.3389/fnbeh.2018.00329.

Axmacher, N., Mormann, F., Fernandez, G., Elger, C.E., Fell, J., 2006. Memory formation by neuronal synchronization. Brain Res. Rev. 52 (1), 170–182. https://doi.org/10.1016/j.brainresrev.2006.01.007.

Baddeley, A., 1988. Cognitive psychology and human memory. Trends Neurosci. 11 (4), 176–181. https://doi.org/10.1016/0166-2236(88)90145-2.

Bailey, C.H., Bartsch, D., Kandel, E.R., 1996. Toward a molecular definition of long-term memory storage. Proc. Natl. Acad. Sci. USA 93 (24), 13445–13452. https://doi.org/10.1073/pnas.93.24.13445.

Bank, B., Nelson, T., Alkon, D.L., 1988. Molecular mechanisms of associative learning in mammal and mollusc. J. Physiol. 83 (3), 119–125. ⟨https://www.ncbi.nlm.nih.gov/pubmed/2483171⟩.

Bannerman, D.M., Rawlins, J.N., McHugh, S.B., Deacon, R.M., Yee, B.K., Bast, T., Zhang, W.N., Pothuizen, H.H., Feldon, J., 2004. Regional dissociations within the hippocampus–memory and anxiety. Neurosci. Biobehav. Rev. 28 (3), 273–283. https://doi.org/10.1016/j.neubiorev.2004.03.004.

Banquet, J.P., Gaussier, P., Cuperlier, N., Hok, V., Save, E., Poucet, B., Quoy, M., Wiener, S.I., 2021. Time as the fourth dimension in the hippocampus. Prog. Neurobiol. 199, 101920 https://doi.org/10.1016/j.pneurobio.2020.101920.

Barker, J.M., Taylor, J.R., Chandler, L.J., 2014. A unifying model of the role of the infralimbic cortex in extinction and habits. Learn. Mem. 21 (9), 441–448. https://doi.org/10.1101/lm.035501.114.

Basu, J., Zaremba, J.D., Cheung, S.K., Hitti, F.L., Zemelman, B.V., Losonczy, A., Siegelbaum, S.A., 2016. Gating of hippocampal activity, plasticity, and memory by entorhinal cortex long-range inhibition. Science 351 (6269), aaa5694. https://doi.org/10.1126/science.aaa5694.

Becker, S., 2017. Neurogenesis and pattern separation: time for a divorce. Wiley Inter. Rev. Cogn. Sci. 8 (3) https://doi.org/10.1002/wcs.1427.

Benson, D.F., Djenderedjian, A., Miller, B.L., Pachana, N.A., Chang, L., Itti, L., Mena, I., 1996. Neural basis of confabulation. Neurology 46 (5), 1239–1243. https://doi.org/10.1212/wnl.46.5.1239.

Bero, A.W., Meng, J., Cho, S., Shen, A.H., Canter, R.G., Ericsson, M., Tsai, L.H., 2014. Early remodeling of the neocortex upon episodic memory encoding. Proc. Natl. Acad. Sci. USA 111 (32), 11852–11857. https://doi.org/10.1073/pnas.1408378111.

Bliss, T.V., Collingridge, G.L., 1993. A synaptic model of memory: long-term potentiation in the hippocampus. Nature 361 (6407), 31–39. https://doi.org/10.1038/361031a0.

Bliss, T.V.P., Lømo, T., 1973. Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. J. Physiol. 232 (2), 331–356. https://doi.org/10.1113/jphysiol.1973.sp010273.

Blum, S., Hebert, A.E., Dash, P.K., 2006. A role for the prefrontal cortex in recall of recent and remote memories. NeuroReport: For Rapid Communication of Neuroscience Research *17*, 341–344. https://doi.org/10.1097/01.wnr.0000201509.53750.bc.

Bolsius, Y.G., Heckman, P.R.A., Paraciani, C., Wilhelm, S., Raven, F., Meijer, E.L., Kas, M.J.H., Ramirez, S., Meerlo, P., Havekes, R., 2023. Recovering object-location memories after sleep deprivation-induced amnesia. e295 Curr. Biol. 33 (2), 298–308. https://doi.org/10.1016/j.cub.2022.12.006.

Bontempi, B., Laurent-Demir, C., Destrade, C., Jaffard, R., 1999. Time-dependent reorganization of brain circuitry underlying long-term memory storage. Nature 400 (6745), 671–675. https://doi.org/10.1038/23270.

Booker, S.A., Vida, I., 2018. Morphological diversity and connectivity of hippocampal interneurons. Cell Tissue Res 373 (3), 619–641. https://doi.org/10.1007/s00441-018-2882-2.

Born, J., Wilhelm, I., 2012. System consolidation of memory during sleep. Psychol. Res. 76 (2), 192–203. https://doi.org/10.1007/s00426-011-0335-6.

Bourtchouladze, R., Abel, T., Berman, N., Gordon, R., Lapidus, K., Kandel, E.R., 1998. Different training procedures recruit either one or two critical periods for contextual memory consolidation, each of which requires protein synthesis and PKA. Learn. Mem. 5 (4-5), 365–374. ⟨https://www.ncbi.nlm.nih.gov/pubmed/10454361⟩.

Boyce, R., Glasgow, S.D., Williams, S., Adamantidis, A., 2016. Causal evidence for the role of REM sleep theta rhythm in contextual memory consolidation. Science 352 (6287), 812–816. https://doi.org/10.1126/science.aad5252.

Brodt, S., Inostroza, M., Niethard, N., Born, J., 2023. Sleep-A brain-state serving systems memory consolidation. Neuron 111 (7), 1050–1075. https://doi.org/10.1016/j.neuron.2023.03.005.

Bruce, D., 2010. Fifty years since Lashley's in search of the engram: refutations and conjectures. J. Hist. Neurosci. 10 (3), 308–318 https://doi.org/DOI: 10.1076/jhin.10.3.308.9086.

Brun, V.H., Leutgeb, S., Wu, H.Q., Schwarcz, R., Witter, M.P., Moser, E.I., Moser, M.B., 2008. Impaired spatial representation in CA1 after lesion of direct input from entorhinal cortex. Neuron 57 (2), 290–302. https://doi.org/10.1016/j.neuron.2007.11.034.

Burgess, P.W., Shallice, T., 1996. Confabulation and the control of recollection. Memory 4 (4), 359–411. https://doi.org/10.1080/096582196388906.

Burke, S.N., Chawla, M.K., Penner, M.R., Crowell, B.E., Worley, P.F., Barnes, C.A., McNaughton, B.L., 2005. Differential encoding of behavior and spatial context in deep and superficial layers of the neocortex. Neuron 45 (5), 667–674. https://doi.org/10.1016/j.neuron.2005.01.042.

Buzsaki, G., 1986. Hippocampal sharp waves: their origin and significance. Brain Res. 398, 242–252.

Buzsaki, G., 2005. Theta rhythm of navigation: link between path integration and landmark navigation, episodic and semantic memory. Hippocampus 15 (7), 827–840. https://doi.org/10.1002/hipo.20113.

Buzsaki, G., 2015. Hippocampal sharp wave-ripple: a cognitive biomarker for episodic memory and planning. Hippocampus 25, 1073–1188.

Carlén, M., 2017. What constitutes the prefrontal cortex? Science 358 (6362), 478–482. https://doi.org/10.1126/science.aan8868.

Cattaneo, A., Mainardi, M., 2022. Editorial: from whole-cell to single synapse engrams - breaking the code for memory formation, storage and recall. Front. Mol. Neurosci. 15, 845516 https://doi.org/10.3389/fnmol.2022.845516.

Cenquizca, L.A., Swanson, L.W., 2006. Analysis of direct hippocampal cortical field CA1 axonal projections to diencephalon in the rat. J. Comp. Neurol. 497 (1), 101–114. https://doi.org/10.1002/cne.20985.

Cenquizca, L.A., Swanson, L.W., 2007. Spatial organization of direct hippocampal field CA1 axonal projections to the rest of the cerebral cortex. Brain Res. Rev. 56 (1), 1–26. https://doi.org/10.1016/j.brainresrev.2007.05.002.

Chao, O.Y., de Souza Silva, M.A., Yang, Y.M., Huston, J.P., 2020. The medial prefrontal cortex - hippocampus circuit that integrates information of object, place and time to construct episodic memory in rodents: Behavioral, anatomical and neurochemical properties. Neurosci. Biobehav. Rev. 113, 373–407. https://doi.org/10.1016/j.neubiorev.2020.04.007.

Chapados, C., Petrides, M., 2015. Ventrolateral and dorsomedial frontal cortex lesions impair mnemonic context retrieval. Proc. Biol. Sci. 282 (1801), 20142555. https://doi.org/10.1098/rspb.2014.2555.

Chen, B.K., Murawski, N.J., Cincotta, C., McKissick, O., Finkelstein, A., Hamidi, A.B., Merfeld, E., Doucette, E., Grella, S.L., Shpokayte, M., Zaki, Y., Fortin, A., Ramirez, S., 2019. Artificially enhancing and suppressing hippocampus-mediated memories. e1884 Curr. Biol. 29 (11), 1885–1894. https://doi.org/10.1016/j.cub.2019.04.065.

Chen, Z.S., Wilson, M.A., 2023. How our understanding of memory replay evolves. J. Neurophysiol. 129 (3), 552–580. https://doi.org/10.1152/jn.00454.2022.

Cho, K.K.A., Shi, J., Phensy, A.J., Turner, M.L., Sohal, V.S., 2023. Long-range inhibition synchronizes and updates prefrontal task activity. Nature 617 (7961), 548–554. https://doi.org/10.1038/s41586-023-06012-9.

Colgin, L.L., Moser, E.I., Moser, M.B., 2008. Understanding memory through hippocampal remapping. Trends Neurosci. 31 (9), 469–477. https://doi.org/10.1016/j.tins.2008.06.008.

Corkin, S., 1984. Lasting consequences of bilateral medial temporal lobectomy: clinical course and experimental findings in H.M. Semin. Neurol. 4, 249–259.

Corkin, S., 2002. What's new with the amnesic patient H.M.? Nat. Rev. Neurosci. 3 (2), 153–160. https://doi.org/10.1038/nrn726.

Cummings, K.A., Clem, R.L., 2020. Prefrontal somatostatin interneurons encode fear memory. Nat. Neurosci. 23 (1), 61–74. https://doi.org/10.1038/s41593-019-0552-7.

Cummings, K.A., Bayshtok, S., Dong, T.N., Kenny, P.J., Clem, R.L., 2022. Control of fear by discrete prefrontal GABAergic populations encoding valence-specific information. e3035 Neuron 110 (18), 3036–3052. https://doi.org/10.1016/j.neuron.2022.07.004.

Danielson, N.B., Zaremba, J.D., Kaifosh, P., Bowler, J., Ladow, M., Losonczy, A., 2016. Sublayer-Specific Coding Dynamics during Spatial Navigation and Learning in Hippocampal Area CA1. Neuron 91 (3), 652–665. https://doi.org/10.1016/j.neuron.2016.06.020.

