The role of adult hippocampal neurogenesis in brain health and disease

Tomohisa Toda[1,*], **Sarah Parylak**[1,*], **Sara B. Linker**[1], and **Fred H. Gage**[1]

[1]Laboratory of Genetics, The Salk Institute for Biological Studies, 10010 North Torrey Pines Road, La Jolla, CA 92037, USA

Abstract

Adult neurogenesis in the dentate gyrus of the hippocampus is highly regulated by a number of environmental and cell-intrinsic factors to adapt to environmental changes. Accumulating evidence suggests that adult-born neurons may play distinct physiological roles in hippocampus-dependent functions such as memory encoding and mood regulation. In addition, several brain diseases, such as neurological diseases and mood disorders, have deleterious effects on adult hippocampal neurogenesis, and some symptoms of those diseases can be partially explained by the dysregulation of adult hippocampal neurogenesis. Here we review a possible link between the physiological functions of adult-born neurons and their roles in pathological conditions.

Introduction

Since the discovery and subsequent affirmation of neurogenesis in the dentate gyrus (DG) of the hippocampus, adult hippocampal neurogenesis has been implicated in cognitive processes under normal physiological conditions such as learning, memory, pattern separation, and cognitive flexibility. The addition of new neurons in the DG provides substantial structural and functional plasticity to the tri-synaptic hippocampal circuit through characterized physiological and connective features of immature adult-born neurons during their critical periods. Feedback inhibition onto mature dentate granule cells (DGCs) from immature adult-born neurons seems to regulate the sparse coding of DGCs, which may underlie contextual discrimination and a degree of meta-plasticity. Importantly, adult hippocampal neurogenesis is conserved in most mammalian brains, including human. Accumulating evidence suggests that dysregulation of adult hippocampal neurogenesis may be associated with cognitive decline in neurological disorders and psychological symptoms in psychiatric disorders. However, most of our knowledge regarding the physiological and pathological contributions of adult-born hippocampal neurons to brain function has been obtained from rodent models, which exhibit a significant amount of adult hippocampal

Correspondence should be addressed to: Dr. Fred H. Gage, Laboratory of Genetics – LOG-G, The Salk Institute for Biological Studies, 10010 N. Torrey Pines Road, La Jolla, CA 92037, gage@salk.edu.
*These authors contributed equally to this work

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neurogenesis and provide technical advantages, such as the availability of genetic, imaging and detailed behavioral analyses. Due to the technical limitations of human studies, our understanding of the functional role of adult hippocampal neurogenesis in humans relies on retrospective analyses using post-mortem tissues. Therefore, it remains unclear how adult-born DGCs functionally modulate complex behavior and how dysregulation of adult neurogenesis mediates brain disorders in the human brain.

In the first half of this review, we summarize the molecular mechanisms underlying the regulation of adult hippocampal neurogenesis and the functional contributions of adult-born neurons to the neural network and to hippocampus-dependent behavior with the main focuses on rodent experiments. In the latter half, we summarize how dysregulation of adult neurogenesis may mediate malfunctions of hippocampus-dependent processing and behavior, and we discuss whether future research can translate the findings from rodent models to humans to develop therapeutic strategies by manipulating adult hippocampal neurogenesis.

Overview of adult neurogenesis

Adult hippocampal neurogenesis is a process that describes the generation of new functional DGCs from adult neural stem cells through the amplification of intermediate progenitors and neuroblasts, as well as the integration of these new neurons into the existing neural circuits. In other words, adult hippocampal neurogenesis provides a substantial degree of structural and functional plasticity in the tri-synaptic hippocampal circuit. Adult hippocampal neural stem cells (radial glia-like cells, RGLs; Type 1 cells) exist in the subgranular zone (SGZ) of the DG (Fig. 1). The evidence for adult hippocampal neurogenesis was first observed in rodents[1, 2] and was subsequently confirmed to exist in humans and non-human primates by several groups [3–8]. Further evidence of adult hippocampal neurogenesis in humans was provided by immunohistochemical analysis, retrospective birth dating methods using the level of ^{14}C[9], double-immunohistochemical analyses[7], and gene expression associated with neurogenesis[10].

