Molecular Brain

Role of adult neurogenesis in hippocampal-cortical memory consolidation

Takashi Kitamura[1] and Kaoru Inokuchi[2,3*]

Abstract

Acquired memory is initially dependent on the hippocampus (HPC) for permanent memory formation. This hippocampal dependency of memory recall progressively decays with time, a process that is associated with a gradual increase in dependency upon cortical structures. This process is commonly referred to as systems consolidation theory. In this paper, we first review how memory becomes hippocampal dependent to cortical dependent with an emphasis on the interactions that occur between the HPC and cortex during systems consolidation. We also review the mechanisms underlying the gradual decay of HPC dependency during systems consolidation from the perspective of memory erasures by adult hippocampal neurogenesis. Finally, we discuss the relationship between systems consolidation and memory precision.

Keywords: Systems consolidation, Remote memory, Hippocampus, Synaptic plasticity, Neurogenesis

Introduction

The hippocampus (HPC) is crucial for the formation of episodic memories during the mnemonic process [1-5]. In memory-impaired humans and experimental animals (e.g., mice, rats, rabbits, cats, and monkeys), damage to the hippocampal structure predominantly affects recently acquired memories, whereas previously acquired old memories remain intact [1,6-9]. In rats, Kim and Fanselow [8] examined the temporal window during which the HPC is important for memory. This study was performed by applying electrolytic lesions to the HPC at various time points after contextual fear conditioning, an associative learning process that requires the HPC and the amygdale, between a chamber (context) and electrical footshocks that occur within that chamber [10,11]. Rats that were lesioned 1 day after training did not retain the contextual fear memory (1 day memory is considered recent memory), whereas animals that received the lesion 28 days later retained the memory (28 days memory is considered remote memory). This process is commonly referred to as systems consolidation

theory [3,12-15]. Pharmacological inactivation studies using lidocaine and CNQX injections into the HPC or cortical regions support this concept [16-22]. Transgenic mice studies also support this concept. The αCaMKII heterozygous knockout mice showed the deficits in the cortical synaptic plasticity, but hippocampal synaptic plasticity was normal [23]. These animals showed an impairment of the remote memory retrieval, but the recent memory was intact. Similarly, forebrain-specific dominant-negative PAK transgenic mice showed the same phenotypes [24].

The systems consolidation process involves a time-limited interaction between the HPC and neocortical areas that eventually store long-term memory traces [22,25]. Studies monitoring the use of cerebral glucose [26], immediate early gene activation [16,17], and dendritic spine formation [22,27] have indicated that rapid on-line encoding of episodic memory in the HPC can be followed by temporally graded neural changes in the medial prefrontal (mPFC), orbitofrontal (Orb), anterior cingulate cortex (ACC), or retrosplenial (RSC) cortices. However, the mechanisms by which memory becomes progressively dependent on the cortical structure and independent of the HPC remain unknown. It is particularly important to determine 1) how the HPC and cortex communicate to consolidate the memory and 2) how the HPC dependency decays with time.

* Correspondence: inokuchi@med.u-toyama.ac.jp
[2]Department of Biochemistry, Faculty of Medicine, Graduate School of Medicine & Pharmaceutical Sciences, University of Toyama, 2630 Sugitani, Toyama 930-0194, Japan
[3]CREST, Japan Science and Technology Agency, Kawaguchi 332-0012, Japan
Full list of author information is available at the end of the article

There is a central question regarding the complementary learning systems framework, as originally articulated by McClelland, McNaughton, and O'Reilly [28]. These authors asked "why is a hippocampal system necessary, if ultimately performance in all sorts of memory tasks depends on changes in connections within the neocortical system? Why does incorporation of new material into the neocortical system take such a long time?" In this review, we also discuss complementary learning systems from the perspective of memory precision and generalization.

Mechanisms of cortical memory consolidation

There is an agreement among various memory systems consolidation models that interaction between the HPC and cortex (PFC, ACC, etc.) after the recent memory formation is crucial for the systems consolidation process [3,12-15,28]. However, little is known regarding which HPC circuit is important for this interaction between the HPC and neocortex. The entorhinal cortex (EC) and HPC neuronal networks contain two major excitatory circuits, the trisynaptic pathway (EC layer II/dentate gyrus/CA3/CA1/EC layer V) and the direct pathway (EC layer III/CA1/EC layer V), that converge onto a common HPC output structure, the CA1 region [29]. The CA1 output layer directly projects to several cortical areas (PFC, ACC, RSC, Orb) or through EC layer V to connect between the HPC and various cortical structures that eventually store long-term memory traces [30].

An initial experiment to investigate these connections was conducted by Remondes and Schuman [31]. These authors cut the ECIII-CA1 direct pathway by physical lesion and demonstrated that the lesion affected remote memories but not recent memories in spatial memory task and contextual fear memory task. However, more recently, Suh et al. [32] showed that triple transgenic mice, in which the output of the medial ECIII was specifically blocked by the expression of tetanus-toxin (TeTX) in medial ECIII, did not show any deficits in remote spatial memory. Thus, direct input from medial ECIII to CA1 may be not crucial for the systems consolidation process.

Nakashiba et al. [33] examined this discrepancy by taking advantage of the CA3-TeTX inducible transgenic mouse, in which a blockade of CA3 output was targeted only in the post-training period that followed contextual fear conditioning. They found that the blockade of CA3 output by TeTX during this period impairs the remote memory of contextual fear conditioning. Previous studies hypothesized that high-frequency field oscillations ("ripples") in CA1 as well as the ripple-associated reactivation of experience-related firing patterns of CA1 pyramidal cells may be involved in systems consolidation [34-40]. Nakashiba et al. [33] showed that the intrinsic frequency of ripples and the reactivation process were both reduced significantly in the CA3-TeTX mice, supporting the hypothesis that these physiological processes are crucial for forming the cortical remote memory and thus are critical for the systems consolidation process.