De Brigard, F., Umanath, S., Irish, M., 2022. Rethinking the distinction between episodic and semantic memory: Insights from the past, present, and future. Mem. Cogn. 50 (3), 459–463. https://doi.org/10.3758/s13421-022-01299-x.

de Lima, M.A.X., Baldo, M.V.C., Oliveira, F.A., Canteras, N.S., 2022. The anterior cingulate cortex and its role in controlling contextual fear memory to predatory threats. Elife 11. https://doi.org/10.7554/eLife.67007.

Dede, A.J., Wixted, J.T., Hopkins, R.O., Squire, L.R., 2016. Autobiographical memory, future imagining, and the medial temporal lobe. Proc. Natl. Acad. Sci. USA 113 (47), 13474–13479. https://doi.org/10.1073/pnas.1615864113.

Delorme, J., Wang, L., Kuhn, F.R., Kodoth, V., Ma, J., Martinez, J.D., Raven, F., Toth, B.A., Balendran, V., Vega Medina, A., Jiang, S., Aton, S.J., 2021. Sleep loss drives acetylcholine- and somatostatin interneuron-mediated gating of hippocampal activity to inhibit memory consolidation. Proc. Natl. Acad. Sci. USA 118 (32). https://doi.org/10.1073/pnas.2019318118.

DeNardo, L., Luo, L., 2017. Genetic strategies to access activated neurons. Curr. Opin. Neurobiol. 45, 121–129. https://doi.org/10.1016/j.conb.2017.05.014.

DeNardo, L.A., Liu, C.D., Allen, W.E., Adams, E.L., Friedmann, D., Fu, L., Guenthner, C.J., Tessier-Lavigne, M., Luo, L., 2019. Temporal evolution of cortical ensembles promoting remote memory retrieval. Nat. Neurosci. 22 (3), 460–469. https://doi.org/10.1038/s41593-018-0318-7.

Denny, C.A., Kheirbek, M.A., Alba, E.L., Tanaka, K.F., Brachman, R.A., Laughman, K.B., Tomm, N.K., Turi, G.F., Losonczy, A., Hen, R., 2014. Hippocampal memory traces are differentially modulated by experience, time, and adult neurogenesis. Neuron 83 (1), 189–201. https://doi.org/10.1016/j.neuron.2014.05.018.

Dixsaut, L., & Gräff, J. (2021). The Medial Prefrontal Cortex and Fear Memory: Dynamics, Connectivity, and Engrams. International journal of molecular sciences, 22(22), 12113. Retrieved 2021/11//, from ⟨http://europepmc.org/abstract/MED/34830009⟩.

Domanski, A.P.F., Kucewicz, M.T., Russo, E., Tricklebank, M.D., Robinson, E.S.J., Durstewitz, D., Jones, M.W., 2023. Distinct hippocampal-prefrontal neural assemblies coordinate memory encoding, maintenance, and recall. e1224 Curr. Biol. 33 (7), 1220–1236. https://doi.org/10.1016/j.cub.2023.02.029.

Do-Monte, F.H., Manzano-Nieves, G., Quiñones-Laracuente, K., Ramos-Medina, L., Quirk, G.J., 2015. Revisiting the role of infralimbic cortex in fear extinction with optogenetics. J Neurosci *35* (8), 3607–3615. https://doi.org/10.1523/jneurosci.3137-14.2015.

Dong, H.W., Swanson, L.W., Chen, L., Fanselow, M.S., Toga, A.W., 2009. Genomic-anatomic evidence for distinct functional domains in hippocampal field CA1. Proc. Natl. Acad. Sci. USA 106 (28), 11794–11799. https://doi.org/10.1073/pnas.0812608106.

Dudai, Y., Karni, A., Born, J., 2015. The consolidation and transformation of memory. Neuron 88 (1), 20–32. https://doi.org/10.1016/j.neuron.2015.09.004.

Dudok, B., Szoboszlay, M., Paul, A., Klein, P.M., Liao, Z., Hwaun, E., Szabo, G.G., Geiller, T., Vancura, B., Wang, B.S., McKenzie, S., Homidan, J., Klaver, L.M.F., English, D.F., Huang, Z.J., Buzsaki, G., Losonczy, A., Soltesz, I., 2021. Recruitment and inhibitory action of hippocampal axo-axonic cells during behavior. e3838 Neuron 109 (23), 3838–3850. https://doi.org/10.1016/j.neuron.2021.09.033.

Eichenbaum, H., 2013. Memory on time. Trends Cogn. Sci. 17 (2), 81–88. https://doi.org/10.1016/j.tics.2012.12.007.

Eichenbaum, H., 2014. Time cells in the hippocampus: a new dimension for mapping memories. Nat. Rev. Neurosci. 15 (11), 732–744. https://doi.org/10.1038/nrn3827.

Eichenbaum, H., 2017a. On the integration of space, time, and memory. Neuron 95 (5), 1007–1018. https://doi.org/10.1016/j.neuron.2017.06.036.

Eichenbaum, H., 2017b. Prefrontal-hippocampal interactions in episodic memory. Nat. Rev. Neurosci. 18 (9), 547–558. https://doi.org/10.1038/nrn.2017.74.

Euston, D.R., Gruber, A.J., McNaughton, B.L., 2012. The role of medial prefrontal cortex in memory and decision making. Neuron 76 (6), 1057–1070. https://doi.org/10.1016/j.neuron.2012.12.002.

Fanselow, M.S., Dong, H.W., 2010. Are the dorsal and ventral hippocampus functionally distinct structures? Neuron 65 (1), 7–19. https://doi.org/10.1016/j.neuron.2009.11.031.

Feld, G.B., Born, J., 2017. Sculpting memory during sleep: concurrent consolidation and forgetting. Curr Opin Neurobiol *44*, 20–27. https://doi.org/10.1016/j.conb.2017.02.012.

Ferbinteanu, J., Shapiro, M.L., 2003. Prospective and retrospective memory coding in the hippocampus. Neuron 40 (6), 1227–1239. https://doi.org/10.1016/s0896-6273(03)00752-9.

Fernandez, L.M.J., Luthi, A., 2020. Sleep spindles: mechanisms and functions. Physiol. Rev. 100 (2), 805–868. https://doi.org/10.1152/physrev.00042.2018.

Findlay, G., Tononi, G., Cirelli, C., 2020. The evolving view of replay and its functions in wake and sleep. Sleep. Adv. 1 (1), zpab002 https://doi.org/10.1093/sleepadvances/zpab002.

Flavell, S.W., Greenberg, M.E., 2008. Signaling mechanisms linking neuronal activity to gene expression and plasticity of the nervous system. Annu Rev. Neurosci. 31, 563–590. https://doi.org/10.1146/annurev.neuro.31.060407.125631.

Fleischmann, A., Hvalby, O., Jensen, V., Strekalova, T., Zacher, C., Layer, L.E., Kvello, A., Reschke, M., Spanagel, R., Sprengel, R., Wagner, E.F., Gass, P., 2003. Impaired long-term memory and NR2A-type NMDA receptor-dependent synaptic plasticity in mice lacking c-Fos in the CNS. J. Neurosci. 23 (27), 9116–9122. https://doi.org/10.1523/JNEUROSCI.23-27-09116.2003.

Forro, T., Klausberger, T., 2023. Differential behavior-related activity of distinct hippocampal interneuron types during odor-associated spatial navigation. e2395 Neuron 111 (15), 2399–2413. https://doi.org/10.1016/j.neuron.2023.05.007.

Forster, E., Zhao, S., Frotscher, M., 2006. Laminating the hippocampus. Nat. Rev. Neurosci. 7 (4), 259–267. https://doi.org/10.1038/nrn1882.

Foster, D.J., 2017. Replay comes of age. Annu Rev. Neurosci. 40, 581–602. https://doi.org/10.1146/annurev-neuro-072116-031538.

Frank, L.M., Brown, E.N., Wilson, M.A., 2001. A comparison of the firing properties of putative excitatory and inhibitory neurons from CA1 and the entorhinal cortex. J. Neurophysiol. 86 (4), 2029–2040. https://doi.org/10.1152/jn.2001.86.4.2029.

Frankland, P.W., Kohler, S., Josselyn, S.A., 2013. Hippocampal neurogenesis and forgetting. Trends Neurosci. 36 (9), 497–503. https://doi.org/10.1016/j.tins.2013.05.002.

Frankland, P.W., Bontempi, B., Talton, L.E., Kaczmarek, L., Silva, A.J., 2004. The involvement of the anterior cingulate cortex in remote contextual fear memory. Science 304 (5672), 881–883. https://doi.org/10.1126/science.1094804.

Fuster, J.M., 1990. Behavioral electrophysiology of the prefrontal cortex of the primate. Prog. Brain Res. 85, 313–323 discussion 323-314. ⟨https://www.ncbi.nlm.nih.gov/pubmed/2094902⟩.

Fuster, J.M., Alexander, G.E., 1971. Neuron activity related to short-term memory. Science 173 (3997), 652–654. https://doi.org/10.1126/science.173.3997.652.

Gabbott, P.L., Warner, T.A., Jays, P.R., Salway, P., Busby, S.J., 2005. Prefrontal cortex in the rat: projections to subcortical autonomic, motor, and limbic centers. J. Comp. Neurol. 492 (2), 145–177. https://doi.org/10.1002/cne.20738.

Garner, A.R., Rowland, D.C., Hwang, S.Y., Baumgaertel, K., Roth, B.L., Kentros, C., Mayford, M., 2012. Generation of a synthetic memory trace. Science 335 (6075), 1513–1516. https://doi.org/10.1126/science.1214985.

Gauthier, J.L., Tank, D.W., 2018. A dedicated population for reward coding in the hippocampus. e177 Neuron 99 (1), 179–193. https://doi.org/10.1016/j.neuron.2018.06.008.

Geiller, T., Vancura, B., Terada, S., Troullinou, E., Chavlis, S., Tsagkatakis, G., Tsakalides, P., Ocsai, K., Poirazi, P., Rozsa, B.J., Losonczy, A., 2020. Large-scale 3D two-photon imaging of molecularly identified CA1 interneuron dynamics in behaving mice. e969 Neuron 108 (5), 968–983. https://doi.org/10.1016/j.neuron.2020.09.013.

Geiller, T., Sadeh, S., Rolotti, S.V., Blockus, H., Vancura, B., Negrean, A., Murray, A.J., Rozsa, B., Polleux, F., Clopath, C., Losonczy, A., 2022. Local circuit amplification of spatial selectivity in the hippocampus. Nature 601 (7891), 105–109. https://doi.org/10.1038/s41586-021-04169-9.

Geva, N., Deitch, D., Rubin, A., Ziv, Y., 2023. Time and experience differentially affect distinct aspects of hippocampal representational drift. e2355 Neuron 111 (15), 2357–2366. https://doi.org/10.1016/j.neuron.2023.05.005.

Ghandour, K., Ohkawa, N., Fung, C.C.A., Asai, H., Saitoh, Y., Takekawa, T., Okubo-Suzuki, R., Soya, S., Nishizono, H., Matsuo, M., Osanai, M., Sato, M., Ohkura, M., Nakai, J., Hayashi, Y., Sakurai, T., Kitamura, T., Fukai, T., Inokuchi, K., 2019. Orchestrated ensemble activities constitute a hippocampal memory engram. Nat. Commun. 10 (1), 2637. https://doi.org/10.1038/s41467-019-10683-2.