Various forms of activation of the environmental niche stimulate quiescent RGLs and facilitate their proliferation. Active RGLs self-renew and also generate intermediate neural progenitors (NPs) that subsequently differentiate into neuroblasts and finally give rise to DGCs or, to a lesser extent, to astrocytes. These processes, including proliferation, differentiation, migration, neurite extension and synaptic integration, are regulated by a number of signals from the environmental niche and local neural circuits, which are summarized in Table 1.

Environmental factors

An intriguing feature of adult hippocampal neurogenesis is that the process is regulated by such factors as the environment and an individual's emotional or physiological status. In other words, adult-born DGCs can in theory be generated on demand in response to environmental signals, which could provide a degree of meta-plasticity in the adult hippocampal neurogenesis-dependent reorganization of hippocampal circuits. An enriched

environment, including a larger cage area, novel objects, and running wheels, has been shown to significantly increase the number of adult-born neurons and the volume of the granule cell layer and to improve the speed of spatial learning in rodents [3]. A follow-up study revealed that voluntary running alone selectively increased proliferation of adult NPs/neuroblasts, whereas environmental enrichment promoted the survival of adult-born DGCs through the increased integration of immature neurons [120].

These processes are mediated by several types of signaling, including glutamatergic and GABAergic inputs from local neural networks [111114, 121–123]. Glutamatergic inputs through NMDA receptors are critical for the survival of immature neurons [121], and surviving neurons are functionally integrated into existing circuits within one month [124]. A short exposure to an enriched environment depolarizes immature neurons through GABAergic inputs that enable activation of NMDA receptors, which in turn allows immature neurons to respond to future glutamatergic synaptic inputs [125]. A recent study revealed that the combination of GABAergic inputs from the molecular layer and the granule cell layer in the gamma frequency range evoked action potentials in young adult-born DGCs [108]. Furthermore, the study revealed the spatial and temporal integration dynamics of the GABAergic and glutamatergic inputs required to elicit action potentials in young adult-born DGCs. Thus, the oscillatory activity in the hippocampus could regulate the integration of young DG neurons into hippocampal neuronal networks through GABAergic signaling. Importantly, the effects of environmental enrichment on the survival and integration of adult-born DGCs are restricted to the first three weeks after the birth of the neurons [122].

Following the survival checkpoint, the time course of neuronal maturation is also modulated by local network activity, which in turn is also modulated by physical activity or exposure to an enriched environment [126, 127]. Optogenetic silencing of the dentate during exposure to a novel environment prevents the environmentally induced increase in integration of immature DGCs [128]. Furthermore, GABAergic inputs from parvalbumin-positive interneurons are essential for an enriched environment to enhance the integration and maturation of young DG neurons [123]. The increase in surviving and integrating immature neurons based on environmental inputs could be crucial, as the surviving adult-born DGCs could potentially be tuned to respond to future occurrences of the same experiences that they experience during their maturation periods [122, 129] (see also the following section for the functional roles of adult-born DGCs). Intriguingly, an enriched environment can also change the connectivity of adult-born DGCs [114], implying that those neurons may play distinct roles in local neural circuits. Exercise itself also alters the connectivity of the DG. Neurogenesis recruits additional inputs from entorhinal cortex but increases the frequency of inhibitory input to mature DGCs, potentially contributing to the overall sparsity of the DG network [130]. Conversely, stress and aging reduce adult neurogenesis in the DG through corticosteroid signaling [4, 33, 131, 132]. Importantly, adverse experiences during childhood can have prolonged effects on adult neurogenesis and hippocampus-mediated stress responses [34], suggesting that experience in early life may epigenetically modulate the process of adult hippocampal neurogenesis. In addition, the levels of hormones such as estrogen and thyroid hormones regulate the rate of adult neurogenesis [25, 133]. Thus, in addition to environmental stimuli from the external world, the physiological state of an individual plays a prominent

role in the regulation of adult hippocampal neurogenesis in the physiological and pathological conditions described below.