Recently, Lesburgueres et al. [22] sought to identify the period during which the memory consolidation process is important for the interaction between the HPC and neocortex using chronic pharmacological inactivation. These authors examined the effects of repeated daily injection of CNQX into the HPC or the Orb after memory acquisition. The inactivation of HPC during days 1–15 (early period) after learning caused a deficit in the remote memory, whereas inactivation during days 16–30 (late period) after learning did not cause a deficit in the remote memory (30-day memory). This suggests that hippocampal activity during the early period is crucial for forming the remote memory. In contrast, the inactivation of the Orb either during early or late periods resulted in a deficit in the remote memory. Thus, hippocampal neuronal activity is transiently required (i.e., during the early period), although cortical activity is always required (i.e., during both the early and late periods). Interestingly, when the Orb was inactivated only during the training period, they found that an impairment in remote memory formation occurred without deficits in the 7-day memory [22]. This indicates that the neuronal activity of the Orb during the training period is required for the formation of remote memory but not recent memory, suggesting an early tagging by cortical networks for the consolidation of a memory into permanent cortical memory.

Based on these studies, it appears that information from networks of various neocortical regions is rapidly and temporarily linked through the HPC [22]. The HPC also activates the neocortex (ACC, PFC, Orb) during periods of inactivity and sleep via sharp-wave ripples (SPWs), during which connections between disparate cortical regions gradually develop [34-40]. Various studies have shown that the source of SPWs is synchronous with population bursts in the CA3 region of HPC [41-43] generated by its recurrent excitatory circuit [44,45]. Reactivation by the HPC serves to gradually strengthen the weak connections between neocortical sites. Eventually, the cortex can represent the memory of the original event in the absence of the HPC. Thus, the highly interconnected nature of the CA3 region may facilitate the integration of distributed memory fragments stored in the cortex to form the cortical permanent memory.

Mechanisms for the decay of hippocampal dependency

During the systems consolidation process, a memory becomes progressively independent from the HPC. This

decay of hippocampal dependency is thought to be an active process and plays a role in clearing old memories out of the HPC once the memory has been stored in the cortical networks, thereby allowing the HPC to continuously store new information [28]. Thus, neuronal systems could exist to erase the memory trace in the HPC.

The HPC is thought to be critical in the formation of the contextual component of episodic memories [30,46]. Contextual memory consists of the associations of objects/events and space (i.e., context), with medial EC and lateral EC inputs into the HPC providing spatial and object information, respectively [47]. Modeling and experimental studies have demonstrated that the dentate gyrus (DG) of the HPC has an essential role for discriminating between similar contexts [48-52]. Immediate early gene experiments showed that a sparse population of granule cells in the DG is activated in a given context, and different environments or different tasks activate different populations of granule cells [53-55]. Interestingly, the same sparse population of granule cells is activated repeatedly by the same environment. Recently, Liu et al. [56] used a strain of c-fos-promoter tTA transgenic mice [57,58] with the delivery of channelrhodopsin-2 (ChR2) into the DG by adeno-associated virus to directly demonstrate that a set of contextual memory-related DG cells that are optogenetically activated during the learning period is sufficient to recall the contextual memory without a conditioned cue. These lines of evidence indicate that the DG encodes the contextual memory engrams that represent discrete environments.

In the DG, new neurons are continuously generated in the subgranular zone throughout adulthood in many mammals, including mice, rats, monkeys, and humans, even during old age [59-62]. The newly generated neurons form synapses and are functionally integrated into existing hippocampal neuronal circuits [63-67]. The level of adult hippocampal neurogenesis is positively and negatively modulated by environmental conditions, neuronal activity, aging, and stress [68-77]. Most research has focused on the functional roles of neurogenesis in memory acquisition and in the early period of memory formation [71,78-83]. Theoretical studies suggest that the continuous insertion of newborn neurons into existing adult circuits could potentially disturb the structure of previously stored context information in the dentate gyrus [69,84]. Feng et al. [85] generated forebrain-specific presenilin-1 knockout mice that exhibited a deficiency in enrichment-induced neurogenesis in the DG. Although exposure to an enriched environment for 2 weeks decreased the freezing responses in contextual fear conditioning in wild type mice, the knockout mice did not show decreased freezing, suggesting a role for adult neurogenesis in hippocampal memory clearance.

Kitamura et al. [19] examined whether the level of hippocampal neurogenesis affects the HPC-dependent periods of recall of contextual fear memory via a transient pharmacological inactivation of hippocampal neuronal activity (Figure 1). Decreased adult neurogenesis, either by X-ray irradiation or suppression of activin signaling [86], results in a prolonged HPC-dependent period of contextual fear memory (Figure 1). Thus, continuous integration of newborn neurons disturbs contextual memory in the dentate gyrus.

