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New neurons and new memories: how does adult hippocampal neurogenesis affect learning and memory?

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Abstract

The integration of adult-born neurons into the circuitry of the adult hippocampus suggests an important role for adult hippocampal neurogenesis in learning and memory, but its specific function in these processes has remained elusive. In this article, we summarize recent progress in this area, including advances based on behavioural studies and insights provided by computational modelling. Increasingly, evidence suggests that newborn neurons might be involved in hippocampal functions that are particularly dependent on the dentate gyrus, such as pattern separation. Furthermore, newborn neurons at different maturation stages may make distinct contributions to learning and memory. In particular, computational studies suggest that, before newborn neurons are fully mature, they might function as a pattern integrator by introducing a degree of similarity to the encoding of events that occur closely in time.

The discovery of neurogenesis in the brain of adult mammals overturned the long-held dogma that the adult brain has no capacity for generating new neurons¹. Although the idea met with scepticism for a long time, it is now generally accepted that new neurons are continuously added in discrete regions of the brain throughout adult life in various species, including humans². Adult neurogenesis, originating from neural progenitor cells (NPCs), has been consistently observed in two regions of the adult brain: the subventricular zone (SVZ) of the lateral ventricle and the subgranular zone (SGZ) of the dentate gyrus in the hippocampus. Neurons born in the SVZ migrate through the rostral migratory stream and become granule neurons and periglomerular neurons of the olfactory bulb. Neurons born in the SGZ differentiate and integrate into the local neural network as granule cells of the dentate gyrus.

The adult-born neurons can be identified by many approaches, such as by incorporation of nucleotide analogues (for example, bromodeoxyuridine (BrdU)), by virus-mediated labelling

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DATABASES

Entrez Gene: <http://www.ncbi.nlm.nih.gov/gene>

Arc | *Egr1* | *Fos* | *Homer1A*

UniProtKB: <http://www.uniprot.org>

CREB | [SLC12A2](#)

FURTHER INFORMATION

Fred H. Gage's homepage: <http://www.salk.edu/faculty/gage.html>

SUPPLEMENTARY INFORMATION

See **online article:** [S1](#) (table)

Competing interests statement

The authors declare **competing financial interests:** see web version for details.

and by genetically engineered reporter genes³⁻⁵. Research in the past decade has led to a greater understanding of the processes involved in adult neurogenesis, including the proliferation of NPCs, the fate determination of NPC progenies, the differentiation, morphogenesis and maturation of adult-born neurons, and the eventual integration of adult-born neurons into the neural networks of both the olfactory bulb and the hippocampus⁶. Furthermore, each of these processes is subject to regulation by numerous intrinsic and extrinsic factors⁷. Despite this progress, many questions regarding the functional importance of adult neurogenesis remain unanswered. However, the putative functions of adult-born olfactory neurons are being revealed by many studies that are in progress⁸⁻¹¹, and recent research has shed light on the role of adult hippocampal neurogenesis in hippocampus-mediated functions.

In the adult brain, the hippocampus (FIG. 1) is a crucial structure for the formation of certain types of memory, such as episodic memory and spatial memory¹². Through its interactions with brain structures associated with emotion, the hippocampus is also implicated in emotional behaviour¹³. Does the integration of new neurons into the existing hippocampal circuit influence hippocampus-related behaviours? If so, how? Correlations between the rate of adult hippocampal neurogenesis and the emotional status of animals have been shown in several studies. However, there is no direct evidence that adult neurogenesis is required for emotional regulation, although it can mediate the efficacy of antidepressants under certain conditions^{13, 14}. By contrast, our understanding of the functions of hippocampal neurogenesis in learning and memory has advanced considerably in the past few years. In this Review, we briefly describe the basic processes involved in adult hippocampal neurogenesis and consider how these processes are regulated by neural activity and how adult-born neurons respond to environmental and behavioural stimuli. We next examine the potential role of hippocampal neurogenesis in learning and memory as proposed by various computational models and based on recent findings from behavioural studies (see [Supplementary information S1](#) (table)). We discuss these observations in the context of the functions of the hippocampus, and of the dentate gyrus in particular.

Maturation of adult-born DGCs

Adult neurogenesis begins with the proliferation of NPCs in the SGZ (FIG. 2). Most progeny of NPCs differentiate into dentate granule cells (DGCs), whereas a small population become glia¹⁵. The newly born DGCs bear little resemblance to their mature counterparts and must undergo a lengthy process of morphological and physiological maturation¹⁶. The kinetics of DGC maturation are species dependent¹⁷. Here, we discuss the maturation of adult-born DGCs in mice because most of the relevant studies have been carried out in this species.

During the first week after birth, after committing to the neuronal lineage, the adult-born DGCs undergo their initial differentiation and migrate a short distance into the inner granule cell layer of the dentate gyrus, where they extend limited cellular processes but do not seem to be synaptically integrated into the network. Notably, these cells are tonically activated by ambient GABA (γ -aminobutyric acid)^{16,18,19}.

During the second week after birth, the adult-born DGCs become more neuron-like: they grow polarized processes, with dendrites extending towards the molecular layer and axons (that is, mossy fibres) growing through the hilus towards CA3 (REFS ^{16,20}) (FIG. 2). Nevertheless, these immature DGCs are still considerably different from mature DGCs. For example, they have a higher membrane resistance and different firing properties¹⁸. Moreover, at this stage, the adult-born DGCs lack glutamatergic input, which is consistent with the absence of dendritic spines in the molecular layer (in which the glutamatergic fibres are located) at this time^{16,18} (FIG. 2). However, these immature DGCs receive synaptic GABAergic input, presumably from local interneurons, and the resulting responses have slow rising and decay kinetics^{18,19,21,22}.

The GABAergic input results in neuronal depolarization owing to the presence of the Na⁺-K⁺-2Cl⁻ cotransporter, solute carrier family 12 member 2 (SLC12A2; also known as NKCC1) on the DGC membrane^{18,19}. The GABA-mediated activity seems to be important for the survival and maturation of adult-born DGCs: knockdown of SLC12A2 by RNA interference reduced the number of adult-born DGCs surviving the second week after birth²³, caused defects in the formation of GABA- and glutamate-mediated synapses and reduced dendrite arborizations¹⁹. By contrast, administration of a GABA receptor agonist promotes dendrite growth of adult-born DGCs¹⁹. The GABA-dependent depolarization is mediated by cyclic AMP response element-binding protein (CREB)²³. The knockdown of SLC12A2 results in loss of CREB phosphorylation (the active form of CREB) in adult-born DGCs, and forced activation of CREB can normalize the impaired maturation of newborn DGCs caused by SLC12A2 knockdown²³.

During the third week after birth, adult-born DGCs start to form afferent and efferent connections with the local neuronal network (FIG. 2). By approximately day 16, spines begin to appear on the dendrites of adult-born DGCs, forming synapses with the afferent axon fibres in the perforant pathway that come from the entorhinal cortex^{16,24}. Initially, filopodia are frequently present on dendrites²⁴. The majority of the filopodia on the adult-born DGCs target axon boutons that already synapse with existing spines on other DGCs by forming multiple synaptic boutons, suggesting that network integration of the adult-born DGCs is influenced by local synaptic activity²⁴. Similarly, the mossy fibre boutons of adult-born DGCs initially form synapses either with the dendritic shaft of CA3 pyramidal neurons in a region near existing thorny excrescences or directly with existing thorny excrescences that already contain a bouton^{25,26}. This suggests that efferent synapse formation of adult-born DGCs can also be affected by existing synapses. Thus, the development of both afferent and efferent synapses from newly generated DGCs seems to involve targeting to pre-existing synaptic partners, which suggests a role for circuit activity in the integration of adult-born DGCs.