Ghosh, V.E., Moscovitch, M., Melo Colella, B., Gilboa, A., 2014. Schema representation in patients with ventromedial PFC lesions. J. Neurosci. 34 (36), 12057–12070. https://doi.org/10.1523/JNEUROSCI.0740-14.2014.

Giorgi, C., Marinelli, S., 2021. Roles and transcriptional responses of inhibitory neurons in learning and memory. Front. Mol. Neurosci. 14, 689952 https://doi.org/10.3389/fnmol.2021.689952.

Girardeau, G., Lopes-Dos-Santos, V., 2021. Brain neural patterns and the memory function of sleep. Science 374 (6567), 560–564. https://doi.org/10.1126/science.abi8370.

Goshen, I., Brodsky, M., Prakash, R., Wallace, J., Gradinaru, V., Ramakrishnan, C., Deisseroth, K., 2011. Dynamics of retrieval strategies for remote memories. Cell 147 (3), 678–689. https://doi.org/10.1016/j.cell.2011.09.033.

Gothard, K.M., Skaggs, W.E., McNaughton, B.L., 1996. Dynamics of mismatch correction in the hippocampal ensemble code for space: interaction between path integration and environmental cues. J. Neurosci. 16 (24), 8027–8040. https://doi.org/10.1523/jneurosci.16-24-08027.1996.

Gothard, K.M., Hoffman, K.L., Battaglia, F.P., McNaughton, B.L., 2001. Dentate gyrus and ca1 ensemble activity during spatial reference frame shifts in the presence and absence of visual input. J. Neurosci. 21 (18), 7284–7292. https://doi.org/10.1523/jneurosci.21-18-07284.2001.

Greenberg, D.L., Verfaellie, M., 2010. Interdependence of episodic and semantic memory: evidence from neuropsychology. J. Int. Neuropsychol. Soc. 16 (5), 748–753. https://doi.org/10.1017/S1355617710000676.

Gu, X., Wu, Y.J., Zhang, Z., Zhu, J.J., Wu, X.R., Wang, Q., Yi, X., Lin, Z.J., Jiao, Z.H., Xu, M., Jiang, Q., Li, Y., Xu, N.J., Zhu, M.X., Wang, L.Y., Jiang, F., Xu, T.L., Li, W.G., 2022. Dynamic tripartite construct of interregional engram circuits underlies forgetting of extinction memory. Mol. Psychiatry 27 (10), 4077–4091. https://doi.org/10.1038/s41380-022-01684-7.

Guise, K.G., Shapiro, M.L., 2017. Medial prefrontal cortex reduces memory interference by modifying hippocampal encoding. e188 Neuron 94 (1), 183–192. https://doi.org/10.1016/j.neuron.2017.03.011.

Hallock, H.L., Wang, A., Griffin, A.L., 2016. Ventral midline thalamus is critical for hippocampal-prefrontal synchrony and spatial working memory. J. Neurosci. 36 (32), 8372–8389. https://doi.org/10.1523/JNEUROSCI.0991-16.2016.

Hampson, R.E., Simeral, J.D., Deadwyler, S.A., 1999. Distribution of spatial and nonspatial information in dorsal hippocampus. Nature 402 (6762), 610–614. https://doi.org/10.1038/45154.

Han, C.J., O'Tuathaigh, C.M., van Trigt, L., Quinn, J.J., Fanselow, M.S., Mongeau, R., Koch, C., Anderson, D.J., 2003. Trace but not delay fear conditioning requires attention and the anterior cingulate cortex. Proc. Natl. Acad. Sci. USA 100 (22), 13087–13092. https://doi.org/10.1073/pnas.2132313100.

Han, J.H., Kushner, S.A., Yiu, A.P., Cole, C.J., Matynia, A., Brown, R.A., Neve, R.L., Guzowski, J.F., Silva, A.J., Josselyn, S.A., 2007. Neuronal competition and selection during memory formation. Science 316 (5823), 457–460. https://doi.org/10.1126/science.1139438.

Hanslmayr, S., Axmacher, N., Inman, C.S., 2019. Modulating human memory via entrainment of brain oscillations. Trends Neurosci. 42 (7), 485–499. https://doi.org/10.1016/j.tins.2019.04.004.

Haubrich, J., Bernabo, M., Baker, A.G., Nader, K., 2020. Impairments to consolidation, reconsolidation, and long-term memory maintenance lead to memory erasure. Annu. Rev. Neurosci. 43, 297–314. https://doi.org/10.1146/annurev-neuro-091319-024636.

Hebscher, M., Gilboa, A., 2016. A boost of confidence: the role of the ventromedial prefrontal cortex in memory, decision-making, and schemas. Neuropsychologia 90, 46–58. https://doi.org/10.1016/j.neuropsychologia.2016.05.003.

Heilbronner, S.R., Rodriguez-Romaguera, J., Quirk, G.J., Groenewegen, H.J., Haber, S. N., 2016. Circuit-based corticostriatal homologies between rat and primate. Biol. Psychiatry 80 (7), 509–521. https://doi.org/10.1016/j.biopsych.2016.05.012.

Henriksen, E.J., Colgin, L.L., Barnes, C.A., Witter, M.P., Moser, M.B., Moser, E.I., 2010. Spatial representation along the proximodistal axis of CA1. Neuron 68 (1), 127–137. https://doi.org/10.1016/j.neuron.2010.08.042.

Holscher, C., Anwyl, R., Rowan, M.J., 1997. Stimulation on the positive phase of hippocampal theta rhythm induces long-term potentiation that can Be depotentiated by stimulation on the negative phase in area CA1 in vivo. J. Neurosci. 17 (16), 6470–6477. https://doi.org/10.1523/JNEUROSCI.17-16-06470.1997.

Hoover, W.B., Vertes, R.P., 2007. Anatomical analysis of afferent projections to the medial prefrontal cortex in the rat. Brain Struct. Funct. 212 (2), 149–179. https://doi.org/10.1007/s00429-007-0150-4.

Hoover, W.B., Vertes, R.P., 2012. Collateral projections from nucleus reuniens of thalamus to hippocampus and medial prefrontal cortex in the rat: a single and double retrograde fluorescent labeling study. Brain Struct. Funct. 217 (2), 191–209. https://doi.org/10.1007/s00429-011-0345-6.

Howard, M.W., Eichenbaum, H., 2013. The hippocampus, time, and memory across scales. J. Exp. Psychol. Gen. 142 (4), 1211–1230. https://doi.org/10.1037/a0033621.

Howe, M.W., Atallah, H.E., McCool, A., Gibson, D.J., Graybiel, A.M., 2011. Habit learning is associated with major shifts in frequencies of oscillatory activity and synchronized spike firing in striatum. Proc. Natl. Acad. Sci. USA 108 (40), 16801–16806. https://doi.org/10.1073/pnas.1113158108.

Huerta, P.T., Lisman, J.E., 1995. Bidirectional synaptic plasticity induced by a single burst during cholinergic theta oscillation in CA1 in vitro. Neuron 15 (5), 1053–1063. https://doi.org/10.1016/0896-6273(95)90094-2.

Hui, M., Beier, K.T., 2022. Defining the interconnectivity of the medial prefrontal cortex and ventral midbrain. Front Mol. Neurosci. 15, 971349 https://doi.org/10.3389/fnmol.2022.971349.

Huxter, J., Burgess, N., O'Keefe, J., 2003. Independent rate and temporal coding in hippocampal pyramidal cells. Nature 425 (6960), 828–832. https://doi.org/10.1038/nature02058.

Hyman, J.M., Zilli, E.A., Paley, A.M., Hasselmo, M.E., 2005. Medial prefrontal cortex cells show dynamic modulation with the hippocampal theta rhythm dependent on behavior. Hippocampus 15 (6), 739–749. https://doi.org/10.1002/hipo.20106.

Hyman, J.M., Zilli, E.A., Paley, A.M., Hasselmo, M.E., 2010. Working memory performance correlates with prefrontal-hippocampal theta interactions but not with prefrontal neuron firing rates. Front Integr. Neurosci. 4 (2) https://doi.org/10.3389/neuro.07.002.2010.

Igarashi, K.M., Ito, H.T., Moser, E.I., Moser, M.B., 2014. Functional diversity along the transverse axis of hippocampal area CA1. FEBS Lett. 588 (15), 2470–2476. https://doi.org/10.1016/j.febslet.2014.06.004.

Inda, M.C., Muravieva, E.V., Alberini, C.M., 2011. Memory retrieval and the passage of time: from reconsolidation and strengthening to extinction. J. Neurosci. 31 (5), 1635–1643. https://doi.org/10.1523/JNEUROSCI.4736-10.2011.

Inostroza, M., Born, J., 2013. Sleep for preserving and transforming episodic memory. Annu. Rev. Neurosci. 36, 79–102. https://doi.org/10.1146/annurev-neuro-062012-170429.

Ishikawa, A., Nakamura, S., 2006. Ventral hippocampal neurons project axons simultaneously to the medial prefrontal cortex and amygdala in the rat. J. Neurophysiol. 96 (4), 2134–2138. https://doi.org/10.1152/jn.00069.2006.

Ito, H.T., Zhang, S.J., Witter, M.P., Moser, E.I., Moser, M.B., 2015. A prefrontal-thalamo-hippocampal circuit for goal-directed spatial navigation. Nature 522 (7554), 50–55. https://doi.org/10.1038/nature14396.

Janowsky, J.S., Shimamura, A.P., Squire, L.R., 1989. Source memory impairment in patients with frontal lobe lesions. Neuropsychologia *27* (8), 1043–1056. https://doi.org/10.1016/0028-3932(89)90184-x.

Jay, T.M., Witter, M.P., 1991. Distribution of hippocampal CA1 and subicular efferents in the prefrontal cortex of the rat studied by means of anterograde transport of Phaseolus vulgaris-leucoagglutinin. J. Comp. Neurol. 313 (4), 574–586. https://doi.org/10.1002/cne.903130404.

Jhang, J., Lee, H., Kang, M.S., Lee, H.S., Park, H., Han, J.H., 2018. Anterior cingulate cortex and its input to the basolateral amygdala control innate fear response. Nat. Commun. 9 (1), 2744. https://doi.org/10.1038/s41467-018-05090-y.

Ji, D., Wilson, M.A., 2007. Coordinated memory replay in the visual cortex and hippocampus during sleep. Nat. Neurosci. 10 (1), 100–107. https://doi.org/10.1038/nn1825.

Jones, M.W., Wilson, M.A., 2005. Theta rhythms coordinate hippocampal-prefrontal interactions in a spatial memory task. PLoS Biol. 3 (12), e402 https://doi.org/10.1371/journal.pbio.0030402.

Josselyn, S.A., Nguyen, P.V., 2005. CREB, synapses and memory disorders: past progress and future challenges. Curr. Drug Targets CNS Neurol. Disord. 4 (5), 481–497. https://doi.org/10.2174/156800705774322058.

Josselyn, S.A., Tonegawa, S., 2020. Memory engrams: Recalling the past and imagining the future. Science 367 (6473). https://doi.org/10.1126/science.aaw4325.

Josselyn, S.A., Kohler, S., Frankland, P.W., 2015. Finding the engram. Nat. Rev. Neurosci. 16 (9), 521–534. https://doi.org/10.1038/nrn4000.