Decreased neurogenesis by irradiation also enhances the long-term retention of long-term potentiation (LTP; [87]) of the rat dentate gyrus, indicating that the synaptic integration of new neurons into existing neuronal circuits actively interferes with LTP persistence, which in turn leads to LTP decay [19]. LTP is a neural activity-dependent, long-lasting enhancement in synaptic efficacy, a typical form of synaptic plasticity [88]. LTP decay in the DG is an active, gradual process that is mediated by the N-Methyl-d-aspartic acid (NMDA) receptor; hence, daily administration of an NMDA receptor antagonist inhibits LTP decay following LTP induction [89]. There is a strong correlation between LTP and learning and memory. Physiological, pharmacological, and genetic interventions that alter or occlude LTP are accompanied by impairments in learning and memory maintenance [4,90]. Furthermore, HPC-dependent learning induces LTP in the HPC [91]. Thus, learning-induced LTP in the
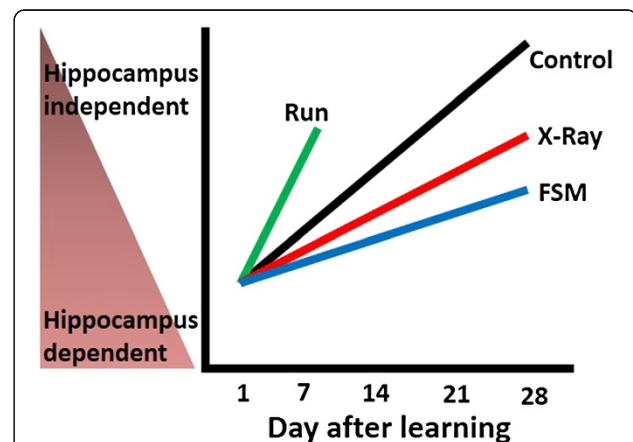

Figure 1 Adult neurogenesis modulates the hippocampus dependent periods of memory. The vertical axis shows the HPC dependence of contextual fear memory. The horizontal axis shows the days after learning. The HPC dependence of contextual fear memory gradually decays with time in control mice. In contrast, X-ray irradiation or genetic overexpression of follistatin (FSM), both of which severely impair hippocampal neurogenesis, prolong the HPC-dependent periods of contextual fear memory, when compared to control mice. Conversely, the running wheel exercises, which promote hippocampal neurogenesis, speed up the decay rate of the HPC dependency of contextual fear memory, when compared to control mice.

dentate gyrus may be gradually reversed by adult neurogenesis, similar to tetanus-induced LTP. This notion implies that the hippocampal memory trace is potentially lost due to interference brought on by neurogenesis. This body of evidence leads us to predict that the gradual decay of the HPC dependency of memory reflects the gradual erasure of the hippocampal memory trace mediated by hippocampal neurogenesis.

Electron microscopic examinations have also suggested that synaptic competition between old and new neurons occurs when newborn neurons form synaptic connections with pre-existing boutons in the DG [65,66]. Specifically, newly generated neurons transiently (at approximately 2–6 weeks of cell age) have enhanced synaptic plasticity, suggesting that at approximately 2–6 weeks of age, newly generated neurons may also have a strong ability to deprive pre-existing synapses of the presynaptic boutons [92,93]. Ohkawa et al. [67] also suggested that the integration of newborn neurons contributes to activity dependent synaptic rewiring in the dentate gyrus. Thus, the integration of newly born neurons disturbs the pre-existing circuits in the dentate gyrus, which may induce memory clearance from the HPC.

Consistent with our idea, Frankland et al. [94] also develop the hypothesis that ongoing hippocampal neurogenesis represents a decay process that continually clears memories from the hippocampus. They proposed, as an anterograde impact, ongoing neurogenesis may work for facilitated acquisition of memory. As retrograde impact, ongoing neurogenesis may work for more forgetting [94].

Kitamura et al. [19] showed that enhanced neurogenesis, resulting from running wheel exercise, hastens the decay of the HPC dependence of memory without any loss of memory (Figure 1). Consistent with this observation, exposure of animals to environmental enrichment accelerates the decay of LTP in dentate gyrus [95] while at the same time enhancing hippocampal neurogenesis [96]. These results imply that the recall of a memory depends on extra-HPC components acting in concert with the decay of HPC-dependency; otherwise, the memory would simply be lost. This interpretation leads us to predict that there may be a coupling mechanism between the decay of HPC-dependence and the increase in neocortex-dependence over time.

How does adult neurogenesis contribute to the acceleration of shift of memory dependency from HPC to cortical structures? One possibility is that adult hippocampal neurogenesis in the DG helps to generate the SPWs in CA3 [34-40]. The SPWs could provide the activation required to drive inter-cortical plasticity and therefore promote cortical consolidation during subsequent periods of inactivity and sleep. In addition, it has been found that the DG can control gene expression in various cortical regions during periods of sleep [97] (Figure 2). Thus, adult neurogenesis in the DG may have two distinct roles in systems consolidation process: 1) erasing the old memories in the HPC to maintain the storage capacity for new memories, and 2) regulating systems consolidation. Adult neurogenesis in the DG decreases with age, which is associated with an age-related decline in spatial memory [98-100]. Given the finite storage capacity of the DG, reduced neurogenesis in aged animals may limit the capacity of the HPC to acquire and store new information by reducing the clearance of old memories that have already been stored in cortical networks. On the other hand, Josselyn and Frankland [101] proposed that extensive early postnatal neurogenesis in the dentate gyrus could explain the biological mechanisms of infantile amnesia.

Memory age vs. Memory precision or generalization

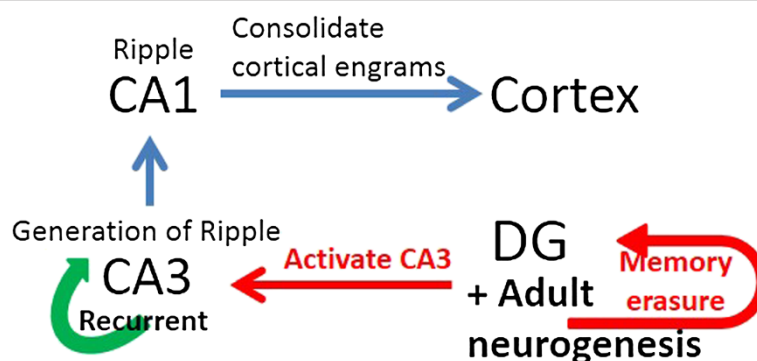It has been suggested that the quality of original memories transforms from a precise (i.e., detailed) form to a