The timing of synaptic integration coincides with the transition of GABAergic input from being excitatory to being inhibitory and with the onset of glutamatergic synaptic inputs^{18,19}. The NMDA (*N*-methyl-D-aspartate) receptor is a glutamate receptor that has been implicated in neuronal development and plasticity²⁷. Between 2 and 3 weeks of age, the survival of adult-born DGCs depends on NMDA-receptor mediated cell-autonomous activity^{18,19,28}. The adult-born DGCs at this stage still have characteristics — such as high membrane resistance and high resting potentials¹⁸ — that could contribute to increased excitability^{29,30}, although their action potentials have kinetic characteristics similar to those of mature DGCs¹⁸.

Around 4–6 weeks of age, together with the gradual maturation of their physiology and connectivity^{16,18,31}, the adult-born DGCs exhibit stronger synaptic plasticity than mature DGCs, as indicated by their lower threshold for the induction of long-term potentiation (LTP) and their higher LTP amplitude²⁹. This enhanced plasticity is mediated by NMDA receptor subunit NR2B²⁹. A transcription factor, *kruppel-like factor 9*, seems to be essential for the survival of adult-born DGCs during this time³². Although the structural modification of dendritic spines and axonal boutons continues to occur as the adult-born DGCs become older^{16,24,25}, the basic physiological properties and synaptic plasticity at 8 weeks of age are indistinguishable from those of mature DGCs. As discussed below, the unique physiological characteristics of adult-born DGCs before 6 weeks of age enable these neurons to be discretely regulated by network activity and possibly to make distinct contributions to learning and memory.

Regulation of adult neurogenesis

One of the implications of a role for adult neurogenesis in learning and memory is that neurogenesis can be regulated by numerous factors associated with an animal's behavioural and cognitive states. Indeed, an animal's experiences, including hippocampus-dependent learning, environmental enrichment and voluntary running, can affect the rate of neurogenesis. These experiences, which are associated with enhanced cognition, presumably do so by stimulating the hippocampal neural network.

Hippocampus-dependent learning is one of the major regulators of hippocampal neurogenesis³³. For example, learning of hippocampus-dependent tasks but not hippocampus-independent tasks increases the number of adult-born DGCs at around 1 week of age³³⁻³⁶. However, proliferation of NPCs in the SGZ immediately after learning is not affected by learning³³. Similarly, hippocampal neurogenesis is exquisitely regulated by spatial navigation learning in the Morris water maze (MWM). For example, learning in the MWM promotes the survival of DGCs that were born 7 days before the onset of MWM training and, at the same time, induces apoptosis in DGCs that were born 3 days before³⁷. Of note, at the onset of MWM training, DGCs born 1 week earlier have begun to form GABAergic synapses with the local network and enter the hyper-excitability stage during MWM learning (see above), and can therefore potentially be influenced by learning or recruited to memories. Furthermore, the late phase of MWM training, when animals show little improvement in performance, is associated with increased apoptosis in the dentate gyrus and a decrease in the number of DGCs that were born during the early phase of training^{37,38}. At the same time, such asymptotic training induces the proliferation of NPCs in the SGZ^{37,38}. Blocking apoptosis in the late phase of learning prevents the enhanced survival of DGCs born 7 days before MWM training and the induction of NPC proliferation, and impairs the performance in the MWM³⁷, suggesting that learning regulates these events interdependently. Together, these findings suggest that learning selectively adds and removes adult-born DGCs according to their maturity and functional relevance.

Living in an enriched environment, which presumably provides a larger number of opportunities for learning than standard laboratory housing³⁹, can also enhance hippocampal neurogenesis by increasing the survival of adult-born DGCs⁴⁰. Environmental enrichment for as little as 1 week is sufficient to increase the survival of the adult-born DGCs that are younger than 3 weeks of age but not of older ones, suggesting that the environmental-enrichment effect is dependent on the maturation state of adult-born DGCs⁴¹. In addition, environmental enrichment improves performance in learning and memory tasks such as the MWM and object recognition tests^{40,42}. However, it is currently debated whether hippocampal neurogenesis is necessary for these behavioural effects of environmental enrichment^{42,43}.

Increasing evidence suggests that physical exercise not only improves the physical health of individuals but also improves cognition and other brain functions^{44,45}. In rodents, voluntary running significantly increases the proliferation of NPCs in the SGZ of both young and aged animals^{46,47}. Moreover, voluntary running for about 3 weeks following BrdU birth-dating enhances the survival of BrdU-labelled adult-born DGCs^{48,49}. In addition, voluntary running increases the amplitude of LTP in the dentate gyrus and improves the performance of animals in the MWM^{47,50}, indicating that increased neurogenesis correlates with increased network activity and improved cognition. However, whether increased neurogenesis is responsible for cognitive improvement remains to be tested. Voluntary running also interacts with other stimuli, such as stress and social interactions, to regulate neurogenesis^{49,51}. Although physical exercise can induce angiogenesis and expression of neurotrophic factors such as brain-derived neurotrophic factor in the brain⁴⁵, the molecular mechanisms responsible for exercise-induced neurogenesis remain undetermined.

Adult hippocampal neurogenesis can also be modulated by artificial induction of network activity. For example, induction of LTP in the dentate gyrus by high-frequency stimulation of the perforant pathway can increase the proliferation of NPCs in the SGZ and enhance the survival of adult-born DGCs at 1–2 weeks of age^{52,53}. Electroconvulsive shock, which induces a brief seizure in the brain and has therapeutic effects in many emotional disorders, also increases both the proliferation of NPCs and neurogenesis in the SGZ^{54,55}.

Finally, adult hippocampal neurogenesis and neuronal integration can be affected by aberrant circuit activity under pathological conditions, as observed in human patients and animal models of neurological disorders (reviewed in REF.⁶). For example, a drug-induced seizure increases NPC proliferation⁵⁶, causes morphological abnormalities in adult-born DGCs⁵⁷, induces ectopic migration of adult-born DGCs⁵⁸ and accelerates the integration of adult-born DGCs⁵⁹. It is currently unknown whether the altered hippocampal neurogenesis further exacerbates the pathological conditions.

Responsiveness of adult-born DGCs

If behavioural stimuli and network activity can modulate the survival and integration of adult-born DGCs, how do adult-born DGCs respond to such stimuli and activity? This question is generally addressed by examining the expression of immediate early genes (IEGs). IEGs, such as FBJ osteosarcoma oncogene (*Fos*), activity regulated cytoskeletal-associated protein (*Arc*), early growth response 1 (*Egr1*; also known as *Zif268*), and *Homer1A*, play key parts in regulating synaptic plasticity. Their expression is tightly coupled to neuronal activity associated with learning and memory and is widely used to study population activity of neurons in various brain regions⁶⁰. Using BrdU to birth-date adult-born DGCs, it was found that neuronal activity (whether at physiological or aberrant levels) does not induce IEG expression in adult-born DGCs until they reach a certain stage of maturation — around 3–4 weeks of age in mice^{17,61} and about 2 weeks of age in rats^{17,52}.

Neural stimuli seem to preferentially activate adult-born DGCs. Compared with their mature counterparts, a higher proportion of 5-month-old adult-born DGCs expressed IEGs when rats were allowed to encounter and explore a novel environment⁶². Moreover, the experiences an animal undergoes when a population of adult-born DGCs are young may influence the responsiveness of these neurons later on. For example, MWM learning by a mouse when a set of adult-born DGCs was at least 4–6 weeks of age led to preferential activation of these cells during memory retrieval in the MWM when the DGCs were 10 weeks old⁶³. Interestingly, this time frame coincides with the stage of enhanced synaptic plasticity of adult-born DGCs.