Physiological maturation of newborn neurons and their synaptic integration

Adult hippocampal neurogenesis begins with the division of NPs in the SGZ of the DG. Progenitors that commit to a neuronal cell fate migrate into the granule cell layer, typically stopping within the inner third [134]. Many of these newborn neurons will not survive to maturity. At least two crucial checkpoints exist for survival: the first within the first few days after cell birth and the second at around three weeks [135]. Ambient GABA provides the first input to immature DGCs [107], followed within the first two weeks of life by synaptic connections from local inhibitory interneurons [113, 134]. GABAergic inputs are depolarizing prior to three weeks of age of the newly born neurons[113] and are capable of triggering action potentials[108]. As immature DGCs develop, they send axons through the mossy fiber pathway to contact CA3 and also send dendrites into the molecular layer to receive perforant path input from the entorhinal cortex. Dendritic growth and connectivity are sensitive to changing conditions during the maturation period, such as exposure to an enriched environment[123, 127]. Synaptic connections from the perforant path are detectable within three to five weeks [113, 134]. Axonal projections to CA3 are detectable within two weeks [136, 137] but appear immature and are targeted to dendritic shafts of CA3 pyramidal neurons rather than to the thorny excrescences where mature DGCs send their boutons [136, 137]. Functional connections to CA3 can be observed by four to six weeks[138]. Proper integration of new DGCs is dependent upon activity in the existing dentate circuitry during the maturation period. Aberrant activity, such as epileptic seizures, can cause ectopic integration of adult-born DGCs in the hilus as well as improper targeting of DGCs axons back to the granule cell layer [94]. Aberrant GABAergic activity due to the presence of the apolipoprotein E 4 (apoE4) allele, which is associated with high Alzheimer's disease (AD) risk, has been observed to reduce dendritic length and complexity in adult-born DGCs [37]. The total time to achieve a mature morphological and electrophysiological phenotype is approximately eight weeks in rodents.

During a window of time four to six weeks after birth, adult-born DGCs are functionally connected to the tri-synaptic circuit but are electrophysiologically distinct from their mature counterparts. In slice preparations, immature DGCs are responsive to a broader range of inputs[139], hyperexcitable to stimulation[140, 141], and have a lower threshold for plasticity [111, 140] than mature DGCs. *In vivo*, at six weeks of age or less, DGCs show greater rates of Ca^{2+} transients and show less spatial tuning than mature cells[142]. Immature DGCs may be more likely to be recruited into the active ensemble of neural networks during learning, as shown by higher rates of immediate early gene (IEG) expression[129]; however, some reports suggest that immature DGCs are no more likely to be recruited than developmentally born cells[143]. Immature neurons receive less inhibition but also lower excitatory drive than mature cells[144]. This distinct physiological state suggests that immature DGCs play a unique role within the circuit. Paradoxically, part of that role appears to be to keep neighboring mature DGCs quiet. Using voltage-sensitive dyes, Ikrar et al. [145] found that ablation of neurogenesis

resulted in a wider spread of depolarization after stimulation. A similar effect of adult-born neurons on sparsity has been observed using IEG staining. Knocking down neurogenesis results in a higher proportion of DGCs that are IEG+ during a reversal learning task[146], whereas optogenetic activation of adult-born cells under seven weeks of age reduced the fraction of IEG+ mature DGCs after exposure to a novel environment[147]. When animals are exposed sequentially to two similar environments, increased neurogenesis has been associated with lower rates of overlap between the DG ensembles activated by each exposure [148]. These results suggest that adult-born DGCs, despite their individual hyperexcitability, support network level sparsity and allow similar events to be represented by distinct neuronal ensembles.

Recent efforts have sought to understand the mechanisms of adult-born DGC-induced sparsity by investigating the maturation of immature DGC connections. Anatomical evidence has identified a transient period around four weeks of age in which immature DGCs have a greater number of filopodia-like synapses on CA3 interneurons than mature DGCs[138]. At the same time, synapses onto excitatory CA3 pyramidal cells do not appear mature until six to eight weeks, and optogenetic stimulation of four-week-old cells is sufficient to induce the IEG FOS in CA3 interneurons but not in pyramidal cells[138]. This finding suggests that one of the earliest impacts of immature DGCs reaching CA3 is feedforward inhibition, not excitation. In support of this hypothesis, neurogenesis knockdown in DG leads to increased overlap of IEG+ CA3 neurons after exposure to two similar contexts [149]. The increased overlap arises from an increase in the number of CA3 neurons responsive to the second exposure, reflecting a loss of sparsity when the network is challenged with a novel yet similar stimulus.