Figure 2 How does adult neurogenesis accelerate the systems consolidation? Adult hippocampal neurogenesis in the DG may help to generate the SPWs in CA3. The SPWs could provide the activation required to drive inter-cortical plasticity through the reactivations of CA1 pyramidal cells, and therefore promote cortical consolidation during subsequent periods of inactivity and sleep. Simultaneously adult neurogenesis erases the pre-exciting memory in the DG.

less precise (i.e., more schematic or generic) form with a time course similar to that of the systems consolidation process [102-104]. Sparse inter-cortical connections may degrade some of the less well-represented content of the original memory, making remote memories more general and semantic-like in nature. Knowledge of this process is important for understanding the physiological significance of the hippocampal-cortical complementary memory systems. Using a contextual fear conditioning paradigm, studies [20,105] have demonstrated that the HPC is always necessary for the precision of place memories, supporting the memory transformation concept [103] in which the quality of place memory correlates with the brain region on which that memory depends. In contrast, another study [106] demonstrated that the HPC is not required for memory precision after the passage of time, supporting the memory reorganization concept [107] in which the quality of place memory does not correlate with the brain region. Importantly, this discrepancy can be attributed to differences in experimental protocols used for association with fear [108,109]. Because association with fear modifies (i.e., strengthen or generalize) the precision, we cannot rule out the possibility that fear association may mask the actual precision of place memory.

To directly evaluate context memory without using fear association protocols, Kitamura et al. [110] examined a one-trial and non-associative place recognition test in mice, and subjected the mice to the remote place memory test (28-days) with or without pharmacological inactivation of the HPC. In the remote memory test, even in the inactivation conditions, mice showed adaptation to a remotely experienced place but not to a novel place (i.e., mice discriminated a known place from a novel place), indicating that the inactivation of the HPC does not inhibit the precision of remote context memory. Thus, the contextual memory is precisely maintained for one month, although the recall of context memory shifts from being HPC-dependent to being HPC-independent with time. This indicates that an extra-HPC structure carries the intact information for context memory even after being independent from the HPC without any loss of context memory precision. Thus, one of the benefits of complementary learning systems could be the maintenance of the precision of memory quality. This is consistent with the idea that a rapid integration of arbitrary new information into neocortical structures would be avoided to prevent catastrophic interference with structured knowledge representations stored in synaptic connections among neocortical neurons [25,111].

Future directions
Considering the mechanisms of systems consolidation of contextual fear memory from the perspective of the levels of memory engram [15,56-58,112,113], several fundamental questions remain. (1) Is the context memory engram in the DG actually erased (or just unused) after the completion of systems consolidation by newly generated neurons? This is very important question, because there are also reports that the HPC is still needed to retrieve the memory even after systems consolidations (for example, the context-dependent food preference memory is always required the hippocampus) [102-105,114]. Goshen et al. [21] also suggest the optogenetic inhibitions of CA1 pyramidal cells inhibited the retrieval of remote contextual fear memory (This discrepancy could be due to the compensation effect or cell-type specific manipulations). (2) How would context memory be represented in a cortical structure (in PFC or ACC) after systems consolidation to precisely maintain the information? To directly address these two questions, promising methodologies include a recently published transgenic approach [115] in which the expression of CreER, a tamoxifen-dependent recombinase, is under the control of an activity-regulated promoter, such as c-fos or activity-regulated cytoskeleton-associated protein (Arc) promoters. This approach may allow for permanent labeling of the memory-related cells in the HPC, cortex, and amygdala and allow for the manipulation of the activity of these cells to evaluate whether these cells remain indispensable for the retrieval of remote memory.

Although pharmacological and lesion approaches continue to be very useful for testing memory dependency on the HPC and cortical regions, an optogenetic approach using transgenic mice combined with viral technologies, in which the manipulation of cellular activity is more restricted to a specific population of memory-related cells, allows improved anatomy- and memory engram-based analyses and is better suited to understanding the mechanisms of the systems consolidation process.

Authors' contributions
TK and KI prepared the manuscript. Both authors read and approved the final manuscript.

Author details
[1]RIKEN-MIT Center for Neural Circuit Genetics at the Picower Institute for Learning and Memory, Department of Biology and Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, Cambridge, MA 02139, USA. [2]Department of Biochemistry, Faculty of Medicine, Graduate School of Medicine & Pharmaceutical Sciences, University of Toyama, 2630 Sugitani, Toyama 930-0194, Japan. [3]CREST, Japan Science and Technology Agency, Kawaguchi 332-0012, Japan.