Furthermore, it has been suggested that the experiences of a mouse when adult-born DGCs are about 1–3 weeks of age — a stage when newly generated DGCs are not capable of expressing IEGs — can enhance the experience-specific responsiveness of these DGCs when they are older^{41,64}. In one study, mice were exposed to an enriched environment when BrdU-labelled adult-born DGCs were about 1–2.5 weeks of age; the mice were subsequently exposed to different experiences and, 6 weeks after BrdU labelling, the expression of IEGs in BrdU-labelled DGCs was examined⁴¹. A higher proportion of BrdU-labelled adult-born DGCs responded to re-exposure to the enriched environment than to MWM training⁴¹.

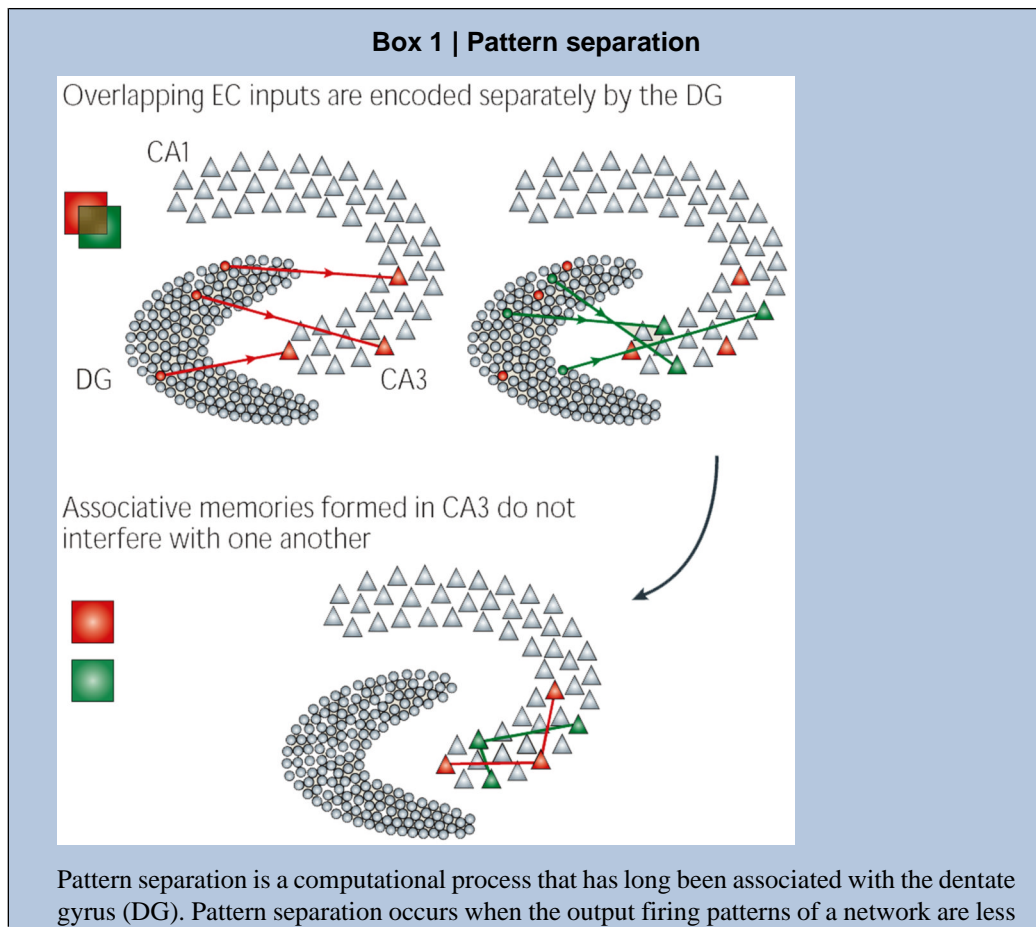
Finally, activation of adult-born DGCs by memory retrieval tasks seems to depend on cognitive demand⁶⁴. In one study, mice were trained in the MWM when BrdU-labelled adult-born DGCs were 9 days old; 30 days later, they were subjected to various paradigms in the MWM and the expression of IEGs in BrdU-labelled DGCs was examined⁶⁴. A higher proportion of BrdU-labelled DGCs expressed IEGs in mice that were subjected to a single trial with the hidden platform in the original training location (matched situation), than in mice subjected to a single trial in the absence of the platform (mismatched situation), suggesting that the activation of

adult-born DGCs is situation-specific⁶⁴. In addition, the proportion of IEG-expressing BrdU-labelled DGCs could be further increased (by more than twofold) if mice underwent nine trials (instead of one trial) with the platform in the original training location, but not with the platform moved to a new location.

Together, these findings suggest that, compared with their mature counterparts, adult-born DGCs may be specifically activated by an animal's experiences and thus can make unique contributions to learning and memory.

Computational models of adult-born DGC function

As adult neurogenesis has become more widely appreciated as an important form of hippocampal plasticity, its potential to affect learning and memory has been increasingly recognized⁶⁵⁻⁶⁷. This interest is largely due to the position of the dentate gyrus within the hippocampal circuit and its presumed role in memory formation. The dentate gyrus, which receives direct inputs from the entorhinal cortex and sends projections to the CA3 region (FIG. 1), is traditionally considered the information gateway to the hippocampus. Following the seminal work of David Marr, who suggested that the hippocampus stores memories in associative networks⁶⁸, several computational studies recognized that highly separated inputs are required to encode different memories in the CA3 and assigned this role — a process known as pattern separation — to the dentate gyrus (BOX 1)⁶⁹⁻⁷². Recent experimental evidence also supports the pattern separation function of the dentate gyrus in information processing⁷³⁻⁷⁵. However, studies of dentate gyrus pattern separation have generally not taken neurogenesis into consideration.



similar to one another than the input firing patterns. Similarity measures such as correlation and cosine similarity (also known as normalized dot product) can be used to quantify separation. If the firing patterns of the output neurons for a set of events are more separated from each other than the firing patterns of its input neurons, the network can be considered a separator (see the figure). This separation can occur either through rate modulation of neurons within a population or by the firing of a unique set of neurons to each input.

There are many reasons why the dentate gyrus is thought to have such a pattern separation function. First, the anatomy of the region seems to be ideally suited for separation: the dentate gyrus contains five to ten times more neurons than its principal input, the entorhinal cortex (EC)¹¹⁵. In this way, the dentate gyrus is similar to support vector machine algorithms in machine learning, by which information is projected into higher-dimension spaces to facilitate discrimination¹¹⁶. Second, it seems to have a sparse coding scheme: dentate granule cells (DGCs) receive substantial feedforward and feedback inhibition from local interneurons¹¹⁷ and *in vivo* recordings suggest that DGCs are rarely active during behaviour^{74,118}. Together, these findings suggest that DGCs are finely tuned, making it possible that even similar inputs activate distinct populations of DGCs^{70,72,119}. Finally, individual DGC mossy fibres are capable of depolarizing downstream CA3 pyramidal neurons¹²⁰, suggesting that, despite their sparse activation, they can drive memory encoding in the hippocampus⁶⁹.

Why is pattern separation important? In the hippocampus, it has been proposed to be an essential step in information processing to avoid interference between memories⁷². In associative networks, as the CA3 is thought to be, memory cues activate a set of neurons that then, by virtue of connections within the network, activate those neurons that represent the stored memory itself — a process known as pattern completion¹²¹. Such a scheme requires that memories be stored ‘far apart’. If two events are encoded too similarly, the stored memories may converge into a single, inappropriate memory, rendering future recall impossible¹²².

Following the long tradition of hippocampal modelling, computational approaches have been increasingly used to identify and understand the role that adult neurogenesis may have in the hippocampal network⁷⁶. These modelling studies have shown that directing learning to adult-born DGCs can have several different effects depending on the specific architecture of the network model and the form of neurogenesis that is being tested. These models have taken different forms, ranging from ‘top-down’, abstract neural network models to ‘bottom-up’, biologically-derived models of the dentate gyrus and hippocampus. Nevertheless, a common thread has emerged across many of these models: neurogenesis allows plasticity to be mostly localized to newborn immature DGCs, preserving the information that is represented by mature DGCs (FIG. 3).