Kandel, E.R., 2001. The molecular biology of memory storage: a dialogue between genes and synapses. Science 294 (5544), 1030–1038. https://doi.org/10.1126/science.1067020.

Kapur, N., Brooks, D.J., 1999. Temporally-specific retrograde amnesia in two cases of discrete bilateral hippocampal pathology. Hippocampus 9 (3), 247–254. https://doi.org/10.1002/(sici)1098-1063(1999)9:3<247::Aid-hipo5>3.0.Co;2-w.

Keinath, A.T., Mosser, C.A., Brandon, M.P., 2022. The representation of context in mouse hippocampus is preserved despite neural drift. Nat. Commun. 13 (1), 2415. https://doi.org/10.1038/s41467-022-30198-7.

Keinath, A.T., Wang, M.E., Wann, E.G., Yuan, R.K., Dudman, J.T., Muzzio, I.A., 2014. Precise spatial coding is preserved along the longitudinal hippocampal axis. Hippocampus 24 (12), 1533–1548. https://doi.org/10.1002/hipo.22333.

Kelemen, E., Fenton, A.A., 2016. Coordinating different representations in the hippocampus. Neurobiol. Learn. Mem. 129, 50–59. https://doi.org/10.1016/j.nlm.2015.12.011.

Kempermann, G., Song, H., Gage, F.H., 2015. Neurogenesis in the Adult Hippocampus. Cold Spring Harb. Perspect. Biol. 7 (9), a018812. https://doi.org/10.1101/cshperspect.a018812.

Kennedy, P.J., Shapiro, M.L., 2009. Motivational states activate distinct hippocampal representations to guide goal-directed behaviors. Proc. Natl. Acad. Sci. USA 106 (26), 10805–10810. https://doi.org/10.1073/pnas.0903259106.

Kentros, C.G., Agnihotri, N.T., Streater, S., Hawkins, R.D., Kandel, E.R., 2004. Increased attention to spatial context increases both place field stability and spatial memory. Neuron 42 (2), 283–295. https://doi.org/10.1016/s0896-6273(04)00192-8.

Kerr, K.M., Agster, K.L., Furtak, S.C., Burwell, R.D., 2007. Functional neuroanatomy of the parahippocampal region: the lateral and medial entorhinal areas. Hippocampus 17 (9), 697–708. https://doi.org/10.1002/hipo.20315.

Kesner, R.P., Holbrook, T., 1987. Dissociation of item and order spatial memory in rats following medial prefrontal cortex lesions. Neuropsychologia 25 (4), 653–664. https://doi.org/10.1016/0028-3932(87)90056-x.

Kesner, R.P., DiMattia, B.V., Crutcher, K.A., 1987. Evidence for neocortical involvement in reference memory. Behav. Neural Biol. 47 (1), 40–53. https://doi.org/10.1016/s0163-1047(87)90145-2.

Khatib, D., Ratzon, A., Sellevoll, M., Barak, O., Morris, G., Derdikman, D., 2023. Active experience, not time, determines within-day representational drift in dorsal CA1. e2345 Neuron 111 (15), 2348–2356. https://doi.org/10.1016/j.neuron.2023.05.014.

Kim, E.J., Park, M., Kong, M.S., Park, S.G., Cho, J., Kim, J.J., 2015. Alterations of hippocampal place cells in foraging rats facing a "predatory" threat. Curr. Biol. 25 (10), 1362–1367. https://doi.org/10.1016/j.cub.2015.03.048.

Kim, J.J., Fanselow, M.S., 1992. Modality-specific retrograde amnesia of fear. Science 256 (5057), 675–677. https://doi.org/10.1126/science.1585183.

Kim, J.J., Clark, R.E., Thompson, R.F., 1995. Hippocampectomy impairs the memory of recently, but not remotely, acquired trace eyeblink conditioned responses. Behav. Neurosci. 109, 195–203. https://doi.org/10.1037/0735-7044.109.2.195.

Kitamura, T., Ogawa, S.K., Roy, D.S., Okuyama, T., Morrissey, M.D., Smith, L.M., Redondo, R.L., Tonegawa, S., 2017. Engrams and circuits crucial for systems consolidation of a memory. Science 356 (6333), 73–78. https://doi.org/10.1126/science.aam6808.

Kitamura, T., Saitoh, Y., Takashima, N., Murayama, A., Niibori, Y., Ageta, H., Sekiguchi, M., Sugiyama, H., Inokuchi, K., 2009. Adult neurogenesis modulates the hippocampus-dependent period of associative fear memory. Cell 139 (4), 814–827. https://doi.org/10.1016/j.cell.2009.10.020.

Kjelstrup, K.B., Solstad, T., Brun, V.H., Hafting, T., Leutgeb, S., Witter, M.P., Moser, E.I., Moser, M.B., 2008. Finite scale of spatial representation in the hippocampus. Science 321 (5885), 140–143. https://doi.org/10.1126/science.1157086.

Klausberger, T., Somogyi, P., 2008. Neuronal diversity and temporal dynamics: the unity of hippocampal circuit operations. Science 321 (5885), 53–57. https://doi.org/10.1126/science.1149381.

Klinzing, J.G., Niethard, N., Born, J., 2019. Mechanisms of systems memory consolidation during sleep. Nat. Neurosci. 22 (10), 1598–1610. https://doi.org/10.1038/s41593-019-0467-3.

Klüver, H., Bucy, P.C., 1938. An analysis of certain effects of bilateral temporal lobectomy in the rhesus monkey, with special reference to “psychic blindness. J. Psychol. 5 (1), 33–54. https://doi.org/10.1080/00223980.1938.9917551.

Kol, A., Adamsky, A., Groysman, M., Kreisel, T., London, M., Goshen, I., 2020. Astrocytes contribute to remote memory formation by modulating hippocampal-cortical communication during learning. Nat. Neurosci. 23 (10), 1229–1239. https://doi.org/10.1038/s41593-020-0679-6.

Koya, E., Golden, S.A., Harvey, B.K., Guez-Barber, D.H., Berkow, A., Simmons, D.E., Bossert, J.M., Nair, S.G., Uejima, J.L., Marin, M.T., Mitchell, T.B., Farquhar, D., Ghosh, S.C., Mattson, B.J., Hope, B.T., 2009. Targeted disruption of cocaine-activated nucleus accumbens neurons prevents context-specific sensitization. Nat. Neurosci. 12 (8), 1069–1073. https://doi.org/10.1038/nn.2364.

Kroes, M.C., Fernández, G., 2012. Dynamic neural systems enable adaptive, flexible memories. Neurosci. Biobehav Rev. 36 (7), 1646–1666. https://doi.org/10.1016/j.neubiorev.2012.02.014.

Kubik, S., Miyashita, T., Guzowski, J.F., 2007. Using immediate-early genes to map hippocampal subregional functions. Learn Mem. 14 (11), 758–770. https://doi.org/10.1101/lm.698107.

Lacagnina, A.F., Brockway, E.T., Crovetti, C.R., Shue, F., McCarty, M.J., Sattler, K.P., Lim, S.C., Santos, S.L., Denny, C.A., Drew, M.R., 2019. Distinct hippocampal engrams control extinction and relapse of fear memory. Nat. Neurosci. 22 (5), 753–761. https://doi.org/10.1038/s41593-019-0361-z.

Lashley, K.S., 1931. Mass action in cerebral function. Science 73 (1888), 245–254. https://doi.org/10.1126/science.73.1888.245.

Lashley, K.S., 1950. In search of the engram. *Physiological mechanisms in animal behavior. (Society's Symposium IV.)*. Academic Press, pp. 454–482.

Laubach, M., Amarante, L.M., Swanson, K., White, S.R., 2018. What, if anything, is rodent prefrontal cortex? eNeuro 5 (5). https://doi.org/10.1523/ENEURO.0315-18.2018.

Laurent, V., Westbrook, R.F., 2009. Inactivation of the infralimbic but not the prelimbic cortex impairs consolidation and retrieval of fear extinction. Learn. Mem. 16, 520–529. https://doi.org/10.1101/lm.1474609.

Leao, R.N., Mikulovic, S., Leao, K.E., Munguba, H., Gezelius, H., Enjin, A., Patra, K., Eriksson, A., Loew, L.M., Tort, A.B., Kullander, K., 2012. OLM interneurons differentially modulate CA3 and entorhinal inputs to hippocampal CA1 neurons. Nat. Neurosci. 15 (11), 1524–1530. https://doi.org/10.1038/nn.3235.

Lee, A.K., Wilson, M.A., 2002. Memory of sequential experience in the hippocampus during slow wave sleep. Neuron 36 (6), 1183–1194. https://doi.org/10.1016/s0896-6273(02)01096-6.

Lee, J.-H., Kim, W.B., Park, E.H., Cho, J.-H., 2023. Neocortical synaptic engrams for remote contextual memories. Nat. Neurosci. 26 (2), 259–273. https://doi.org/10.1038/s41593-022-01223-1.

Lee, J.L.C., Nader, K., Schiller, D., 2017. An update on memory reconsolidation updating. Trends Cogn. Sci. 21 (7), 531–545. https://doi.org/10.1016/j.tics.2017.04.006.

Lesburguères, E., Gobbo, O.L., Alaux-Cantin, S., Hambucken, A., Trifilieff, P., Bontempi, B., 2011. Early tagging of cortical networks is required for the formation of enduring associative memory. Science 331 (6019), 924–928. https://doi.org/10.1126/science.1196164.

Leutgeb, S., Leutgeb, J.K., 2007. Pattern separation, pattern completion, and new neuronal codes within a continuous CA3 map. Learn Mem. 14 (11), 745–757. https://doi.org/10.1101/lm.703907.

Leutgeb, S., Leutgeb, J.K., Moser, E.I., Moser, M.B., 2006. Fast rate coding in hippocampal CA3 cell ensembles. Hippocampus 16 (9), 765–774. https://doi.org/10.1002/hipo.20201.

Liberti, W.A., 3rd, Schmid, T.A., Forli, A., Snyder, M., Yartsev, M.M., 2022. A stable hippocampal code in freely flying bats. Nature 604 (7904), 98–103. https://doi.org/10.1038/s41586-022-04560-0.

Lisman, J., Cooper, K., Sehgal, M., Silva, A.J., 2018. Memory formation depends on both synapse-specific modifications of synaptic strength and cell-specific increases in excitability. Nat. Neurosci. 21 (3), 309–314. https://doi.org/10.1038/s41593-018-0076-6.

Liu, X., Ramirez, S., Pang, P.T., Puryear, C.B., Govindarajan, A., Deisseroth, K., Tonegawa, S., 2012. Optogenetic stimulation of a hippocampal engram activates fear memory recall. Nature 484 (7394), 381–385. https://doi.org/10.1038/nature11028.

Louie, K., Wilson, M.A., 2001. Temporally structured replay of awake hippocampal ensemble activity during rapid eye movement sleep. Neuron 29 (1), 145–156. https://doi.org/10.1016/s0896-6273(01)00186-6.