References

1. Scoville WB, Milner B: **Loss of recent memory after bilateral hippocampal lesions.** *J Neurol Neurosurg Psychiatry* 1957, **20:**11–21.
2. O'Keefe J, Nadel L: *The Hippocampus as a Cognitive Map.* Oxford.: Clarendon Press; 1978.
3. Eichenbaum H: **A cortical-hippocampal system for declarative memory.** *Nat Rev Neurosci* 2000, **1:**41–50.
4. Morris RG, Moser EI, Riedel G, Martin SJ, Sandin J, Day M, O'Carroll C: **Elements of a neurobiological theory of the hippocampus: the role of activity-dependent synaptic plasticity in memory.** *Philos Trans R Soc Lond B Biol Sci* 2003, **358:**773–786.
5. Neves G, Cooke SF, Bliss TV: **Synaptic plasticity, memory and the hippocampus: a neural network approach to causality.** *Nat Rev Neurosci* 2008, **9:**65–75.
6. Zola-Morgan SM, Squire LR: **The primate hippocampal formation: evidence for a time-limited role in memory storage.** *Science* 1990, **250:**288–290.
7. Squire LR: **Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans.** *Psychol Rev* 1992, **99:**195–231.
8. Kim JJ, Fanselow MS: **Modality-specific retrograde amnesia of fear.** *Science* 1992, **256:**675–677.
9. Squire LR, Stark CE, Clark RE: **The medial temporal lobe.** *Annu Rev Neurosci* 2004, **27:**279–306.
10. Phillips RG, LeDoux JE: **Differential contribution of amygdala and hippocampus to cued and contextual fear conditioning.** *Behav Neurosci* 1992, **106:**274–285.
11. Kim JJ, Rison RA, Fanselow MS: **Effects of amygdala, hippocampus, and periaqueductal gray lesions on short- and long-term contextual fear.** *Behav Neurosci* 1993, **107:**1093–1098.
12. Willshaw DJ, Buckingham JT: **An assessment of Marr's theory of the hippocampus as a temporary memory store.** *Philos Trans R Soc Lond B Biol Sci* 1990, **329:**205–215.
13. Wiltgen BJ, Brown RA, Talton LE, Silva AJ: **New circuits for old memories: the role of the neocortex in consolidation.** *Neuron* 2004, **44:**101–108.
14. Frankland PW, Bontempi B: **The organization of recent and remote memories.** *Nat Rev Neurosci* 2005, **6:**119–130.
15. Dudai Y: **The restless engram: consolidations never end.** *Annu Rev Neurosci* 2012, **35:**227–247.
16. Frankland PW, Bontempi B, Talton LE, Kaczmarek L, Silva AJ: **The involvement of the anterior cingulate cortex in remote contextual fear memory.** *Science* 2004, **304:**881–883.
17. Maviel T, Durkin TP, Menzaghi F, Bontempi B: **Sites of neocortical reorganization critical for remote spatial memory.** *Science* 2004, **305:**96–99.
18. Frankland PW, Teixeira CM, Wang S-H: **Grading the gradient: Evidence for time-dependent memory reorganization in experimental animals.** *Debates Neurosci* 2007, **1:**67–78.
19. Kitamura T, Saitoh Y, Takashima N, Murayama A, Niibori Y, Ageta H, Sekiguchi M, Sugiyama H, Inokuchi K: **Adult neurogenesis modulates the hippocampus-dependent period of associative fear memory.** *Cell* 2009, **139:**814–827.
20. Wiltgen BJ, Zhou M, Cai Y, Balaji J, Karlsson MG, Parivash SN, Li W, Silva AJ: **The hippocampus plays a selective role in the retrieval of detailed contextual memories.** *Curr Biol* 2010, **20:**1336–1344.
21. Goshen I, Brodsky M, Prakash R, Wallace J, Gradinaru V, Ramakrishnan C, Deisseroth K: **Dynamics of retrieval strategies for remote memories.** *Cell* 2011, **147:**678–689.
22. Lesburgueres E, Gobbo OL, Alaux-Cantin S, Hambucken A, Trifilieff P, Bontempi B: **Early tagging of cortical networks is required for the formation of enduring associative memory.** *Science* 2011, **331:**924–928.
23. Frankland PW, O'Brien C, Ohno M, Kirkwood A, Silva AJ: **Alpha-CaMKII-dependent plasticity in the cortex is required for permanent memory.** *Nature* 2001, **411:**309–313.
24. Hayashi ML, Choi SY, Rao BS, Jung HY, Lee HK, Zhang D, Chattarji S, Kirkwood A, Tonegawa S: **Altered cortical synaptic morphology and impaired memory consolidation in forebrain- specific dominant-negative PAK transgenic mice.** *Neuron* 2004, **42:**773–787.
25. Lisman J, Morris RG: **Memory. Why is the cortex a slow learner?** *Nature* 2001, **411:**248–249.
26. Bontempi B, Laurent-Demir C, Destrade C, Jaffard R: **Time-dependent reorganization of brain circuitry underlying long-term memory storage.** *Nature* 1999, **400:**671–675.
27. Restivo L, Vetere G, Bontempi B, Ammassari-Teule M: **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* 2009, **29:**8206–8214.
28. McClelland JL, McNaughton BL, O'Reilly RC: **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* 1995, **102:**419–457.
29. Amaral DG, Witter MP: **The three-dimensional organization of the hippocampal formation: a review of anatomical data.** *Neuroscience* 1989, **31:**571–591.
30. Andersen P, Morris R, Amaral D, Bliss T, O'Keefe J (Eds): *The Hippocampus Book.* New York: Oxford University Press; 2007.
31. Remondes M, Schuman EM: **Role for a cortical input to hippocampal area CA1 in the consolidation of a long-term memory.** *Nature* 2004, **431:**699–703.
32. Suh J, Rivest AJ, Nakashiba T, Tominaga T, Tonegawa S: **Entorhinal cortex layer III input to the hippocampus is crucial for temporal association memory.** *Science* 2011, **334:**1415–1420.
33. Nakashiba T, Buhl DL, McHugh TJ, Tonegawa S: **Hippocampal CA3 output is crucial for ripple-associated reactivation and consolidation of memory.** *Neuron* 2009, **62:**781–787.
34. Buzsaki G: **Two-stage model of memory trace formation: a role for "noisy" brain states.** *Neuroscience* 1989, **31:**551–570.
35. Wilson MA, McNaughton BL: **Reactivation of hippocampal ensemble memories during sleep.** *Science* 1994, **265:**676–679.
36. Buzsaki G: **The hippocampo-neocortical dialogue.** *Cereb Cortex* 1996, **6:**81–92.
37. Siapas AG, Wilson MA: **Coordinated interactions between hippocampal ripples and cortical spindles during slow-wave sleep.** *Neuron* 1998, **21:**1123–1128.
38. Skaggs WE, McNaughton BL: **Replay of neuronal firing sequences in rat hippocampus during sleep following spatial experience.** *Science* 1996, **271:**1870–1873.
39. Lee AK, Wilson MA: **Memory of sequential experience in the hippocampus during slow wave sleep.** *Neuron* 2002, **36:**1183–1194.
40. Ji D, Wilson MA: **Coordinated memory replay in the visual cortex and hippocampus during sleep.** *Nat Neurosci* 2007, **10:**100–107.
41. Ylinen A, Bragin A, Nadasdy Z, Jando G, Szabo I, Sik A, Buzsaki G: **Sharp wave-associated high-frequency oscillation (200 Hz) in the intact hippocampus: network and intracellular mechanisms.** *J Neurosci* 1995, **15:**30–46.
42. Csicsvari J, Hirase H, Mamiya A, Buzsaki G: **Ensemble patterns of hippocampal CA3-CA1 neurons during sharp wave-associated population events.** *Neuron* 2000, **28:**585–594.
43. Maier N, Nimmrich V, Draguhn A: **Cellular and network mechanisms underlying spontaneous sharp wave-ripple complexes in mouse hippocampal slices.** *J Physiol* 2003, **550:**873–887.
44. Miles R, Wong RK: **Inhibitory control of local excitatory circuits in the guinea-pig hippocampus.** *J Physiol* 1987, **388:**611–629.
45. Traub RD, Miles R, Wong RK: **Model of the origin of rhythmic population oscillations in the hippocampal slice.** *Science* 1989, **243:**1319–1325.
46. Guzowski JF, McNaughton BL, Barnes CA, Worley PF: **Environment-specific expression of the immediate-early gene Arc in hippocampal neuronal ensembles.** *Nat Neurosci* 1999, **2:**1120–1124.
47. Hargreaves EL, Rao G, Lee I, Knierim JJ: **Major dissociation between medial and lateral entorhinal input to dorsal hippocampus.** *Science* 2005, **308:**1792–1794.
48. Marr D: **Simple memory: a theory for archicortex.** *Philos Trans R Soc Lond B Biol Sci* 1971, **262:**23–81.
49. Treves A, Rolls ET: **Computational analysis of the role of the hippocampus in memory.** *Hippocampus* 1994, **4:**374–391.
50. Leutgeb S, Leutgeb JK, Barnes CA, Moser EI, McNaughton BL, Moser MB: **Independent codes for spatial and episodic memory in hippocampal neuronal ensembles.** *Science* 2005, **309:**619–623.
51. McHugh TJ, Jones MW, Quinn JJ, Balthasar N, Coppari R, Elmquist JK, Lowell BB, Fanselow MS, Wilson MA, Tonegawa S: **Dentate gyrus NMDA receptors**