New neurons and memory capacity: addition or replacement?

The greatest distinction in how neurogenesis is implemented in these different computational models is whether new neurons replace existing neurons (‘replacement models’) or whether they are added to the network (‘addition models’). In replacement models, old DGCs are simply removed and replaced by new DGCs with random (or naive) synapses. In simple feedforward architectures, replacement of neurons in this manner accelerates learning considerably because the random connections made by the new neurons are flexible and can therefore participate in various network learning paradigms (for example, neurogenesis allows the network to avoid local minima, which are a problem with some learning rules)^{77,78}. A possible downside indicated by these models is that this learning improvement is accompanied by the forgetting of older memories through the loss of information that was encoded by the removed neurons, although targeted cell death could mitigate this problem⁷⁹. In contrast to the abstract networks

in these replacement models, the replacement model described by Becker⁸⁰ considers neurogenesis in a model of the full hippocampal loop (entorhinal cortex–dentate gyrus–CA3–CA1–entorhinal cortex). Becker’s model shows that, if the role of the dentate gyrus is limited to encoding (with no involvement in retrieval), the storage and subsequent recall of highly similar items by the full hippocampal circuit are considerably improved if there is substantial neuronal replacement in the dentate gyrus, without disrupting the retrieval of older memories⁸⁰.

In contrast to the replacement models, more recent models have considered the possibility that the granule cell layer continues to grow through the addition of new neurons. By not removing existing neurons and directing plasticity towards new neurons, these models have suggested that neurogenesis allows the mature neurons within the dentate gyrus network to remain specialized for the same memories for long periods of time. Wiskott and colleagues described how limiting synaptic plasticity to synapses made by new neurons in the network can keep the network from suffering catastrophic interference, a process by which the attractor structure of the network breaks down⁸¹. This interference is avoided because the attractors using old neurons are not affected by new information that is being stored in the network (although the old attractors are still useful for encoding familiar components of new memories). Similarly, in the full hippocampal model by Weisz and Argibay⁸² — which, like the Becker model, incorporates neurogenesis into a simulation of the entorhinal cortex–dentate gyrus–CA3–CA1–entorhinal cortex loop but treats neurogenesis as an additive process — after a certain memory load was reached, new information could not be effectively encoded if no neurogenesis took place; however, if neurogenesis was incorporated into the model (simulated as a one-off 30% increase in dentate gyrus size), the network could effectively store and retrieve the new memories. Aimone and colleagues⁸³ investigated the long-term effects of this addition. Their model showed that if all DGCs ‘grow’ into the network through neurogenesis (and thus move from a high-plasticity, immature state to a lower-plasticity, mature state), a network ultimately results in which most DGCs permanently encode their past ‘experience’⁸³. Such an arrangement could bias the dentate gyrus to preferentially use subsets of mature DGCs during the encoding of new information in familiar contexts. The experience-specific modification of adult-born DGC activity described above is consistent with this hypothesis⁴¹.

Pattern separation in models of neurogenesis

Although most computational models that investigate the role of neurogenesis in hippocampal function have not explicitly addressed the pattern separation function of the dentate gyrus, many of these results have implications that are relevant to the role of neurogenesis in pattern separation. In replacement models, the complete replacement of neurons within a layer could be considered a potent form of separation that ensures that different memories are always represented by distinct DGC populations without the potential for overlap. For example, the benefits of neurogenesis on the ability for the Becker model to store and recall similar memories could be attributed to the substantial pattern separation between the entorhinal cortex signals in the model. Similarly, the results that emerge from the Wiskott and Aimone addition models (which involve a reduction of interference or a specialization of neurons) can be considered ‘separation effects’ in the sense that new memories are more likely to involve new neurons that were not available for older memories. In these cases, however, the contribution of new neurons to pattern separation occurs over a long timescale — probably days to weeks — because neurogenesis ensures that the populations of immature DGCs change continuously over several days. What occurs over shorter timescales that are relevant to hippocampal processing, such as minutes and hours, during which the population of immature neurons probably does not change substantially? One prediction from Aimone’s model is that immature DGCs make a distinct contribution to the separation properties of the dentate gyrus⁸³. Although mature DGCs are presumably very selective in their responses (that is, tightly tuned), allowing

them to contribute to pattern separation by making the stimulus inputs independent of one another, the physiological properties of immature DGCs probably make them less selective (that is, broadly tuned), allowing them to fire in response to multiple events. We refer to this effect as pattern integration and propose that this added similarity between the representations of encoded memories might make a crucial contribution to the global pattern separation function of the dentate gyrus. Importantly, this pattern integration effect, which prevents new memories from becoming completely separated during encoding, is distinct from the pattern completion that occurs during memory retrieval. Incidentally, the full hippocampal model of Weisz and Argibay also showed that neurogenesis decreases pattern separation because new neurons in their model are more likely to participate indiscriminately in the encoding of new memories⁸².

The different potential effects of adult-born DGCs on pattern separation at different timescales has led to an additional hypothesis — namely, that adult-born DGCs contribute to the encoding of temporal information^{80,83-85}. According to our model⁸³, events (stimuli) that occur close to each other in time will be associated with each other owing to pattern integration by immature adult-born DGCs, but the memories of events that occur far apart in time (and that thus will be represented by different immature DGC populations) will be better separated⁸⁴. Modelling results showed that immature DGCs make an important contribution in this respect and that the pattern integration effect decreases over several days, ensuring that memories that are formed at different times are encoded distinctly⁸³. From a different mechanistic perspective, Becker and Wojtowicz proposed that temporal information could be encoded by ‘waves’ of new DGCs, whereby DGCs arising from the same NPC encode different features of the same temporal context⁸⁶.

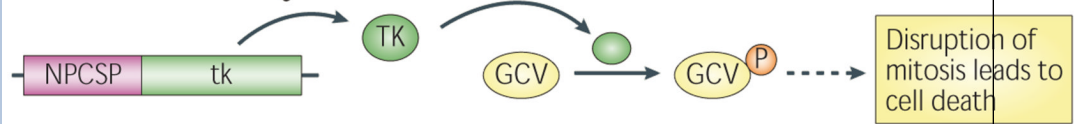
In summary, the varied approaches to using computational models to study the role of neurogenesis in hippocampal function have suggested several potential functions for adult-born DGCs in the dentate gyrus. Despite differences in design and assumptions, these models point towards similar conclusions. First, how neurogenesis might affect learning and memory will depend on the timescale that is being studied; the effect of immature DGCs on the encoding of individual events is likely to be distinct from the contribution of persistent neurogenesis over a lifetime. Second, the specific plasticity-related and physiological properties of immature DGCs probably have an effect on the function of the entire dentate gyrus and hippocampal circuit. As a result, conditions that affect immature DGCs are predicted to have a substantial effect on overall hippocampal function.

Behavioural studies of adult-born DGC function

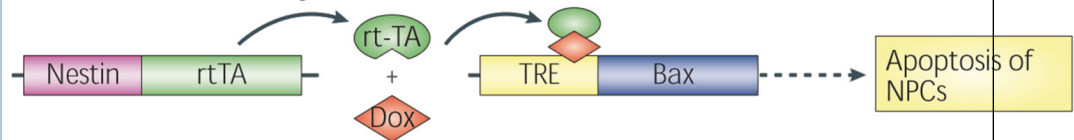
In the past decade, accumulating evidence has suggested a correlation between the number of adult-born DGCs and an animal’s cognitive ability (see above). Nevertheless, studies that directly investigated the effect of depletion of adult-born DGCs on an animal’s cognitive ability have generated inconsistent results (see Supplementary information S1 (table)), making it difficult to formulate basic principles regarding the function of adult neurogenesis in learning and memory. In this section, we describe the experimental observations, discuss possible causes for the inconsistencies and propose potential strategies to resolve them.