How immature DGCs might inhibit mature DGCs within the granule cell layer is less clear. Optogenetic stimulation of immature four-week-old DGCs recruited less feedback inhibition than stimulating seven-week-old DGCs[109], suggesting that the development of connections providing feedback inhibition occurs relatively late in the maturation process. Similarly, stimulation of the perforant path in combination with a pre-stimulation of DGCs resulted in a greater overall reduction in the population spike when seven-week-old rather than four-week-old cells were stimulated. When a broader range of zero- to seven-week-old old adult-born DGCs were stimulated in another study, however, the net effect of immature cell activation was increased inhibition to mature cells[147]. Ablating neurogenesis with irradiation resulted in a pronounced drop in inhibition, with a significant but smaller reduction in excitation[147]. In both of these studies, data were collected from *ex vivo* slices, where some connections were inevitably severed. The net balance of excitatory and inhibitory forces provided by specific ages of DGCs *in vivo* remains unresolved. *In vivo,* competition over synaptic contacts may also impact the contribution of mature DGCs. Increasing neurogenesis by deleting the pro-apoptotic gene *Bax* leads to a loss of spine density and reduced excitatory postsynaptic currents (EPSCs) in mature DGCs. In contrast, neurogenesis knockdown enhances EPSCs in mature cells [150]. These results suggest that some existing synaptic contacts may be redistributed from mature neurons to immature neurons as the latter integrate into the DG circuitry.

The functional role of adult-born neurons in cognition and behavior

The incorporation of adult-born neurons into the hippocampal circuitry is a remarkable example of plasticity. The conservation across mammals of such an energetically expensive process of generating and culling new neurons suggests that adult-born DGCs must serve some important function that developmentally born DGCs alone are insufficient to provide. Although the precise nature of that function is still being debated (Table 2), a common theme is the appropriate separation of overlapping or conflicting information.

Pattern separation vs. interference

The most pervasive proposed function of adult neurogenesis in the current literature is to aid in pattern separation. This term arises from computational models of hippocampus function, in which the DG transforms overlapping patterns of input from cortex into outputs to CA3 that are more distinct[151–153]. For example, if two patterns of activity arriving in the DG overlapped by 50% but the activity of CA3 pyramidal cells following exposure to those two patterns only overlapped by 20%, it would be concluded that pattern separation occurred. The reduction in overlap is thought to be achieved in part by the sparse coding of the DG, in which rates of activity are notoriously low based on electrophysiological and immunohistochemical evidence[154–157]. Overlapping patterns from cortical inputs can be dispersed over a large number of sparsely active DGCs, which in turn have few but strong synapses onto CA3 pyramidal cells [158].

At the behavioral level, the presumed manifestation of pattern separation is an improvement in distinguishing highly similar events or environments. A role for adult-born neurons in such 'behavioral pattern separation' has been demonstrated by knocking down neurogenesis and assessing the ability to distinguish similar fear conditioning contexts [142, 159, 160], nearby locations on a radial arm maze[161], and object-location pairings[162]. Adult-born neurons most consistently impact performance on these tasks when new or conflicting information is presented, i.e., conditions that would be predicted to send overlapping patterns of sensory input to DG and tax pattern separation heavily. Indeed, knocking down neurogenesis impairs reversal learning on the Morris water maze[163], active avoidance tasks [146, 164], and touchscreen-based location discrimination[165]. Manipulations to increase neurogenesis can have the opposite effect, improving the ability to distinguish nearby locations on a touchscreen task[166] or similar fear conditioning contexts[167]. A recent meta analysis supports the general conclusion that adult neurogenesis is important for behavioral pattern separation tasks as described above [168]. However, behavioral findings exploring other facets of hippocampus-dependent processes have not been entirely consistent. Adult-born neurons do not typically seem to be necessary for the initial acquisition of most hippocampus-dependent memories, such as associating contexts with an aversive shock[169] or navigating to a hidden platform in the Morris water maze [163, 170]. However, there are a few reports of neurogenesis knockdown impairing the initial acquisition of the Morris water maze[171] or contextual fear conditioning[172, 173], and increasing neurogenesis via running does not universally lead to improvement[174]. Some of these differences may be byproducts of the knockdown or enhancement strategy. Multiple methods have been employed to impair neurogenesis, including genetic ablation of proliferating progenitor cells [146, 169, 173], anti-mitotic

agents[163], and focal x-irradiation [161, 164, 175]. Of these, x-irradiation achieves the greatest knockdown, but it is also permanent. Ablating proliferating progenitors in nestin-tk transgenic mice achieves lower levels of knockdown but neurogenesis recovers within a few weeks, allowing specific ages of newborn cells to be assessed[169].