Lourenco, J., De Stasi, A.M., Deleuze, C., Bigot, M., Pazienti, A., Aguirre, A., Giugliano, M., Ostojic, S., Bacci, A., 2020. Modulation of Coordinated Activity across Cortical Layers by Plasticity of Inhibitory Synapses. e635 Cell Rep. 30 (3), 630–641. https://doi.org/10.1016/j.celrep.2019.12.052.

Lovett-Barron, M., Kaifosh, P., Kheirbek, M.A., Danielson, N., Zaremba, J.D., Reardon, T. R., Turi, G.F., Hen, R., Zemelman, B.V., Losonczy, A., 2014. Dendritic inhibition in the hippocampus supports fear learning. Science 343 (6173), 857–863. https://doi.org/10.1126/science.1247485.

Maccaferri, G., McBain, C.J., 1995. Passive propagation of LTD to stratum oriens-alveus inhibitory neurons modulates the temporoammonic input to the hippocampal CA1 region. Neuron 15 (1), 137–145. https://doi.org/10.1016/0896-6273(95)90071-3.

MacDonald, C.J., Lepage, K.Q., Eden, U.T., Eichenbaum, H., 2011. Hippocampal "time cells" bridge the gap in memory for discontiguous events. Neuron 71 (4), 737–749. https://doi.org/10.1016/j.neuron.2011.07.012.

Majak, K., Pitkänen, A., 2003. Projections from the periamygdaloid cortex to the amygdaloid complex, the hippocampal formation, and the parahippocampal region: a PHA-L study in the rat. Hippocampus 13 (8), 922–942. https://doi.org/10.1002/hipo.10134.

Mangels, J.A., Gershberg, F.B., Shimamura, A.P., Knight, R.T., 1996. Impaired retrieval from remote memory in patients with frontal lobe damage. Neropsychology *10* (1), 32–41.

Mankin, E.A., Sparks, F.T., Slayyeh, B., Sutherland, R.J., Leutgeb, S., Leutgeb, J.K., 2012. Neuronal code for extended time in the hippocampus. Proc. Natl. Acad. Sci. USA 109 (47), 19462–19467. https://doi.org/10.1073/pnas.1214107109.

Manns, J.R., Hopkins, R.O., Squire, L.R., 2003. Semantic memory and the human hippocampus. Neuron 38 (1), 127–133. https://doi.org/10.1016/s0896-6273(03)00146-6.

Marek, R., Jin, J., Goode, T.D., Giustino, T.F., Wang, Q., Acca, G.M., Holehonnur, R., Ploski, J.E., Fitzgerald, P.J., Lynagh, T., Lynch, J.W., Maren, S., Sah, P., 2018. Hippocampus-driven feed-forward inhibition of the prefrontal cortex mediates relapse of extinguished fear. Nat. Neurosci. 21 (3), 384–392. https://doi.org/10.1038/s41593-018-0073-9.

Markus, E., Qin, Y., Leonard, B., Skaggs, W., McNaughton, B., Barnes, C., 1995. Interactions between location and task affect the spatial and directional firing of hippocampal neurons. J. Neurosci. 15 (11), 7079–7094. https://doi.org/10.1523/jneurosci.15-11-07079.1995.

Marr, D., 1971. Simple memory: a theory for archicortex. Philos. Trans. R. Soc. Lond. B Biol. Sci. 262 (841), 23–81. https://doi.org/10.1098/rstb.1971.0078.

Masurkar, A.V., Srinivas, K.V., Brann, D.H., Warren, R., Lowes, D.C., Siegelbaum, S.A., 2017. Medial and Lateral Entorhinal Cortex Differentially Excite Deep versus Superficial CA1 Pyramidal Neurons. Cell Rep. 18 (1), 148–160. https://doi.org/10.1016/j.celrep.2016.12.012.

Matos, M.R., Visser, E., Kramvis, I., van der Loo, R.J., Gebuis, T., Zalm, R., Rao-Ruiz, P., Mansvelder, H.D., Smit, A.B., van den Oever, M.C., 2019. Memory strength gates the involvement of a CREB-dependent cortical fear engram in remote memory. Nat. Commun. 10 (1), 2315. https://doi.org/10.1038/s41467-019-10266-1.

Mau, W., Hasselmo, M.E., Cai, D.J., 2020. The brain in motion: How ensemble fluidity drives memory-updating and flexibility. Elife 9. https://doi.org/10.7554/eLife.63550.

Maviel, T., Durkin, T.P., Menzaghi, F., Bontempi, B., 2004. Sites of neocortical reorganization critical for remote spatial memory. Science 305 (5680), 96–99. https://doi.org/10.1126/science.1098180.

Mazo, C., Nissant, A., Saha, S., Peroni, E., Lledo, P.M., Lepousez, G., 2022. Long-range GABAergic projections contribute to cortical feedback control of sensory processing. Nat. Commun. 13 (1), 6879. https://doi.org/10.1038/s41467-022-34513-0.

McClelland, J.L., 2013. Incorporating rapid neocortical learning of new schema-consistent information into complementary learning systems theory. J. Exp. Psychol. Gen. 142 (4), 1190–1210. https://doi.org/10.1037/a0033812.

McClelland, J.L., McNaughton, B.L., O'Reilly, R.C., 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 (3), 419–457. https://doi.org/10.1037/0033-295x.102.3.419.

McKenzie, S., Eichenbaum, H., 2011. Consolidation and reconsolidation: two lives of memories? Neuron 71 (2), 224–233. https://doi.org/10.1016/j.neuron.2011.06.037.

McNaughton, B.L., Nadel, L., 1990. Hebb-Marr networks and the neurobiological representation of action in space. In *Neuroscience and connectionist theory*. Lawrence Erlbaum Associates, Inc, pp. 1–63.

Milner, B., 2005. The medial temporal-lobe amnesic syndrome, 609 Psychiatr. Clin. North Am. 28 (3), 599–611. https://doi.org/10.1016/j.psc.2005.06.002.

Misanin, J.R., Miller, R.R., Lewis, D.J., 1968. Retrograde amnesia produced by electroconvulsive shock after reactivation of a consolidated memory trace. Science 160 (3827), 554–555. https://doi.org/10.1126/science.160.3827.554.

Moita, M.A., Rosis, S., Zhou, Y., LeDoux, J.E., Blair, H.T., 2003. Hippocampal place cells acquire location-specific responses to the conditioned stimulus during auditory fear conditioning. Neuron 37 (3), 485–497. https://doi.org/10.1016/s0896-6273(03)00033-3.

Moita, M.A., Rosis, S., Zhou, Y., LeDoux, J.E., Blair, H.T., 2004. Putting Fear in Its Place: Remapping of Hippocampal Place Cells during Fear Conditioning. J. Neurosci. 24 (31), 7015–7023. https://doi.org/10.1523/jneurosci.5492-03.2004.

Morici, J.F., Weisstaub, N.V., Zold, C.L., 2022. Hippocampal-medial prefrontal cortex network dynamics predict performance during retrieval in a context-guided object memory task. Proc. Natl. Acad. Sci. USA 119 (20), e2203024119. https://doi.org/10.1073/pnas.2203024119.

Morris, R.G., 2013. NMDA receptors and memory encoding. Neuropharmacology 74, 32–40. https://doi.org/10.1016/j.neuropharm.2013.04.014.

Moscovitch, M., Melo, B., 1997. Strategic retrieval and the frontal lobes: evidence from confabulation and amnesia. Neuropsychologia 35 (7), 1017–1034. https://doi.org/10.1016/s0028-3932(97)00028-6.

Muller, R.U., Kubie, J.L., 1987. The effects of changes in the environment on the spatial firing of hippocampal complex-spike cells. J. Neurosci. 7 (7), 1951–1968. https://doi.org/10.1523/JNEUROSCI.07-07-01951.1987.

Murray, J.D., Bernacchia, A., Roy, N.A., Constantinidis, C., Romo, R., Wang, X.J., 2017. Stable population coding for working memory coexists with heterogeneous neural dynamics in prefrontal cortex. Proc. Natl. Acad. Sci. USA 114 (2), 394–399. https://doi.org/10.1073/pnas.1619449114.

Muzzio, I.A., Levita, L., Kulkarni, J., Monaco, J., Kentros, C., Stead, M., Abbott, L.F., Kandel, E.R., 2009. Attention enhances the retrieval and stability of visuospatial and olfactory representations in the dorsal hippocampus. PLoS Biol. 7 (6), e1000140 https://doi.org/10.1371/journal.pbio.1000140.

Myers-Schulz, B., Koenigs, M., 2012. Functional anatomy of ventromedial prefrontal cortex: implications for mood and anxiety disorders. Mol. Psychiatry 17 (2), 132–141. https://doi.org/10.1038/mp.2011.88.

Myroshnychenko, M., Seamans, J.K., Phillips, A.G., Lapish, C.C., 2017. Temporal dynamics of hippocampal and medial prefrontal cortex interactions during the delay period of a working memory-guided foraging task. Cereb. Cortex 27 (11), 5331–5342. https://doi.org/10.1093/cercor/bhx184.

Nadel, L., Moscovitch, M., 1997. Memory consolidation, retrograde amnesia and the hippocampal complex. Curr. Opin. Neurobiol. 7 (2), 217–227. https://doi.org/10.1016/s0959-4388(97)80010-4.

Nadel, L., Samsonovich, A., Ryan, L., Moscovitch, M., 2000. Multiple trace theory of human memory: computational, neuroimaging, and neuropsychological results. Hippocampus 10 (4), 352–368. https://doi.org/10.1002/1098-1063(2000)10:4<352::Aid-hipo2>3.0.Co;2-d.

Nader, K., 2015. Reconsolidation and the dynamic nature of memory. Cold Spring Harb. Perspect. Biol. 7 (10), a021782. https://doi.org/10.1101/cshperspect.a021782.

Nader, K., Schafe, G.E., Le Doux, J.E., 2000. Fear memories require protein synthesis in the amygdala for reconsolidation after retrieval. Nature 406 (6797), 722–726. https://doi.org/10.1038/35021052.

Nakazawa, Y., Pevzner, A., Tanaka, K.Z., Wiltgen, B.J., 2016. Memory retrieval along the proximodistal axis of CA1. Hippocampus 26 (9), 1140–1148. https://doi.org/10.1002/hipo.22596.

Ng, C.W., Elias, G.A., Asem, J.S.A., Allen, T.A., Fortin, N.J., 2018. Nonspatial sequence coding varies along the CA1 transverse axis. Behav. Brain Res 354, 39–47. https://doi.org/10.1016/j.bbr.2017.10.015.

O''Keefe, J. a N., L.. (1978). *The hippocampus as a cognitive map*. Oxford University Press.

Ognjanovski, N., Schaeffer, S., Wu, J., Mofakham, S., Maruyama, D., Zochowski, M., Aton, S.J., 2017. Parvalbumin-expressing interneurons coordinate hippocampal network dynamics required for memory consolidation. Nat. Commun. 8, 15039 https://doi.org/10.1038/ncomms15039.

Ohara, S., Rannap, M., Tsutsui, K.I., Draguhn, A., Egorov, A.V., Witter, M.P., 2023. Hippocampal-medial entorhinal circuit is differently organized along the dorsoventral axis in rodents. Cell Rep. 42 (1), 112001 https://doi.org/10.1016/j.celrep.2023.112001.