Box 2 | Methodologies for ablating neurogenesis

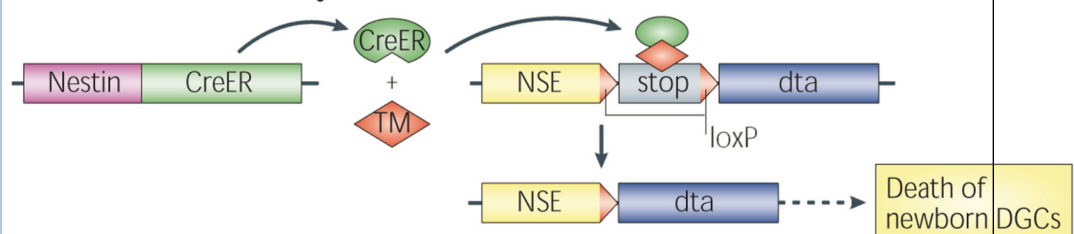
GFAP-tk or nestin-tk system



Nestin-rtTA/TRE-BAX system



Nestin-CreER/NSE-DTA system



The early approaches for ablating neurogenesis such as anti-mitotic drug treatments (for example, methylazoxymethanol acetate and temozolomide) and irradiation^{89,95} were traditionally used in cancer therapy. These methods take advantage of the fact that the proliferative neural progenitor cells (NPCs) are more sensitive than differentiated neurons to these insults, which disrupt cell cycle progression. Although these methods are effective in reducing neurogenesis, they have considerable side effects in animals, such as general health deterioration and inflammation^{123,124}.

More precise, cell type-specific targeting of neurogenesis could be achieved through the development of numerous transgenic mouse models by expressing suicide genes driven by NPC-specific promoters (NPCSPs), such as nestin and glial fibrillary acidic protein (GFAP) promoters (see the figure). In an example of such a method, expression of thymidine kinase (tk) from herpes simplex virus in NPCs facilitates the incorporation of the nucleotide analogue ganciclovir (GCV) into DNA during replication, which disrupts DNA replication and leads to cell death (top panel)^{88,125}. In the nestin-rtTA/TRE-BAX (nestin-reverse tetracycline-controlled transactivator/tetracycline response element-BAX) mice (middle panel), the expression of the pro-apoptotic protein BAX is induced by doxycycline (Dox), which activates the apoptosis pathway in NPCs⁸⁷. In the nestin-CreER/NSE-DTA (nestin-CRE recombinase-modified oestrogen receptor/neuron-specific enolase 2-diphtheria toxin fragment A) mice (bottom panel), nestin-CreER targets the expression of a tamoxifen (TM)-inducible form of *Cre* in NPCs and a CRE-inducible DTA is engineered into the locus of the *Nse* gene⁹⁷. TM-induced CRE activity leads to the recombination of *loxP* sites (red triangles) and removal of the stop cassette upstream of the *dta* gene, thus allowing the expression of *dta* from the NSE promoter. This strategy allows tamoxifen-dependent ablation of NPC progeny that are committed to a neuronal lineage.

Our increasing understanding of the molecular mechanisms of adult neurogenesis allows the development of new techniques for blocking neurogenesis. WNT signalling is important for neuronal fate determination at the early stages of neurogenesis. A lentivirus-mediated

overexpression of a dominant-negative WNT protein that blocks WNT signalling suppresses the production of adult-born dentate granule cells (DGCs) in the subgranular zone⁹⁴. TLX is an orphan nuclear receptor that is of key importance for the proliferation of NPCs. Induced deletion of *Tlx* in the adult mouse brain by cytomegalovirus CreER also suppresses adult neurogenesis⁹³. Polycomb 3 homologue (PC3; also known as CBX8) is a factor that promotes terminal differentiation in the CNS. Ectopic expression of PC3 in NPCs results in a smaller NPC population, which is accompanied by accelerated differentiation and impaired morphogenesis of adult-born DGCs¹²⁶.

A common strategy for studying the function of adult neurogenesis is to examine the consequences of neurogenesis ablation on cognitive performance. Several methods have been developed to suppress the production of new neurons in the adult brain (BOX 2). Most of the studies evaluated cognitive performance by using common behavioural paradigms designed to examine the role of the hippocampus in learning and memory (see Supplementary information S1 (table)). These studies have revealed that neurogenesis is required for some but not other hippocampus-dependent tasks, and is not required for tasks that do not involve the hippocampus⁸⁷⁻⁸⁹. For example, the ablation of adult neurogenesis in rats by methylazoxymethanol acetate (MAM) treatment results in deficits in hippocampus-dependent trace conditioning tasks but not in hippocampus-independent delay conditioning tasks^{89,90}. Among several other hippocampus-dependent tasks, MAM treatment prevents the improvement of long-term recognition memory by environmental enrichment, but it does not alter contextual fear conditioning or spatial navigation learning in the MWM^{42,90}. Similar task-dependent involvement of hippocampal neurogenesis has been observed in other studies in both rats and mice^{87,88,91-94}. Therefore, the involvement of adult neurogenesis in learning and memory seems to depend on the demands in each task, similar to the task-specific responsiveness of adult-born DGCs discussed above⁶⁴.

Even among studies that used the same task to investigate the cognitive effects of hippocampal neurogenesis, the data can be inconsistent (see Supplementary information S1 (table)). The reference memory version of the MWM is one of the most frequently used tests for the functional assessment of neurogenesis. Surprisingly, an apparent deficit in spatial-navigation learning, as measured by the latency or the distance travelled to reach the hidden platform, was only detected in two mouse studies using genetic ablation of neurogenesis^{87,93}, but not in studies using other knockdown methods to prevent neurogenesis^{88,90,94-96}. However, many studies showed impairments in the long-term but not the short-term retention of spatial memory as a consequence of reduced adult neurogenesis^{92,94,96,97}. Similarly, inconsistent data have been obtained regarding the role of adult neurogenesis in contextual fear conditioning, which is another commonly used hippocampus-dependent learning and memory task. Deficits in this task have been repeatedly observed in rodents in which neurogenesis was almost completely eliminated by irradiation^{88,98,99} and in two lines of transgenic mice with genetic ablation of neurogenesis^{88,97}. However, such defects were not detected in several other rodent studies in which neurogenesis was suppressed using different methods^{87,90,92,93}.

Some of these results support the hypotheses that have arisen from computational studies. For example, the observations of impaired long-term spatial memory retention in some studies are consistent with the prediction from computational studies that the addition of newborn neurons helps to maintain the stability of old memories during the encoding of new information⁸⁰⁻⁸². Similarly, the involvement of neurogenesis in tasks such as trace conditioning and contextual fear conditioning support the hypothesis that newborn neurons are involved in associating events that occur within a short time span^{83,84,86}. However, these roles for neurogenesis are not corroborated by other studies (see Supplementary information S1 (table)).

Possible factors underlying contradictory findings

Many factors in the details of experimental design might have contributed to these discrepancies, including the species and strains of animals tested, the efficiency and side effects of ablation methods, the specific parameters in the design of behavioural paradigms and the parameters for evaluation of the behavioural phenotype (see Supplementary information S1 (table)). For example, recent studies revealed that contextual learning was defective in irradiated rats and in some but not other strains of mice^{17,88}. Even in the same mouse strain, contextual fear conditioning deficits were detected if mice were treated with a high dose but not a low dose of irradiation, with the high dose of irradiation causing a greater reduction of neurogenesis¹⁰⁰. Blocking neurogenesis (the rate of which declines exponentially with ageing^{101,102}) at different ages can result in substantially different behavioural phenotypes^{103,104}.