mediate rapid pattern separation in the hippocampal network. *Science* 2007, **317**:94–99.

52. Nakashiba T, Cushman JD, Pelkey KA, Renaudineau S, Buhl DL, McHugh TJ, Rodriguez Barrera V, Chittajallu R, Iwamoto KS, McBain CJ, Fanselow MS, Tonegawa S: Young dentate granule cells mediate pattern separation, whereas old granule cells facilitate pattern completion. *Cell* 2012, **149**:188–201.

53. Chawla MK, Guzowski JF, Ramirez-Amaya V, Lipa P, Hoffman KL, Marriott LK, Worley PF, McNaughton BL, Barnes CA: Sparse, environmentally selective expression of Arc RNA in the upper blade of the rodent fascia dentata by brief spatial experience. *Hippocampus* 2005, **15**:579–586.

54. Satvat E, Schmidt B, Argraves M, Marrone DF, Markus EJ: Changes in task demands alter the pattern of zif268 expression in the dentate gyrus. *J Neurosci* 2011, **31**:7163–7167.

55. Schmidt B, Marrone DF, Markus EJ: Disambiguating the similar: the dentate gyrus and pattern separation. *Behav Brain Res* 2012, **226**:56–65.

56. Liu X, Ramirez S, Pang PT, Puryear CB, Govindarajan A, Deisseroth K, Tonegawa S: Optogenetic stimulation of a hippocampal engram activates fear memory recall. *Nature* 2012, **484**:381–385.

57. Reijmers LG, Perkins BL, Matsuo N, Mayford M: Localization of a stable neural correlate of associative memory. *Science* 2007, **317**:1230–1233.

58. Matsuo N, Reijmers L, Mayford M: Spine-type-specific recruitment of newly synthesized AMPA receptors with learning. *Science* 2008, **319**:1104–1107.

59. Altman J, Das GD: Autoradiographic and histological evidence of postnatal hippocampal neurogenesis in rats. *J Comp Neurol* 1965, **124**:319–335.

60. Eriksson PS, Perfilieva E, Bjork-Eriksson T, Alborn AM, Nordborg C, Peterson DA, Gage FH: Neurogenesis in the adult human hippocampus. *Nat Med* 1998, **4**:1313–1317.

61. Gould E, Reeves AJ, Fallah M, Tanapat P, Gross CG, Fuchs E: Hippocampal neurogenesis in adult Old World primates. *Proc Natl Acad Sci USA* 1999, **96**:5263–5267.

62. Spalding KL, Bergmann O, Alkass K, Bernard S, Salehpour M, Huttner HB, Boström E, Westerlund I, Vial C, Buchholz BA, Possnert G, Mash DC, Druid H, Frisén J: Dynamics of hippocampal neurogenesis in adult humans. *Cell* 2013, **153**:1219–1227.

63. van Praag H, Schinder AF, Christie BR, Toni N, Palmer TD, Gage FH: Functional neurogenesis in the adult hippocampus. *Nature* 2002, **415**:1030–1034.