Despite some inconsistencies, a general consensus is emerging that adult-born neurons do play a role in learning and memory. The missing link is whether this behavioral-level improvement actually reflects differences in pattern separation at the level of underlying coding mechanisms. It is also important to note that theories implicating the DG in pattern separation predated the widespread acceptance of adult neurogenesis in the hippocampus by a decade or more. Incorporating adult-born neurons into computational models is an area of active study[176], and it has been difficult to reconcile how the addition of hyperexcitable cells to the dentate would improve overall pattern separation. The lack of a clear link between 'behavioral pattern separation' and neuronal activity has also sparked a sometimes-heated debate over whether this terminology is appropriate. It has been suggested that the essential feature common to behaviors impacted by neurogenesis is the presence of a high level of potential interference [177–179], which can occur due to the overlap between features of the environment or can be due to the presence of prior learning (reversal tasks) or the passage of time that erodes the fine details of a memory. Although a few studies have observed both changes in the ability to distinguish similar contexts at the behavioral level and a corresponding change in the overlap of active neuronal ensembles in either DG [148] or CA3 [149], this assessment of cell activity has been limited to a single subfield. A more comprehensive assessment of activation throughout entorhinal cortex, DG, and CA3 during multiple behavioral pattern separation tasks might serve to defuse some of these arguments.

Forgetting and memory clearance

Recently, it has been proposed that adult neurogenesis may play a role not just in learning new conflicting information but also in forgetting. In contrast to the vast majority of studies that first manipulate neurogenesis levels and then test memory function, Akers et al[180] first trained mice to perform hippocampus-dependent tasks and then kept them sedentary or provided running wheels for six weeks. When tested at the end of the running period, running mice with enhanced neurogenesis showed poorer memory for a context or spatial location learned prior to their running experience than sedentary controls. Blocking the running-induced neurogenesis using a transgenic system prevented the running-induced memory deficit. In contrast, reducing neurogenesis in infant mice, which normally show infantile amnesia, mitigated signs of forgetting four weeks later. These results suggest that high rates of neurogenesis during the early postnatal period contribute to the infantile amnesia effects, and boosting neurogenesis during adulthood may open a new period of enhanced forgetting. Why would adult neurogenesis be conserved across most mammals if it promotes forgetting? One possibility is that there is a tradeoff between minimizing interference and maintaining stability of memories. If memory storage capacity is limited, perhaps some old memories must be destabilized and cleared away so that new memories can be incorporated into their own distinct circuit. Epp et al[181] reported that, although increasing neurogenesis via running produced a less robust memory for the platform location in a Morris water maze test, running did produce an increase in the rate of reversal learning.

On another task where mice had to learn to associate particular odors with particular contexts, running similarly reduced the ability to correctly identify odor-context pairs. However, when challenged to reverse this information and associate the odors with the opposite context, running animals performed better than sedentary controls. No advantage was observed in a low-conflict condition, where entirely novel odor-context pairs had to be learned. This study adds further evidence that adult neurogenesis offers an advantage in situations where the potential for interference with previous memories is high. The specific theory that adult neurogenesis promotes forgetting is relatively controversial, as the field is not in agreement about whether forgetting is a categorically separate process from plasticity. Indeed, the experiments described above could also be interpreted as examples of an extreme form of plasticity. With the passage of time, no two experiences will ever truly be identical, and even subtle changes in the environment between two testing experiences could be interpreted as a clue to the animal that conditions may have changed.