The designs of behavioural paradigms are another source of discrepancies in the aforementioned studies. For example, prolonged pre-training procedures may mask defective performance in behavioural tasks^{90,93}. In addition, different studies use different parameters to evaluate behavioural phenotypes, which are not equally sensitive for revealing learning and memory deficits. For example, a recent study¹⁰⁵ showed that ablation of neurogenesis by temozolomide treatment in mice did not alter path length or latency to find the hidden platform during the learning phase of the MWM task; however, it did affect the ability of the animals to efficiently adopt a precise, place-specific strategy to localize the hidden platform, a function that is presumably dependent on the hippocampus. It is therefore likely that the most commonly used parameters in the MWM, such as path length and latency to find the platform, may not be sensitive enough to reveal the subtle defects in learning caused by loss of adult neurogenesis.

In addition to the differences in the experimental details discussed above, there are two issues that are worth particular consideration when comparing data from different studies. First, a lack of adult-born DGCs at different maturation stages may lead to different behavioural phenotypes. As discussed in previous sections, newly generated DGCs that are less than 1 week old have not yet made connections with the local network and would probably not be involved in learning and memory. Indeed, rats that had received a 6-day MAM treatment were not impaired in eye blink trace conditioning when tested 2 days after treatment, in contrast to rats that had undergone a 14-day treatment scheme⁸⁹. Furthermore, adult-born DGCs aged between 1 and 6 weeks may make distinct contributions to learning and memory owing to their enhanced excitability and plasticity, which could also account for the memory impairment in rats treated with MAM for 14 days⁸⁹. Using pharmacogenetic approaches to reduce the number of adult-born DGCs at particular maturation stages in mice, a recent study detected deficits in long-term spatial memory and extinction of spatial preference and contextually evoked fear by specifically ablating adult-born DGCs of approximately 1–4 weeks of age — that is, before they were fully mature⁹². The transient nature of this transgenic model also allowed the authors to show that the phenotype was restored after replenishment of the affected DGC population, further corroborating the notion that the behavioural deficits were caused by reduced adult neurogenesis⁹². Finally, the survival of adult-born DGCs was compromised around 4–6 weeks after their birth in mice lacking *kruppel-like factor 9*. These mice were impaired in contextual discriminative learning, implying a role for adult-born DGCs at 4–6 weeks of age in pattern separation³². Together, these observations suggest that adult-born DGCs at the immature stage may make a distinct contribution to learning and memory.

Another major reason for data discrepancy in the field is that the behavioural paradigms used in most studies do not directly assess the function of the dentate gyrus, despite the fact that adult-born neurons differentiate and integrate into the neural network exclusively as DGCs. Instead, the majority of studies of adult neurogenesis investigate the role of adult-born DGCs in hippocampus-dependent functions. It is possible that learning and memory in some common

hippocampus-dependent behavioural tasks do not rely on the dentate gyrus, as direct inputs from the entorhinal cortex to CA3 and CA1 might underlie the tasks (FIG. 1). Recent studies suggest that the monosynaptic pathway (entorhinal cortex–CA1–entorhinal cortex) is sufficient for MWM learning under certain conditions¹⁰⁶. In fact, this monosynaptic pathway is necessary for forming precise spatial representations, as suggested by physiological studies in rats¹⁰⁷. Additionally, the absence of NMDA receptor-mediated plasticity in the dentate gyrus does not affect the performance of mice in the MWM task or in the contextual fear conditioning task⁷⁵. Therefore, examining the role of hippocampal neurogenesis using such tasks may result in inconsistent observations.

Previous studies suggest that pattern separation might be a role of the dentate gyrus in both animals and humans^{73,75,108}. Does adult neurogenesis have a role in pattern separation, and if so, how? Computational modelling suggests that immature adult-born DGCs might function as pattern integrators by responding indiscriminately to events that occur closely in time⁸³. A lack of neurogenesis may allow each event to be encoded more distinctly, which could be beneficial when a large amount of information needs to be learned in a short time. Indeed, mice in which neurogenesis was suppressed by two independent approaches performed better than controls in a spatial working memory task in an eight-arm radial maze with high interference (for example, the sample arms and/or goal arm being used repeatedly and interchangeably) and long delays between the sample trial and the test trial¹⁰⁹. In this case, it is possible that a lack of pattern integration mediated by adult-born DGCs may have allowed each learning trial to be encoded more distinctly, resulting in less intra-trial or inter-trial interferences and eventually the observed performance improvement.

The role of adult-born DGCs in pattern separation has recently been examined directly in behavioural tasks for spatial pattern discrimination. Chronic ablation of neurogenesis by either irradiation or lentivirus-mediated overexpression of dominant-negative *Wnt* in mice impaired performance in two spatial discrimination tasks when two stimuli were presented with limited spatial separation but not when two stimuli were widely separated in space⁹¹. Although the function of the dentate gyrus in these two specific tasks awaits validation, this finding provides the first evidence for a possible involvement of adult-born DGCs in pattern separation. How does this observation relate to the pattern integration function of adult-born DGCs? One possible explanation is that the integrative ability of adult-born DGCs facilitates the association of the target stimuli with other elements in the context and leads to better pattern separation and eventually better spatial discrimination ability.

In summary, despite all of these inconsistent results, accumulating evidence suggests that adult-born DGCs do make contributions to learning and memory, consistent with computational theories that newborn neurons in the networks are likely to be selected for encoding new information. To resolve the controversies discussed above, future studies need to take into consideration both the design of behavioural paradigms (for example, by directly targeting the function of the dentate gyrus and carefully selecting the experimental timeline) and characteristics of the experimental animals (for example, the species and age).

Conclusions and future directions

Neurogenesis in the hippocampus represents a form of cellular plasticity in the adult brain that had not been previously recognized. Activity-dependent regulation of neurogenesis and experience-dependent participation of adult-born DGCs in information processing both imply a relationship between adult neurogenesis and learning and memory. Despite mixed results, behavioural evaluation of rodents with reduced adult neurogenesis has consistently suggested an involvement of adult-born DGCs in learning and memory. Nevertheless, the precise function of adult-born DGCs in cognitive processes remains elusive. Although many hypotheses have

been proposed by computational modelling, most of them have not been explicitly tested in experimental studies.

Emerging data have already suggested that hippocampal neurogenesis is involved in pattern separation⁹¹, which can be modulated by pattern integration⁸³. The observation that adult-born DGCs between 2 and 6 weeks of age are hyper-excitabile^{18,29,30} might mean that these DGCs are particularly suited to mediating pattern integration. It will be intriguing to investigate whether these adult-born DGCs have a distinct influence on pattern separation and integration in a maturation stage-dependent manner. Furthermore, the long-lasting nature of these properties (that is, hyper-excitability and enhanced plasticity) and the constant turnover of immature DGCs suggest that adult-born DGCs could have a role in temporal association and separation during learning and memory. Experimental evidence is needed to support this hypothesis. Moreover, adult-born DGCs at 4–6 weeks of age show enhanced plasticity²⁹, which makes them more suited to encoding new information, as predicted by computational studies (see above). These hypotheses are consistent with the finding that adult-born DGCs are preferentially activated upon memory retrieval once they reach a certain stage of maturation^{62,63}. Further studies are needed to clarify the functional importance of this preferential activation and recruitment and whether it is dependent on the maturation stage of adult-born DGCs.