O'Keefe, J., Dostrovsky, J., 1971. The hippocampus as a spatial map. Preliminary evidence from unit activity in the freely-moving rat. Brain Res 34 (1), 171–175. https://doi.org/10.1016/0006-8993(71)90358-1.

O'Neill, P.K., Gordon, J.A., Sigurdsson, T., 2013. Theta oscillations in the medial prefrontal cortex are modulated by spatial working memory and synchronize with the hippocampus through its ventral subregion. J. Neurosci. 33 (35), 14211–14224. https://doi.org/10.1523/JNEUROSCI.2378-13.2013.

Ortega-de San Luis, C., Ryan, T.J., 2022. Understanding the physical basis of memory: molecular mechanisms of the engram. J. Biol. Chem. 298 (5), 101866 https://doi.org/10.1016/j.jbc.2022.101866.

Park, S., Kramer, E.E., Mercaldo, V., Rashid, A.J., Insel, N., Frankland, P.W., Josselyn, S. A., 2016. Neuronal allocation to a hippocampal engram. Neuropsychopharmacology 41 (13), 2987–2993. https://doi.org/10.1038/npp.2016.73.

Pastalkova, E., Itskov, V., Amarasingham, A., Buzsaki, G., 2008. Internally generated cell assembly sequences in the rat hippocampus. Science 321 (5894), 1322–1327. https://doi.org/10.1126/science.1159775.

Pavlides, C., Greenstein, Y.J., Grudman, M., Winson, J., 1988. Long-term potentiation in the dentate gyrus is induced preferentially on the positive phase of theta-rhythm. Brain Res. 439 (1-2), 383–387. https://doi.org/10.1016/0006-8993(88)91499-0.

Paw Min Thein, O., Sakimoto, Y., Kida, H., Mitsushima, D., 2020. Proximodistal Heterogeneity in Learning-promoted Pathway-specific Plasticity at Dorsal CA1 Synapses. Neuroscience 437, 184–195. https://doi.org/10.1016/j.neuroscience.2020.04.040.

Peak, J., Chieng, B., Hart, G., Balleine, B.W., 2020. Striatal direct and indirect pathway neurons differentially control the encoding and updating of goal-directed learning. Elife 9, e58544. https://doi.org/10.7554/eLife.58544.

Pelkey, K.A., Chittajallu, R., Craig, M.T., Tricoire, L., Wester, J.C., McBain, C.J., 2017. Hippocampal GABAergic inhibitory interneurons. Physiol. Rev. 97 (4), 1619–1747. https://doi.org/10.1152/physrev.00007.2017.

Penfield, W., Milner, B., 1958. Memory deficit produced by bilateral lesions in the hippocampal zone. AMA Arch. Neurol. Psychiatry 79 (5), 475–497. https://doi.org/10.1001/archneurpsyc.1958.02340050003001.

Perusini, J.N., Cajigas, S.A., Cohensedgh, O., Lim, S.C., Pavlova, I.P., Donaldson, Z.R., Denny, C.A., 2017. Optogenetic stimulation of dentate gyrus engrams restores memory in Alzheimer's disease mice. Hippocampus 27 (10), 1110–1122. https://doi.org/10.1002/hipo.22756.

Petrovich, G.D., Canteras, N.S., Swanson, L.W., 2001. Combinatorial amygdalar inputs to hippocampal domains and hypothalamic behavior systems. Brain Res. Rev. 38 (1-2), 247–289. https://doi.org/10.1016/s0165-0173(01)00080-7.

Pettit, N.L., Yap, E.L., Greenberg, M.E., Harvey, C.D., 2022. Fos ensembles encode and shape stable spatial maps in the hippocampus. Nature 609 (7926), 327–334. https://doi.org/10.1038/s41586-022-05113-1.

Peyrache, A., 2022. Querying hippocampal replay with subcortical inputs. Curr. Opin. Neurobiol. 77, 102645 https://doi.org/10.1016/j.conb.2022.102645.

Peyrache, A., Battaglia, F.P., Destexhe, A., 2011. Inhibition recruitment in prefrontal cortex during sleep spindles and gating of hippocampal inputs. Proc. Natl. Acad. Sci. USA 108 (41), 17207–17212. https://doi.org/10.1073/pnas.1103612108.

Peyrache, A., Khamassi, M., Benchenane, K., Wiener, S.I., Battaglia, F.P., 2009. Replay of rule-learning related neural patterns in the prefrontal cortex during sleep. Nat. Neurosci. 12 (7), 919–926. https://doi.org/10.1038/nn.2337.

Pfeiffer, B.E., 2020. The content of hippocampal "replay. Hippocampus 30 (1), 6–18. https://doi.org/10.1002/hipo.22824.

Poe, G.R., 2017. Sleep is for forgetting. J. Neurosci. 37 (3), 464–473. https://doi.org/10.1523/JNEUROSCI.0820-16.2017.

Poe, G.R., Nitz, D.A., McNaughton, B.L., Barnes, C.A., 2000. Experience-dependent phase-reversal of hippocampal neuron firing during REM sleep. Brain Res 855 (1), 176–180. https://doi.org/10.1016/s0006-8993(99)02310-0.

Poo, M.M., Pignatelli, M., Ryan, T.J., Tonegawa, S., Bonhoeffer, T., Martin, K.C., Rudenko, A., Tsai, L.H., Tsien, R.W., Fishell, G., Mullins, C., Goncalves, J.T., Shtrahman, M., Johnston, S.T., Gage, F.H., Dan, Y., Long, J., Buzsaki, G., Stevens, C., 2016. What is memory? The present state of the engram. BMC Biol. 14, 40. https://doi.org/10.1186/s12915-016-0261-6.

Preston, A.R., Eichenbaum, H., 2013. Interplay of hippocampus and prefrontal cortex in memory. Curr. Biol. 23 (17), R764–R773. https://doi.org/10.1016/j.cub.2013.05.041.

Przybyslawski, J., Sara, S.J., 1997. Reconsolidation of memory after its reactivation. Behav. Brain Res 84 (1-2), 241–246. https://doi.org/10.1016/s0166-4328(96)00153-2.

Przybyslawski, J., Roullet, P., Sara, S.J., 1999. Attenuation of emotional and nonemotional memories after their reactivation: role of beta adrenergic receptors. J. Neurosci. 19 (15), 6623–6628. https://doi.org/10.1523/JNEUROSCI.19-15-06623.1999.

Quirk, G.J., Beer, J.S., 2006. Prefrontal involvement in the regulation of emotion: convergence of rat and human studies. Curr. Opin. Neurobiol. 16 (6), 723–727. https://doi.org/10.1016/j.conb.2006.07.004.

Quirk, G.J., Mueller, D., 2008. Neural mechanisms of extinction learning and retrieval. Neuropsychopharmacology 33 (1), 56–72. https://doi.org/10.1038/sj.npp.1301555.

Ramanathan, K.R., Maren, S., 2019. Nucleus reuniens mediates the extinction of contextual fear conditioning. Behav. Brain Res 374, 112114. https://doi.org/10.1016/j.bbr.2019.112114.

Ramanathan, K.R., Ressler, R.L., Jin, J., Maren, S., 2018. Nucleus reuniens is required for encoding and retrieving precise, hippocampal-dependent contextual fear memories in rats. J. Neurosci. 38 (46), 9925–9933. https://doi.org/10.1523/JNEUROSCI.1429-18.2018.

Ramanathan, K.R., Jin, J., Giustino, T.F., Payne, M.R., Maren, S., 2018. Prefrontal projections to the thalamic nucleus reuniens mediate fear extinction. Nat. Commun. 9 (1), 4527. https://doi.org/10.1038/s41467-018-06970-z.

Ramirez, S., Liu, X., Lin, P.A., Suh, J., Pignatelli, M., Redondo, R.L., Ryan, T.J., Tonegawa, S., 2013. Creating a false memory in the hippocampus. Science 341 (6144), 387–391. https://doi.org/10.1126/science.1239073.

Ranganath, C., 2022. What is episodic memory and how do we use it? Trends Cogn. Sci. 26 (12), 1059–1061. https://doi.org/10.1016/j.tics.2022.09.023.

Redondo, R.L., Kim, J., Arons, A.L., Ramirez, S., Liu, X., Tonegawa, S., 2014. Bidirectional switch of the valence associated with a hippocampal contextual memory engram. Nature 513 (7518), 426–430. https://doi.org/10.1038/nature13725.

Reijmers, L.G., Perkins, B.L., Matsuo, N., Mayford, M., 2007. Localization of a stable neural correlate of associative memory. Science 317 (5842), 1230–1233. https://doi.org/10.1126/science.1143839.

Restivo, L., Vetere, G., Bontempi, B., Ammassari-Teule, M., 2009. The formation of recent and remote memory is associated with time-dependent formation of dendritic spines in the hippocampus and anterior cingulate cortex. J. Neurosci. 29 (25), 8206–8214. https://doi.org/10.1523/jneurosci.0966-09.2009.

Robins, S., 2023. The 21st century engram. Wiley Inter. Rev. Cogn. Sci. 14 (5), e1653 https://doi.org/10.1002/wcs.1653.

Rock, C., Apicella, A.J., 2015. Callosal projections drive neuronal-specific responses in the mouse auditory cortex. J. Neurosci. 35 (17), 6703–6713. https://doi.org/10.1523/JNEUROSCI.5049-14.2015.

Rock, C., Zurita, H., Wilson, C., Apicella, A.J., 2016. An inhibitory corticostriatal pathway. Elife 5. https://doi.org/10.7554/eLife.15890.

Rock, C., Zurita, H., Lebby, S., Wilson, C.J., Apicella, A.J., 2018. Cortical circuits of callosal GABAergic neurons. Cereb. Cortex 28 (4), 1154–1167. https://doi.org/10.1093/cercor/bhx025.

Rogerson, T., Cai, D.J., Frank, A., Sano, Y., Shobe, J., Lopez-Aranda, M.F., Silva, A.J., 2014. Synaptic tagging during memory allocation. Nat. Rev. Neurosci. 15 (3), 157–169. https://doi.org/10.1038/nrn3667.

Roth, Z.N., Merriam, E.P., 2023. Representations in human primary visual cortex drift over time. Nat. Commun. 14 (1), 4422. https://doi.org/10.1038/s41467-023-40144-w.

Roullet, P., Sara, S., 1998. Consolidation of memory after its reactivation: involvement of beta noradrenergic receptors in the late phase. Neural Plast. 6 (3), 63–68. https://doi.org/10.1155/NP.1998.63.

Roy, D.S., Arons, A., Mitchell, T.I., Pignatelli, M., Ryan, T.J., Tonegawa, S., 2016. Memory retrieval by activating engram cells in mouse models of early Alzheimer's disease. Nature 531 (7595), 508–512. https://doi.org/10.1038/nature17172.

Roy, D.S., Park, Y.G., Kim, M.E., Zhang, Y., Ogawa, S.K., DiNapoli, N., Gu, X., Cho, J.H., Choi, H., Kamentsky, L., Martin, J., Mosto, O., Aida, T., Chung, K., Tonegawa, S., 2022. Brain-wide mapping reveals that engrams for a single memory are distributed across multiple brain regions. Nat. Commun. 13 (1), 1799. https://doi.org/10.1038/s41467-022-29384-4.