64. Zhao C, Teng EM, Summers RG Jr, Ming GL, Gage FH: Distinct morphological stages of dentate granule neuron maturation in the adult mouse hippocampus. *J Neurosci* 2006, **26**:3–11.

65. Toni N, Teng EM, Bushong EA, Aimone JB, Zhao C, Consiglio A, van Praag H, Martone ME, Ellisman MH, Gage FH: Synapse formation on neurons born in the adult hippocampus. *Nat Neurosci* 2007, **10**:727–734.

66. Toni N, Laplagne DA, Zhao C, Lombardi G, Ribak CE, Gage FH, Schinder AF: Neurons born in the adult dentate gyrus form functional synapses with target cells. *Nat Neurosci* 2008, **11**:901–907.

67. Ohkawa N, Saitoh Y, Tokunaga E, Nihonmatsu I, Ozawa F, Murayama A, Shibata F, Kitamura T, Inokuchi K: Spine formation pattern of adult-born neurons is differentially modulated by the induction timing and location of hippocampal plasticity. *PLoS One* 2012, **7**:e45270.

68. Ming GL, Song H: Adult neurogenesis in the mammalian central nervous system. *Annu Rev Neurosci* 2005, **28**:223–250.

69. Lledo PM, Alonso M, Grubb MS: Adult neurogenesis and functional plasticity in neuronal circuits. *Nat Rev Neurosci* 2006, **7**:179–193.

70. Tashiro A, Sandler VM, Toni N, Zhao C, Gage FH: NMDA-receptor-mediated, cell-specific integration of new neurons in adult dentate gyrus. *Nature* 2006, **442**:929–933.

71. Zhao C, Deng W, Gage FH: Mechanisms and functional implications of adult neurogenesis. *Cell* 2008, **132**:645–660.

72. Ma DK, Jang MH, Guo JU, Kitabatake Y, Chang ML, Pow-Anpongkul N, Flavell RA, Lu B, Ming GL, Song H: Neuronal activity-induced Gadd45b promotes epigenetic DNA demethylation and adult neurogenesis. *Science* 2009, **323**:1074–1077.

73. Kitamura T, Mishina M, Sugiyama H: Enhancement of neurogenesis by running wheel exercises is suppressed in mice lacking NMDA receptor epsilon 1 subunit. *Neurosci Res* 2003, **47**:55–63.

74. Kitamura T, Mishina M, Sugiyama H: Dietary restriction increases hippocampal neurogenesis by molecular mechanisms independent of NMDA receptors. *Neurosci Lett* 2006, **393**:94–96.

75. Kitamura T, Sugiyama H: Running wheel exercises accelerate neuronal turnover in mouse dentate gyrus. *Neurosci Res* 2006, **56**:45–52.

76. Kitamura T, Saitoh Y, Murayama A, Sugiyama H, Inokuchi K: LTP induction within a narrow critical period of immature stages enhances the survival of newly generated neurons in the adult rat dentate gyrus. *Mol Brain* 2010, **3**:13.

77. Inokuchi K: Adult neurogenesis and modulation of neural circuit function. *Curr Opin Neurobiol* 2011, **21**:360–364.

78. Shors TJ, Miesegaes G, Beylin A, Zhao M, Rydel T, Gould E: Neurogenesis in the adult is involved in the formation of trace memories. *Nature* 2001, **410**:372–376.

79. Winocur G, Wojtowicz JM, Sekeres M, Snyder JS, Wang S: Inhibition of neurogenesis interferes with hippocampus-dependent memory function. *Hippocampus* 2006, **16**:296–304.

80. Saxe MD, Battaglia F, Wang JW, Malleret G, David DJ, Monckton JE, Garcia AD, Sofroniew MV, Kandel ER, Santarelli L, Hen R, Drew MR: Ablation of hippocampal neurogenesis impairs contextual fear conditioning and synaptic plasticity in the dentate gyrus. *Proc Natl Acad Sci USA* 2006, **103**:17501–17506.

81. Zhang CL, Zou Y, He W, Gage FH, Evans RM: A role for adult TLX-positive neural stem cells in learning and behaviour. *Nature* 2008, **451**:1004–1007.

82. Dupret D, Revest JM, Koehl M, Ichas F, De Giorgi F, Costet P, Abrous DN, Piazza PV: Spatial relational memory requires hippocampal adult neurogenesis. *PLoS ONE* 2008, **3**:e1959.

83. Imayoshi I, Sakamoto M, Ohtsuka T, Takao K, Miyakawa T, Yamaguchi M, Mori K, Ikeda T, Itohara S, Kageyama R: Roles of continuous neurogenesis in the structural and functional integrity of the adult forebrain. *Nat Neurosci* 2008, **11**:1153–1161.

84. Meltzer LA, Yabaluri R, Deisseroth K: A role for circuit homeostasis in adult neurogenesis. *Trends Neurosci* 2005, **28**:653–660.

85. Feng R, Rampon C, Tang YP, Shrom D, Jin J, Kyin M, Sopher B, Miller MW, Ware CB, Martin GM, Kim SH, Langdon RB, Sisodia SS, Tsien JZ: Deficient neurogenesis in forebrain-specific presenilin-1 knockout mice is associated with reduced clearance of hippocampal memory traces. *Neuron* 2001, **32**:911–926.

86. Ageta H, Murayama A, Migishima R, Kida S, Tsuchida K, Yokoyama M, Inokuchi K: Activin in the brain modulates anxiety-related behavior and adult neurogenesis. *PLoS ONE* 2008, **3**:e1869.

87. Bliss TV, Lomo T: Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. *J Physiol* 1973, **232**:331–356.

88. Bliss TV, Collingridge GL: A synaptic model of memory: long-term potentiation in the hippocampus. *Nature* 1993, **361**:31–39.