An important consideration when interpreting both IEG expression and behavioural studies is that it remains unclear whether adult neurogenesis is involved in the encoding, the consolidation or the recall of memory. Combining optogenetic techniques¹¹⁰ with retrovirus-mediated labelling of adult-born DGCs²⁸ could provide a system to examine the physiology of adult-born DGCs in awake, behaving animals. Furthermore, some computational models suggest that addition of new neurons to the network increases memory capacity in the hippocampus⁸⁰⁻⁸². Intriguingly, a recent study in mice suggested that adult neurogenesis facilitated memory reorganization that led to a gradual reduction of the hippocampus-dependence of memories and the permanent storage of these memories in extra-hippocampal regions¹¹¹. Finally, both computational and experimental studies are needed to investigate whether (and if so, how) adult-born DGCs are involved in other dentate gyrus-mediated functions, such as conjunctive encoding¹¹². In summary, future studies using a combination of molecular, genetic, behavioural and physiological approaches will be helpful in testing these hypotheses and elucidating the involvement of adult-born DGCs in cognition.

Hippocampal neurogenesis in humans is affected by various neurological disorders, including depression, epilepsy, cerebral ischaemia, Alzheimer's disease and Parkinson's disease, many of which are associated with cognitive decline⁶. Recently, several non-invasive imaging techniques have been developed for monitoring neurogenesis in human subjects^{113,114}. Although their robustness and reproducibility await further testing, these techniques might allow the function of neurogenesis to be investigated in humans under various physiological or pathological conditions. Combined with sophisticated cognitive tasks and psychiatric examinations in humans, such studies have the potential to reveal functional mechanisms of adult neurogenesis that cannot be addressed in animal models, and will hopefully lead to improvement in therapies for these neurological disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Glossary

Filopodia	Thin, long and highly motile protrusions that are the predecessors of spines in an early stage of spine formation.
Thorny excrescences	The complex spines on the dendrites of CA3 pyramidal neurons in the stratum lucidum. These spines form multiple synapses with mossy fibres of dentate granule cells.
Morris water maze (MWM)	A spatial learning paradigm in which an animal must learn a fixed location of a platform using distal spatial cues. Animals are released from a variable start point in each trial to encourage them to use a spatial strategy to solve the task.
BrdU birth-dating	The thymidine analogue bromodeoxyuridine (BrdU) is injected into adult animals and incorporated into cells synthesizing DNA in preparation for division, which are visualized using immunocytochemistry. Because the <i>in vivo</i> half-life of BrdU is ~2 hours, it only labels dividing cells in a short time window.
Sparse coding	A type of neural code in which each event is encoded by the strong activation of a small set of neurons.
Attractor	A stable point in a dynamic system. Attractors are typically found in neural networks with strong feedback connections and are determined by the weights of the recurrent connections between units (neurons) in the network. Depending on the initial conditions and external inputs, the network will evolve towards one of these stable states.
Pattern integration	The ability of immature dentate granule cells to provide an association between events owing to their indiscriminate responses to inputs.
Pattern completion	A process by which a stored neural representation is reactivated by a cue that consists of a subset of that representation.
Trace conditioning	A form of classical conditioning in which the conditioned stimulus occurs before the unconditioned stimulus with a stimulus-free period (the 'trace interval' or 'conditioning interval') between the two.
Delay conditioning	A form of classical conditioning in which the onset of the conditioned stimulus precedes the onset of the unconditioned stimulus, with an overlap between the presentation of the conditioned stimulus and the presentation of the unconditioned stimulus.
Recognition memory	The ability to correctly remember something that has been previously encountered. It is a subcategory of declarative memory.
Contextual fear conditioning	A form of conditioning in which animals associate the conditioning context (the 'neutral' conditioned stimulus) with an aversive stimulus — for example, a foot shock.
Spatial discrimination	The ability to discriminate separate locations in space.

Conjunctive encoding A form of information encoding in which a neuron requires the concurrent activity of multiple input neurons. In the hippocampus, dentate granule cells can associate spatial information from the medial entorhinal cortex with non-spatial information from the lateral entorhinal cortex to form a multi-dimensional representation of an event.

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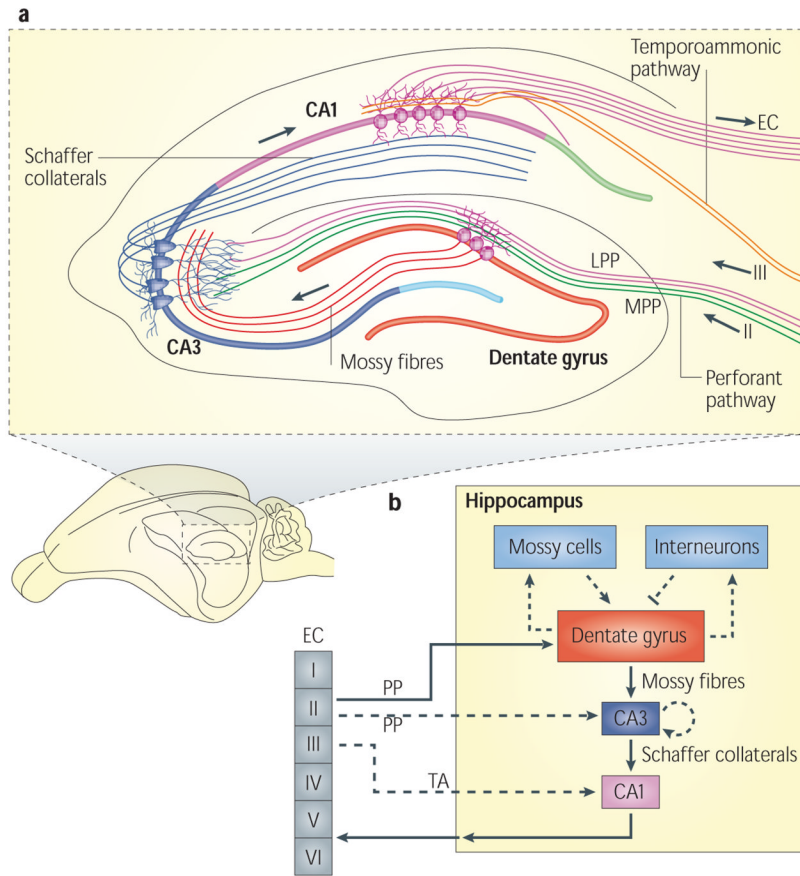


Figure 1. The neural circuitry in the rodent hippocampus

a | An illustration of the hippocampal circuitry. **b** | Diagram of the hippocampal neural network. The traditional excitatory trisynaptic pathway (entorhinal cortex (EC)–dentate gyrus–CA3–CA1–EC) is depicted by solid arrows. The axons of layer II neurons in the entorhinal cortex project to the dentate gyrus through the perforant pathway (PP), including the lateral perforant pathway (LPP) and medial perforant pathway (MPP). The dentate gyrus sends projections to the pyramidal cells in CA3 through mossy fibres. CA3 pyramidal neurons relay the information to CA1 pyramidal neurons through Schaffer collaterals. CA1 pyramidal neurons send back-projections into deep-layer neurons of the EC. CA3 also receives direct projections from EC layer II neurons through the PP. CA1 receives direct input from EC layer III neurons through the temporoammonic pathway (TA). The dentate granule cells also project to the mossy cells in the hilus and hilar interneurons, which send excitatory and inhibitory projections, respectively, back to the granule cells.