Royer, S., Sirota, A., Patel, J., Buzsaki, G., 2010. Distinct representations and theta dynamics in dorsal and ventral hippocampus. J. Neurosci. 30 (5), 1777–1787. https://doi.org/10.1523/JNEUROSCI.4681-09.2010.

Ryan, T.J., Frankland, P.W., 2022. Forgetting as a form of adaptive engram cell plasticity. Nat. Rev. Neurosci. 23 (3), 173–186. https://doi.org/10.1038/s41583-021-00548-3.

Ryan, T.J., Roy, D.S., Pignatelli, M., Arons, A., Tonegawa, S., 2015. Memory. Engram cells retain memory under retrograde amnesia. Science 348 (6238), 1007–1013. https://doi.org/10.1126/science.aaa5542.

Sakaguchi, M., Hayashi, Y., 2012. Catching the engram: strategies to examine the memory trace. Mol. Brain 5, 32. https://doi.org/10.1186/1756-6606-5-32.

Salz, D.M., Tiganj, Z., Khasnabish, S., Kohley, A., Sheehan, D., Howard, M.W., Eichenbaum, H., 2016. Time Cells in Hippocampal Area CA3. J. Neurosci. 36 (28), 7476–7484. https://doi.org/10.1523/JNEUROSCI.0087-16.2016.

Santos-Anderson, R.M., Routtenberg, A., 1976. Stimulation of rat medial or sulcal prefrontal cortex during passive avoidance learning selectively influences retention performance. Brain Res. 103 (2), 243–259. https://doi.org/10.1016/0006-8993(76)90797-6.

Sara, S.J., 2000. Retrieval and reconsolidation: toward a neurobiology of remembering. Learn Mem. 7 (2), 73–84. https://doi.org/10.1101/lm.7.2.73.

Schacter, D.L., 2001. Forgotten Ideas, Neglected Pioneers: Richard Semon and the Story of memory. Psychology Press.

Schacter, D.L., Tulving, E. (Eds.), 1994. Memory Systems 1994. The MIT Press. https://doi.org/10.7551/mitpress/4545.001.0001.

Schacter, D.L., Eich, J.E., Tulving, E., 1978. Richard Semon's theory of memory. J. Verbal Learn. Verbal Behav. 17, 721–743. https://doi.org/10.1016/S0022-5371(78)90443-7.

Schafe, G.E., LeDoux, J.E., 2000. Memory consolidation of auditory pavlovian fear conditioning requires protein synthesis and protein kinase A in the amygdala. J. Neurosci. 20 (18), RC96. https://doi.org/10.1523/JNEUROSCI.20-18-j0003.2000.

Schapiro, A.C., Turk-Browne, N.B., Botvinick, M.M., Norman, K.A., 2017. Complementary learning systems within the hippocampus: a neural network modelling approach to reconciling episodic memory with statistical learning. Philos Trans R Soc Lond B Biol Sci *372* (1711). https://doi.org/10.1098/rstb.2016.0049.

Schiller, D., 2022. Reconsolidation: a paradigm shift. Brain Res Bull. 189, 184–186. https://doi.org/10.1016/j.brainresbull.2022.09.008.

Schlichting, M.L., Zeithamova, D., Preston, A.R., 2014. CA1 subfield contributions to memory integration and inference. Hippocampus 24 (10), 1248–1260. https://doi.org/10.1002/hipo.22310.

Schneider, A.M., Sherman, W., 1968. Amnesia: a function of the temporal relation of footshock to electroconvulsive shock. Science 159 (3811), 219–221. https://doi.org/10.1126/science.159.3811.219.

Schoch, H., Abel, T., 2014. Transcriptional co-repressors and memory storage. Neuropharmacology 80, 53–60. https://doi.org/10.1016/j.neuropharm.2014.01.003.

Schoonover, C.E., Ohashi, S.N., Axel, R., Fink, A.J.P., 2021. Representational drift in primary olfactory cortex. Nature 594 (7864), 541–546. https://doi.org/10.1038/s41586-021-03628-7.

Scoville, W.B., Milner, B., 1957. Loss of recent memory after bilateral hippocampal lesions. J. Neurol., Neurosurg. Psychiatry 20, 11–21. https://doi.org/10.1136/jnnp.20.1.11.

Semon, R.W. (1923). Mnemic psychology (B. Duffy, Trans.). Allen and Unwin.

Sheintuch, L., Geva, N., Deitch, D., Rubin, A., Ziv, Y., 2023. Organization of hippocampal CA3 into correlated cell assemblies supports a stable spatial code. Cell Rep. 42 (2), 112119 https://doi.org/10.1016/j.celrep.2023.112119.

Shpokayte, M., McKissick, O., Guan, X., Yuan, B., Rahsepar, B., Fernandez, F.R., Ruesch, E., Grella, S.L., White, J.A., Liu, X.S., Ramirez, S., 2022. Hippocampal cells segregate positive and negative engrams. Commun. Biol. 5 (1), 1009. https://doi.org/10.1038/s42003-022-03906-8.

Siapas, A.G., Wilson, M.A., 1998. Coordinated interactions between hippocampal ripples and cortical spindles during slow-wave sleep. Neuron 21 (5), 1123–1128. https://doi.org/10.1016/s0896-6273(00)80629-7.

Siapas, A.G., Lubenov, E.V., Wilson, M.A., 2005. Prefrontal phase locking to hippocampal theta oscillations. Neuron 46 (1), 141–151. https://doi.org/10.1016/j.neuron.2005.02.028.

Silva, A.J., Kogan, J.H., Frankland, P.W., Kida, S., 1998. CREB and memory. Annu. Rev. Neurosci. 21, 127–148. https://doi.org/10.1146/annurev.neuro.21.1.127.

Sirota, A., Csicsvari, J., Buhl, D., Buzsaki, G., 2003. Communication between neocortex and hippocampus during sleep in rodents. Proc. Natl. Acad. Sci. USA 100 (4), 2065–2069. https://doi.org/10.1073/pnas.0437938100.

Sloviter, R.S., Lomo, T., 2012. Updating the lamellar hypothesis of hippocampal organization. Front Neural Circuits 6, 102. https://doi.org/10.3389/fncir.2012.00102.

Smith, D.M., Mizumori, S.J., 2006. Learning-related development of context-specific neuronal responses to places and events: the hippocampal role in context processing. J. Neurosci. 26 (12), 3154–3163. https://doi.org/10.1523/jneurosci.3234-05.2006.

Squire, L.R., 1992. Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans. Psychol. Rev. 99, 195–231. https://doi.org/10.1037/0033-295X.99.2.195.

Squire, L.R., Zola-Morgan, S., 1991. The medial temporal lobe memory system. Science 253 (5026), 1380–1386. https://doi.org/10.1126/science.1896849.

Squire, L.R., Alvarez, P., 1995. Retrograde amnesia and memory consolidation: a neurobiological perspective. Curr. Opin. Neurobiol. 5 (2), 169–177. https://doi.org/10.1016/0959-4388(95)80023-9.

Staresina, B.P., Bergmann, T.O., Bonnefond, M., van der Meij, R., Jensen, O., Deuker, L., Elger, C.E., Axmacher, N., Fell, J., 2015. Hierarchical nesting of slow oscillations, spindles and ripples in the human hippocampus during sleep. Nat. Neurosci. 18 (11), 1679–1686. https://doi.org/10.1038/nn.4119.

Stefanelli, T., Bertollini, C., Luscher, C., Muller, D., Mendez, P., 2016. Hippocampal somatostatin interneurons control the size of neuronal memory ensembles. Neuron 89 (5), 1074–1085. https://doi.org/10.1016/j.neuron.2016.01.024.

Sun, X., Lin, Y., 2016. Npas4: linking neuronal activity to memory. Trends Neurosci. 39 (4), 264–275. https://doi.org/10.1016/j.tins.2016.02.003.

Sun, X., Bernstein, M.J., Meng, M., Rao, S., Sorensen, A.T., Yao, L., Zhang, X., Anikeeva, P.O., Lin, Y., 2020. Functionally distinct neuronal ensembles within the memory engram. e417 Cell 181 (2), 410–423. https://doi.org/10.1016/j.cell.2020.02.055.

Takehara, K., Kawahara, S., Kirino, Y., 2003. Time-dependent reorganization of the brain components underlying memory retention in trace eyeblink conditioning. J. Neurosci. 23 (30), 9897–9905. https://doi.org/10.1523/jneurosci.23-30-09897.2003.

Takeuchi, T., Duszkiewicz, A.J., Morris, R.G., 2014. The synaptic plasticity and memory hypothesis: encoding, storage and persistence. Philos. Trans. R. Soc. Lond. B Biol. Sci. 369 (1633), 20130288. https://doi.org/10.1098/rstb.2013.0288.

Tamura, M., Spellman, T.J., Rosen, A.M., Gogos, J.A., Gordon, J.A., 2017. Hippocampal-prefrontal theta-gamma coupling during performance of a spatial working memory task. Nat. Commun. 8 (1), 2182. https://doi.org/10.1038/s41467-017-02108-9.

Tanaka, K.Z., Pevzner, A., Hamidi, A.B., Nakazawa, Y., Graham, J., Wiltgen, B.J., 2014. Cortical representations are reinstated by the hippocampus during memory retrieval. Neuron 84 (2), 347–354. https://doi.org/10.1016/j.neuron.2014.09.037.

Tanaka, K.Z., He, H., Tomar, A., Niisato, K., Huang, A.J.Y., McHugh, T.J., 2018. The hippocampal engram maps experience but not place. Science 361 (6400), 392–397. https://doi.org/10.1126/science.aat5397.

Terranova, J.I., Yokose, J., Osanai, H., Ogawa, S.K., Kitamura, T., 2023. Systems consolidation induces multiple memory engrams for a flexible recall strategy in observational fear memory in male mice. Nat. Commun. 14 (1), 3976. https://doi.org/10.1038/s41467-023-39718-5.

Teyler, T.J., Rudy, J.W., 2007. The hippocampal indexing theory and episodic memory: updating the index. Hippocampus 17 (12), 1158–1169. https://doi.org/10.1002/hipo.20350.

Thompson, C.L., Pathak, S.D., Jeromin, A., Ng, L.L., MacPherson, C.R., Mortrud, M.T., Cusick, A., Riley, Z.L., Sunkin, S.M., Bernard, A., Puchalski, R.B., Gage, F.H., Jones, A.R., Bajic, V.B., Hawrylycz, M.J., Lein, E.S., 2008. Genomic anatomy of the hippocampus. Neuron 60 (6), 1010–1021. https://doi.org/10.1016/j.neuron.2008.12.008.

Thompson, L.T., Best, P.J., 1989. Place cells and silent cells in the hippocampus of freely-behaving rats. J. Neurosci. 9 (7), 2382–2390. https://doi.org/10.1523/JNEUROSCI.09-07-02382.1989.

Tolman, E.C., 1948. Cognitive maps in rats and men. Psychol. Rev. 55, 189–208.

Tolman, E.C., Ritchie, B.F., Kalish, D., 1946. Studies in spatial learning. I. Orientation and short-cut. *J. Exp. Psychol.* 36 (1), 13–24.

Tonegawa, S., Morrissey, M.D., Kitamura, T., 2018. The role of engram cells in the systems consolidation of memory. Nat. Rev. Neurosci. 19 (8), 485–498. https://doi.org/10.1038/s41583-018-0031-2.