Adult neurogenesis in aging and pathological conditions

Soon after the discovery of adult hippocampal neurogenesis, it was found that the adult neurogenesis process is highly sensitive to environmental factors and pathological conditions in rodents and non-human primates, and possibly in humans. Accumulating evidence suggests that physical and psychological stresses can impair the process of adult neurogenesis in model animals, which might further augment the symptoms of disorders. Therefore, it is possible that dysregulation of adult hippocampal neurogenesis in humans is also linked to several brain disorders, such as age-dependent cognitive decline, AD, major depressive disorders (MDD) and medial-temporal lobe epilepsy (mTLE), although clear links between the impairment of adult hippocampal neurogenesis and these diseases need to be shown in future studies. Although our knowledge regarding the interaction of these disorders with adult hippocampal neurogenesis and related functions in the human brain is very limited, animal models provide some indications of links between them. In this section, we summarize the effect of neurological disorders on adult neurogenesis in humans, the possibility of dysregulation of adult neurogenesis as a cause of those disorders, and future directions to develop adult hippocampal neurogenesis-based treatment.

Aging

One prominent negative biological factor in adult hippocampal neurogenesis is aging. Although aging itself is not a pathological process, it is a process that interacts with health and disease states, and it is one of the most significant risk factors for cognitive decline and neurodegenerative disorders. Understanding the process of brain aging is crucial to understand successful cognitive brain aging. In parallel with aging, the rate of adult hippocampal neurogenesis, the number of RGLs, and the number of intermediate progenitors decrease in the DG of rodents, carnivores, non-human primates, and humans[4, 9, 182–185]. A recent immunohistochemical analysis of adult hippocampal neurogenesis with unbiased stereology across the age of 0.2 to 59 years revealed that proliferating cells in the SGZ rapidly decline in early childhood [186], consistent with an earlier study[7]. Thus, the decline of adult hippocampal neurogenesis during aging could reduce forms of structural and functional plasticity that depend on adult-born neurons.

Interestingly, the level of adult neurogenesis in the hippocampus has been linked to cognitive abilities both in rodents and non-human primates[183]. Hippocampus-dependent cognitive abilities also decline with age in humans[187, 188], but it is not clear whether the levels of adult hippocampal neurogenesis correlate with cognitive abilities in human subjects. Technical advances in non-invasive *in vivo* imaging of neurogenesis using magnetic resonance imaging (MRI) or positron emission tomography (PET) may allow investigators to obtain quantitative data relating adult hippocampal neurogenesis to cognitive metrics in humans [189, 190].

In addition, the amount of gliogenesis increases whereas that of neurogenesis decreases during aging[9, 191]. These alterations could be due to both intrinsic changes in adult neural stem cells and environmental changes. Interestingly, activated RGLs differentiate into astrocytes after several rounds of cell division, which raises the possibility of a "disposable" stem cell model[182]. This observation implies that the reduction of adult hippocampal neurogenesis during aging is a unidirectional process due to the depletion of the adult neural cell pool. However, the capacity for proliferation and survival can be reversed by voluntary running or environmental enrichment in aged mice[104, 191–193], suggesting that environmental cues can induce some capacity for adult hippocampal neurogenesis in aged brains, and the ability to generate new DGCs in the aged brain is suppressed by aging of the environmental niche. In fact, recent reports uncovered that the levels of *Bmp4* and *Bmp6* are increased during aging in the hippocampus in both mice and humans [194, 195], and the attenuation of BMP signaling increased the proliferation of neural progenitors in the aged hippocampus. These findings suggest that the increase in BMP secretion as a result of aging of the environmental niche could be part of the reason behind reduced neurogenesis, implying that the reduction of adult neurogenesis during aging seems to be the consequence of systemic changes in the brain. Importantly, increasing adult-born DGCs in aged mice by overexpressing Klf9 or attenuating BMP signaling improved cognitive abilities and long-term memory[148, 194, 195]. These results suggest that cognitive decline with aging can be reversed at least in part by increasing hippocampal adult neurogenesis.