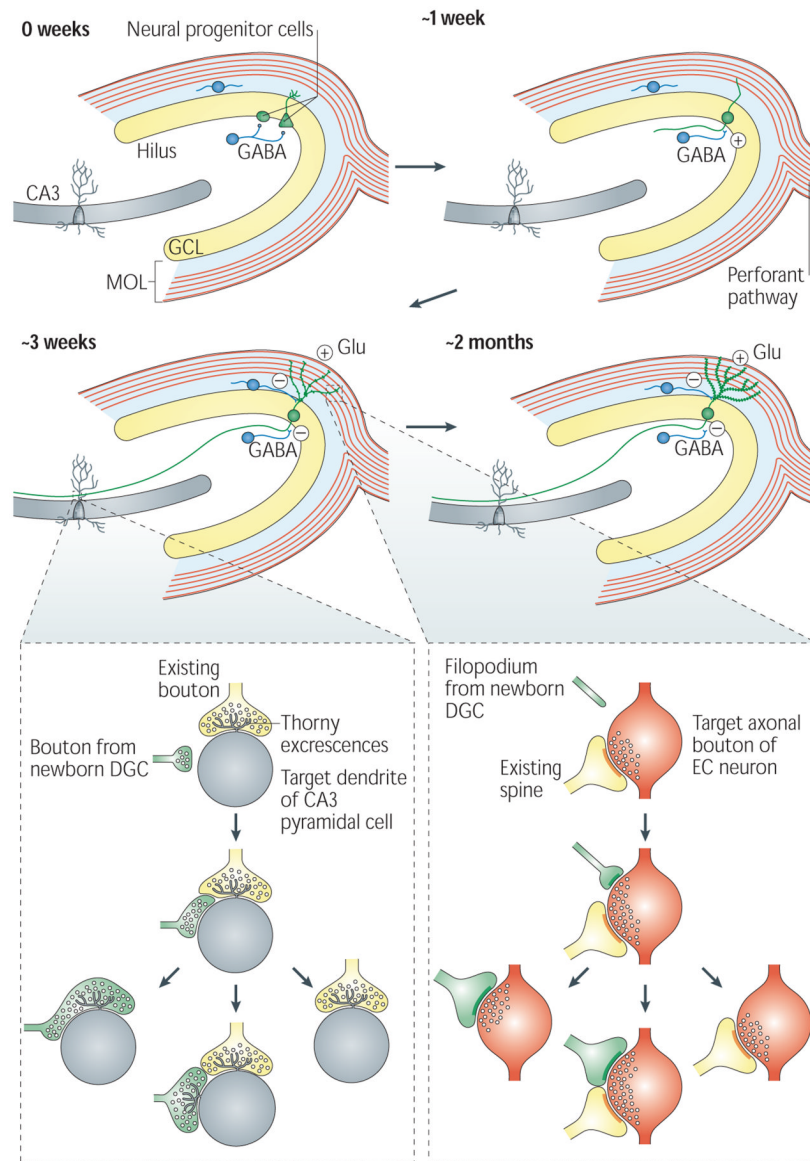


Figure 2. Adult hippocampal neurogenesis

The proliferation of neural progenitor cells (NPCs) with two different morphologies gives rise to adult-born dentate granule cells (DGCs) (shown in green). The fate-committed, adult-born DGCs undergo several stages of development, with gradual changes in morphological and physiological characteristics. About 1 week after birth, the adult-born DGC extends its dendrite into the granule cell layer (GCL) and molecular layer (MOL) and projects the axon into the hilus toward CA3. The DGC receives excitatory GABA (γ -aminobutyric acid)-ergic input, presumably from local interneurons (shown as blue cells). During the third week after birth, the DGC receives glutamatergic input (Glu) from the perforant pathway. At this stage, the GABA input changes from being excitatory to being inhibitory¹⁹. Both efferent and afferent synapses of the adult-born DGCs begin to form around this time²⁴⁻²⁶.

At around 2 months of age, the basic structural and physiological properties of the adult-born DGCs are indistinguishable from those of mature DGCs. The inset panels illustrate the competitive nature of synapse formation²⁴⁻²⁵. Left inset: a small bouton (shown in green) from the axon of an adult-born DGC contacts the dendritic shaft (shown in grey) of a CA3 pyramidal

neuron at a site near the thorny excrescences that contact an existing axonal bouton (shown in yellow). During the subsequent development of the new synapse, the bouton from the newborn DGC either replaces the existing axonal bouton or forms a new thorny excrescence nearby, or retracts. Right inset: the filopodium (shown in green) from an adult-born DGC dendrite extends to an axonal bouton (shown in red) that is associated with another spine (shown in yellow), which leads to the eventual formation of either a monosynaptic bouton targeting spines from the adult-born DGC or a multisynaptic bouton, or leads to retraction.

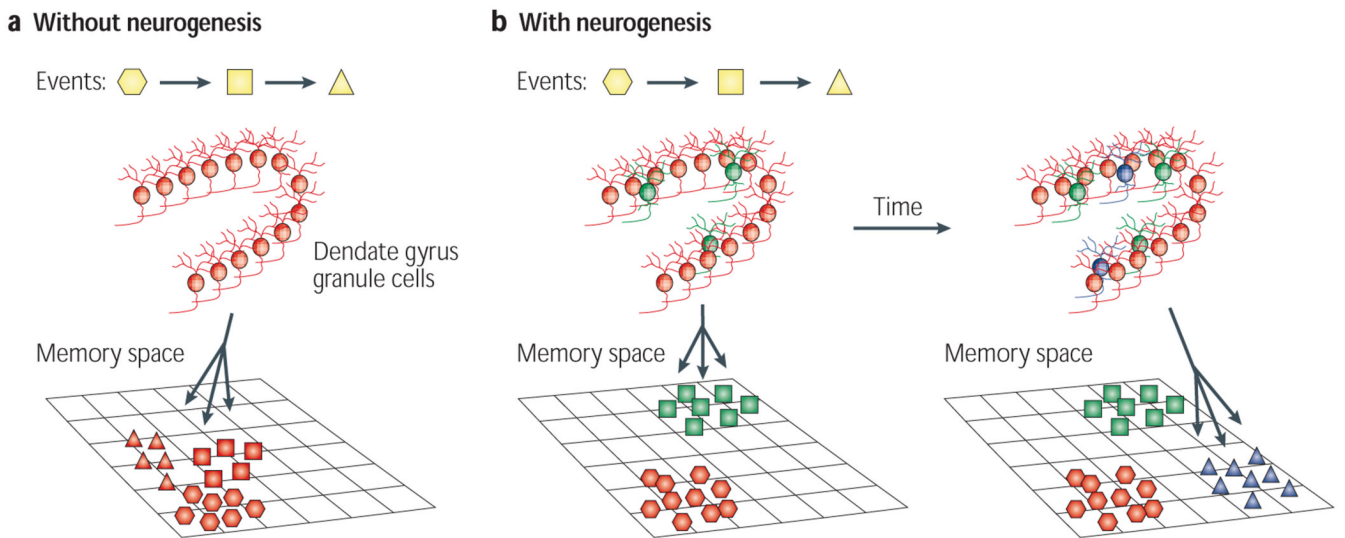


Figure 3. Computational theories of neurogenesis

a | Without neurogenesis, new events (represented by different shapes) are limited by the set of sparse ‘codes’ (combinations of active neurons) provided by mature granule cells in the dentate gyrus. This can lead to the dentate gyrus not having the flexibility to encode new memories well^{80,82} or to interference between memories formed in the hippocampus (shown as a cluster of memories in a projection of the high-dimension hippocampal ‘memory space’)⁸¹. **b** | New neurons (shown in green) provide new sparse codes for encoding new information, while older memories are preserved because they are represented by older neurons (shown in red). This can facilitate the formation of new memories while avoiding catastrophic interference, saving older memories⁸⁰⁻⁸² (shown in the left panel as two separate clusters of memories in a projection of the high-dimension hippocampal memory space). The three-way arrow indicates that new neurons can change how memories are encoded in the hippocampal network. Neurons born at different times (shown in green and blue in the right panel) represent different inputs, and the sparse codes generated at a particular time are clustered together (active neurons in a population are similar in composition to one another), separately from sparse codes that were generated at a different time, essentially encoding time into new memories^{83,84,86}.