Tononi, G., Cirelli, C., 2020. Sleep and synaptic down-selection. Eur. J. Neurosci. 51 (1), 413–421. https://doi.org/10.1111/ejn.14335.

Topolnik, L., Tamboli, S., 2022. The role of inhibitory circuits in hippocampal memory processing. Nat. Rev. Neurosci. 23 (8), 476–492. https://doi.org/10.1038/s41583-022-00599-0.

Tremblay, R., Lee, S., Rudy, B., 2016. GABAergic Interneurons in the Neocortex: From Cellular Properties to Circuits. Neuron 91 (2), 260–292. https://doi.org/10.1016/j.neuron.2016.06.033.

Troyner, F., Bicca, M.A., Bertoglio, L.J., 2018. Nucleus reuniens of the thalamus controls fear memory intensity, specificity and long-term maintenance during consolidation. Hippocampus *28* (8), 602–616. https://doi.org/10.1002/hipo.22964.

Tse, D., Takeuchi, T., Kakeyama, M., Kajii, Y., Okuno, H., Tohyama, C., Bito, H., Morris, R.G., 2011. Schema-dependent gene activation and memory encoding in neocortex. Science 333 (6044), 891–895. https://doi.org/10.1126/science.1205274.

Tully, T., Boynton, S., Brandes, C., Dura, J.M., Mihalek, R., Preat, T., Villella, A., 1990. Genetic dissection of memory formation in Drosophila melanogaster. Cold Spring Harb. Symp. Quant. Biol. 55, 203–211. https://doi.org/10.1101/sqb.1990.055.01.022.

Tulving, E. (1972). Episodic and semantic memory. In Organization of memory. (pp. xiii, 423-xiii, 423). Academic Press.

Urrutia-Pinones, J., Morales-Moraga, C., Sanguinetti-Gonzalez, N., Escobar, A.P., Chiu, C.Q., 2022. Long-Range GABAergic Projections of Cortical Origin in Brain Function. Front Syst. Neurosci. 16, 841869 https://doi.org/10.3389/fnsys.2022.841869.

Varela, C., Kumar, S., Yang, J.Y., Wilson, M.A., 2014. Anatomical substrates for direct interactions between hippocampus, medial prefrontal cortex, and the thalamic nucleus reuniens. Brain Struct. Funct. 219 (3), 911–929. https://doi.org/10.1007/s00429-013-0543-5.

Vertes, R.P., 2004. Differential projections of the infralimbic and prelimbic cortex in the rat. Synapse 51 (1), 32–58. https://doi.org/10.1002/syn.10279.

Vetere, G., Kenney, J.W., Tran, L.M., Xia, F., Steadman, P.E., Parkinson, J., Josselyn, S.A., Frankland, P.W., 2017. Chemogenetic Interrogation of a Brain-wide Fear Memory Network in Mice. e364 Neuron 94 (2), 363–374. https://doi.org/10.1016/j.neuron.2017.03.037.

Vetere, G., Tran, L.M., Moberg, S., Steadman, P.E., Restivo, L., Morrison, F.G., Ressler, K. J., Josselyn, S.A., Frankland, P.W., 2019. Memory formation in the absence of experience. Nat. Neurosci. 22 (6), 933–940. https://doi.org/10.1038/s41593-019-0389-0.

Vidal-Gonzalez, I., Vidal-Gonzalez, B., Rauch, S.L., Quirk, G.J., 2006. Microstimulation reveals opposing influences of prelimbic and infralimbic cortex on the expression of conditioned fear. Learn Mem *13* (6), 728–733. https://doi.org/10.1101/lm.306106.

Vijayan, S., Lepage, K.Q., Kopell, N.J., Cash, S.S., 2017. Frontal beta-theta network during REM sleep. Elife 6. https://doi.org/10.7554/eLife.18894.

Visser, R.M., Lau-Zhu, A., Henson, R.N., Holmes, E.A., 2018. Multiple memory systems, multiple time points: how science can inform treatment to control the expression of unwanted emotional memories. Philos. Trans. R. Soc. Lond. B Biol. Sci. 373 (1742) https://doi.org/10.1098/rstb.2017.0209.

Voorn, P., Vanderschuren, L.J., Groenewegen, H.J., Robbins, T.W., Pennartz, C.M., 2004. Putting a spin on the dorsal-ventral divide of the striatum. Trends Neurosci. 27 (8), 468–474. https://doi.org/10.1016/j.tins.2004.06.006.

Wang, M.E., Yuan, R.K., Keinath, A.T., Ramos Álvarez, M.M., Muzzio, I.A., 2015. Extinction of Learned Fear Induces Hippocampal Place Cell Remapping. J. Neurosci. 35 (24), 9122–9136. https://doi.org/10.1523/jneurosci.4477-14.2015.

Wang, M.E., Wann, E.G., Yuan, R.K., Ramos Álvarez, M.M., Stead, S.M., Muzzio, I.A., 2012. Long-term stabilization of place cell remapping produced by a fearful experience. J. Neurosci. 32 (45), 15802–15814. https://doi.org/10.1523/jneurosci.0480-12.2012.

Weiskrantz, L., 1956. Behavioral changes associated with ablation of the amygdaloid complex in monkeys. J. Comp. Physiol. Psychol. 49 (*4*), 381–391.

Weng, F.J., Garcia, R.I., Lutzu, S., Alvina, K., Zhang, Y., Dushko, M., Ku, T., Zemoura, K., Rich, D., Garcia-Dominguez, D., Hung, M., Yelhekar, T.D., Sorensen, A.T., Xu, W., Chung, K., Castillo, P.E., Lin, Y., 2018. Npas4 Is a Critical Regulator of Learning-Induced Plasticity at Mossy Fiber-CA3 Synapses during Contextual Memory Formation. e1135 Neuron 97 (5), 1137–1152. https://doi.org/10.1016/j.neuron.2018.01.026.

Westermann, J., Lange, T., Textor, J., Born, J., 2015. System consolidation during sleep - a common principle underlying psychological and immunological memory formation. Trends Neurosci. 38 (10), 585–597. https://doi.org/10.1016/j.tins.2015.07.007.

White, N.M., McDonald, R.J., 2002. Multiple parallel memory systems in the brain of the rat. Neurobiol. Learn Mem. 77 (2), 125–184. https://doi.org/10.1006/nlme.2001.4008.

Wiesel, E. (1986). *Hope, depair and memory*. 〈https://www.nobelprize.org/prizes/peace/1986/wiesel/lecture/〉.

Wilent, W.B., Nitz, D.A., 2007. Discrete place fields of hippocampal formation interneurons. J. Neurophysiol. 97 (6), 4152–4161. https://doi.org/10.1152/jn.01200.2006.

Wilson, M.A., McNaughton, B.L., 1994. Reactivation of hippocampal ensemble memories during sleep. Science 265 (5172), 676–679. https://doi.org/10.1126/science.8036517.

Wiltgen, B.J., Tanaka, K.Z., 2013. Systems consolidation and the content of memory. Neurobiol. Learn Mem. 106, 365–371. https://doi.org/10.1016/j.nlm.2013.06.001.

Winocur, G., Moscovitch, M., 2011. Memory transformation and systems consolidation. J. Int Neuropsychol. Soc. 17 (5), 766–780. https://doi.org/10.1017/S1355617711000683.

Wojtowicz, J.M., 2012. Adult neurogenesis. From circuits to models. Behav. Brain Res. 227 (2), 490–496. https://doi.org/10.1016/j.bbr.2011.08.013.

Wood, E.R., Dudchenko, P.A., Eichenbaum, H., 1999. The global record of memory in hippocampal neuronal activity. Nature 397 (6720), 613–616. https://doi.org/10.1038/17605.

Xu, M., Chung, S., Zhang, S., Zhong, P., Ma, C., Chang, W.C., Weissbourd, B., Sakai, N., Luo, L., Nishino, S., Dan, Y., 2015. Basal forebrain circuit for sleep-wake control. Nat. Neurosci. 18 (11), 1641–1647. https://doi.org/10.1038/nn.4143.

Yassa, M.A., Stark, C.E., 2011. Pattern separation in the hippocampus. Trends Neurosci. 34 (10), 515–525. https://doi.org/10.1016/j.tins.2011.06.006.

Ye, X., Kapeller-Libermann, D., Travaglia, A., Inda, M.C., Alberini, C.M., 2017. Direct dorsal hippocampal-prelimbic cortex connections strengthen fear memories. Nat. Neurosci. 20 (1), 52–61. https://doi.org/10.1038/nn.4443.

Yoshii, T., Hosokawa, H., Matsuo, N., 2017. Pharmacogenetic reactivation of the original engram evokes an extinguished fear memory. *Neuropharmacology*, *113*(Pt A) 1–9. https://doi.org/10.1016/j.neuropharm.2016.09.012.

Yuan, R.K., Lopez, M.R., Ramos-Alvarez, M.-M., Normandin, M.E., Thomas, A.S., Uygun, D.S., Cerda, V.R., Grenier, A.E., Wood, M.T., Gagliardi, C.M., Guajardo, H., Muzzio, I.A., 2021. Differential effect of sleep deprivation on place cell representations, sleep architecture, and memory in young and old mice. Cell Rep. 35 (11) https://doi.org/10.1016/j.celrep.2021.109234.

Zhang, S.J., Ye, J., Couey, J.J., Witter, M., Moser, E.I., Moser, M.B., 2014. Functional connectivity of the entorhinal-hippocampal space circuit. Philos. Trans. R. Soc. Lond. B Biol. Sci. 369 (1635), 20120516. https://doi.org/10.1098/rstb.2012.0516.

Zhou, Y., Won, J., Karlsson, M.G., Zhou, M., Rogerson, T., Balaji, J., Neve, R., Poirazi, P., Silva, A.J., 2009. CREB regulates excitability and the allocation of memory to subsets of neurons in the amygdala. Nat. Neurosci. 12 (11), 1438–1443. https://doi.org/10.1038/nn.2405.

Zinyuk, L., Kubik, S., Kaminsky, Y., Fenton, A.A., Bures, J., 2000. Understanding hippocampal activity by using purposeful behavior: place navigation induces place cell discharge in both task-relevant and task-irrelevant spatial reference frames. Proc. Natl. Acad. Sci. USA 97 (7), 3771–3776. https://doi.org/10.1073/pnas.97.7.3771.

Ziv, Y., Burns, L.D., Cocker, E.D., Hamel, E.O., Ghosh, K.K., Kitch, L.J., El Gamal, A., Schnitzer, M.J., 2013. Long-term dynamics of CA1 hippocampal place codes. Nat. Neurosci. 16 (3), 264–266. https://doi.org/10.1038/nn.3329.

Zola-Morgan, S.M., Squire, L.R., 1990. The primate hippocampal formation: evidence for a time-limited role in memory storage. Science 250 (4978), 288–290. https://doi.org/10.1126/science.2218534.

Zurita, H., Rock, C., Perkins, J., Apicella, A.J., 2018. A layer-specific corticofugal input to the mouse superior colliculus. Cereb. Cortex 28 (8), 2817–2833. https://doi.org/10.1093/cercor/bhx161.