In addition to changes in the local environment, changes in the systemic milieu during aging have a significant impact on adult hippocampal neurogenesis. Wyss-Coray and colleagues have used heterochronic parabiosis to show that the systemic milieu from old animals inhibits adult neurogenesis and synaptic plasticity and impairs hippocampus-dependent memory[42]. Using a proteomics approach, they demonstrated that several chemokines such as CCL11 increased with aging, and the injection of CCL11 into young animals decreased adult neurogenesis and impaired hippocampus-dependent spatial memory. Subsequent studies showed that the levels of b2-microglobulin, a component of the major histocompatibility complex class 1 (MHC1) molecule, which is involved in synaptic plasticity[196, 197], were also identified as an aging-dependent negative regulator of adult hippocampal neurogenesis[43], suggesting that immune signaling could have other unconventional functions in the regulation of adult hippocampal neurogenesis. In contrast, the systemic milieu from young animals can increase adult neurogenesis and improve synaptic plasticity as well as hippocampus-dependent cognitive performance, likely through the CREB pathway[198]. Based on these findings, the same group hypothesized that plasma from an early developmental stage might contain beneficial systemic factors for adult hippocampal neurogenesis; surprisingly, they demonstrated that tissue inhibitor of

metalloproteinase (TIMP2) is enriched in human umbilical cord and young mouse plasma and TIMP2 is necessary for the effect of human umbilical cord plasma on synaptic plasticity and cognitive improvement[41]. These observations suggest that the reduction in adult hippocampal neurogenesis during aging can be at least in part reversed by cell-extrinsic factors. However, it is not entirely clear how these systemic factors in the plasma and blood affect adult neurogenesis and hippocampal function, whether these factors directly affect the process of adult neurogenesis (ex. changes in synaptic plasticity in the hippocampus may indirectly affect adult neurogenesis), and whether the few already-identified factors in the systemic milieu are the only factors. In addition, it is not clear yet whether the changes of systemic milieu during aging affect cognitive abilities and adult hippocampal neurogenesis in other species, including humans. As part of future studies, understanding the underlying mechanisms and functional relevance in humans could help develop therapeutic tools.

Alzheimer's disease (AD)

In addition to aging, accumulating evidence suggests that aging-related neurological diseases such as AD and Parkinson's Disease (PD) may impair adult hippocampal neurogenesis, although available data from human research is very limited. Modeling in animals by overexpressing proteins linked to familial AD such as mutant amyloid precursor proteins (APP) and presenilin partially recapitulates AD pathology, but the animals also have unrelated phenotypes due to the overexpression of transgenes, and therefore interpretations based on studies using those animal models should be approached cautiously [199]. AD is the most common dementia, and AD patients show functional impairment in memory and cognitive function. The accumulation of tau and APP, which is a hallmark of AD, starts in the entorhinal cortex (EC), a gateway to the hippocampus (Fig. 1), and spreads to the cortex and the hippocampus[200]. Accumulation of APP and tau elicits synaptic and neuronal loss, which is believed to induce functional impairments at least in part. The effect of AD on human adult hippocampal neurogenesis is limited and somewhat controversial. Some studies have reported that adult hippocampal neurogenesis and neuronal maturation are inhibited in AD patients whereas gliogenesis is increased [201–203]. On the other hand, Jin et al. reported that adult hippocampal neurogenesis is increased in AD patients[204]. These discrepancies may reflect different stages of AD or the heterogeneous nature of AD pathology. In addition, all human AD studies relied on the expression of marker proteins, which could be misexpressed under pathological conditions. More comprehensive analyses using different technical approaches to quantitatively measure the number of adult neural stem cells, intermediate progenitor cells, and newborn cells using double-labeling immunohistochemistry, BrdU labeling[4] or the detection of ^{14}C in genomic DNA will be essential in future human studies[9].

Similarly, studies using animal models of AD have shown variable effects of AD pathology on adult hippocampal neurogenesis depending on the specific AD-model transgenic mouse lines used and their ages. Several mouse models of AD with distinct genetic mutations have been found to have impairments in adult hippocampal neurogenesis and neuronal maturation [205–211]. However, in contrast, cell proliferation in the adult DG has been found to be increased[204, 212]. The increased proliferation is observed with relatively earlier timing (three to six months of age), and increased proliferation may not reflect increased neurogenesis but

rather gliogenesis, suggesting that the effect of AD pathology could indeed differ depending on the stage of AD as well as genetic background. Interestingly, GABAergic signaling is enhanced in immature DGCs in a human APP transgenic mouse line, which consequently impairs morphological and functional maturation of adult-born DGCs[203]. Since GABAergic signaling from the local neural network appears to be crucial for the regulation of adult hippocampal neurogenesis in many aspects (Table 1), defective GABAergic signaling could be one of the mediators of AD pathology. Importantly, knockout of apoE and knockin of human apoE4, one of the major genetic risk factors for AD, impairs GABAeric signaling onto immature adult-born DGCs and reduce neurogenesis while increasing gliogenesis[37]. Thus, known genetic risk factors for AD can affect adult hippocampal neurogenesis. Further investigation of other genetic risk factors for AD may help us to understand the heterogeneous nature of AD pathology through the lens of adult hippocampal neurogenesis.