89. Villarreal DM, Do V, Haddad E, Derrick BE: NMDA receptor antagonists sustain LTP and spatial memory: active processes mediate LTP decay. *Nat Neurosci* 2002, **5**:48–52.

90. Pastalkova E, Serrano P, Pinkhasova D, Wallace E, Fenton AA, Sacktor TC: Storage of spatial information by the maintenance mechanism of LTP. *Science* 2006, **313**:1141–1144.

91. Whitlock JR, Heynen AJ, Shuler MG, Bear MF: Learning induces long-term potentiation in the hippocampus. *Science* 2006, **313**:1093–1097.

92. Schmidt-Hieber C, Jonas P, Bischofberger J: Enhanced synaptic plasticity in newly generated granule cells of the adult hippocampus. *Nature* 2004, **429**:184–187.

93. Ge S, Yang CH, Hsu KS, Ming GL, Song H: A critical period for enhanced synaptic plasticity in newly generated neurons of the adult brain. *Neuron* 2007, **54**:559–566.

94. Frankland PW, Kohler S, Josselyn SA: Hippocampal neurogenesis and forgetting. *Trends Neurosci* 2013, **36**:497–503.

95. Abraham WC, Logan B, Greenwood JM, Dragunow M: Induction and experience-dependent consolidation of stable long-term potentiation lasting months in the hippocampus. *J Neurosci* 2002, **22**:9626–9634.

96. Kempermann G, Kuhn HG, Gage FH: More hippocampal neurons in adult mice living in an enriched environment. *Nature* 1997, **386**:493–495.

97. Ribeiro S, Mello CV, Velho T, Gardner TJ, Jarvis ED, Pavlides C: Induction of hippocampal long-term potentiation during waking leads to increased extrahippocampal zif-268 expression during ensuing rapid-eye-movement sleep. *J Neurosci* 2002, **22**:10914–10923.

98. Drapeau E, Mayo W, Aurousseau C, Le Moal M, Piazza PV, Abrous DN: Spatial memory performances of aged rats in the water maze predict levels of hippocampal neurogenesis. *Proc Natl Acad Sci USA* 2003, **100**:14385–14390.

99. Drapeau E, Montaron MF, Aguerre S, Abrous DN: Learning-induced survival of new neurons depends on the cognitive status of aged rats. *J Neurosci* 2007, **27**:6037–6044.

100. Lazarov O, Mattson MP, Peterson DA, Pimplikar SW, van Praag H: **When neurogenesis encounters aging and disease.** *Trends Neurosci* 2010, **33**:569–579.

101. Josselyn SA, Frankland PW: **Infantile amnesia: a neurogenic hypothesis.** *Learn Mem* 2013, **19**:423–433.

102. Nadel L, Moscovitch M: **Memory consolidation, retrograde amnesia and the hippocampal complex.** *Curr Opin Neurobiol* 1997, **7**:217–227.

103. Moscovitch M, Nadel L, Winocur G, Gilboa A, Rosenbaum RS: **The cognitive neuroscience of remote episodic, semantic and spatial memory.** *Curr Opin Neurobiol* 2006, **16**:179–190.

104. McKenzie S, Eichenbaum H: **Consolidation and reconsolidation: two lives of memories?** *Neuron* 2011, **71**:224–233.

105. Winocur G, Moscovitch M, Sekeres M: **Memory consolidation or transformation: context manipulation and hippocampal representations of memory.** *Nat Neurosci* 2007, **10**:555–557.

106. Wang SH, Teixeira CM, Wheeler AL, Frankland PW: **The precision of remote context memories does not require the hippocampus.** *Nat Neurosci* 2009, **12**:253–255.

107. Squire LR, Bayley PJ: **The neuroscience of remote memory.** *Curr Opin Neurobiol* 2007, **17**:185–196.

108. Houston FP, Stevenson GD, McNaughton BL, Barnes CA: **Effects of age on the generalization and incubation of memory in the F344 rat.** *Learn Mem* 1999, **6**:111–119.

109. Balogh SA, Radcliffe RA, Logue SF, Wehner JM: **Contextual and cued fear conditioning in C57BL/6 J and DBA/2 J mice: context discrimination and the effects of retention interval.** *Behav Neurosci* 2002, **116**:947–957.

110. Kitamura T, Okubo-Suzuki R, Takashima N, Murayama A, Hino T, Nishizono H, Kida S, Inokuchi K: **Hippocampal function is not required for the precision of remote place memory.** *Mol Brain* 2012, **5**:5.

111. McClelland JL: **Incorporating rapid neocortical learning of New schema-consistent information into complementary learning systems theory.** *J Exp Psychol Gen* 2013, **142**:1190–1210.

112. Han JH, Kushner SA, Yiu AP, Cole CJ, Matynia A, Brown RA, Neve RL, Guzowski JF, Silva AJ, Josselyn SA: **Neuronal competition and selection during memory formation.** *Science* 2007, **316**:457–460.

113. Han JH, Yiu AP, Cole CJ, Hsiang HL, Neve RL, Josselyn SA: **Increasing CREB in the auditory thalamus enhances memory and generalization of auditory conditioned fear.** *Learn Mem* 2008, **15**:443–453.

114. Sutherland RJ, Lehmann H: **Alternative conceptions of memory consolidation and the role of the hippocampus at the systems level in rodents.** *Curr Opin Neurobiol* 2011, **21**:446–451.

115. Guenthner CJ, Miyamichi K, Yang HH, Heller HC, Luo L: **Permanent genetic access to transiently active neurons via TRAP: targeted recombination in active populations.** *Neuron* 2013, **78**:773–784.