Parkinson's disease (PD)

PD is the most common movement disorder. It is strongly linked to the aggregation of a–synuclein in Lewy bodies and the degeneration of dopaminergic neurons in the substantia nigra pars compacta. Dopaminergic signaling regulates adult hippocampal neurogenesis in rodent models (Table 1). Postmortem analysis of adult hippocampal neurogenesis in PD is very limited, but a few reports have consistently shown that adult neural stem cells were reduced in PD individuals and correlated with a–synuclein accumulation [213, 214]. Several genes related to PD, including a–synuclein, leucin-rich repeat kinase 2 (LRRK2), and PINK1, have been studied using transgenic mouse models[214–218]. An important physiological function of a–synuclein is the regulation of presynaptic transmission. A/b–synuclein-double knockout mice have exhibited increased adult hippocampal neurogenesis[214], whereas overexpression of a–synuclein decreased neurogenesis and impaired morphological maturation of adult-born DGCs[214, 216–218]. Therefore, adequate levels of a–synuclein are crucial for proper regulation of adult hippocampal neurogenesis. Similarly, a transgenic mouse line harboring the most frequent G2019S mutation in Lrrk2 exhibited high expression of Lrrk2 in the hippocampus and showed defects in proliferation/morphogenesis and survival of adult neural progenitors/adult-born DGCs[214]. These data suggest that genetic mutations in PD patients could affect adult hippocampal neurogenesis, which mediates at least some of the pathology of PD.

Mood disorders

In addition to neurological diseases, anxiety and depression have links to adult hippocampal neurogenesis. Adult neurogenesis is required for some of the beneficial effects of antidepressants through $5HT_{1A}$ receptors[219]. In human subjects, hippocampal volume and adult hippocampal neural progenitors are reduced in depression [220, 221], and antidepressant treatments in MDD patients increase the numbers of adult neural progenitors in the DG and the volume of DG[222–226]. Thus, it is possible that the increase in adult hippocampal neurogenesis mediates the effect of antidepressants in human patients, although whether the effects of antidepressants are mediated by adult hippocampal neurogenesis seems to depend on signaling pathways modulated by antidepressants in rodent models[100, 221, 225, 227]. Importantly, no consensus has been reached on the role of adult hippocampal neurogenesis in the effects of antidepressants[228, 229].

Conversely, environmental challenges such as unpredictable chronic mild stress, prenatal stress, chronic social defeat, early life stress, and glucocorticoid administration all impair adult hippocampal neurogenesis [34, 35, 131, 132, 219, 224, 227, 230, 231]. The adult-born cells in the ventral DG appear particularly susceptible to such stressors[35, 232, 233]. Prolonged stressors may create a vicious cycle in which stress impairs neurogenesis, low neurogenesis fails to mitigate stress, and further adult-born neurons are lost. Augmented stress responses might eventually increase anxiety and depression-like behavior[131, 234–237].

However, determining precisely how adult hippocampal neurogenesis contributes to regulating the emotional state has remained elusive. Most studies, but not all[238], have shown that the ablation of adult-born neurons does not affect baseline levels of anxiety but rather that adult-born neurons modulate the stress response[100, 234, 239–241]. Adult-born cells in the ventral DG may be especially important in this modulation. The ventral hippocampus is associated with social memory and anxiety, and the activation of ventral DG neurons by optogenetic approaches can reduce anxiety levels [242, 243], possibly by regulating the activity of the HPA axis. The ability of adult-born DGCs to increase circuit plasticity in the hippocampus, as described above, may provide an additional buffer against stress. Interestingly, genetic ablation of adult hippocampal neurogenesis by knocking out *Tbr2* in the adult brain reduced anxiety-related behavior during the dark cycle, and the recovery of corticosterone levels after restraint stress was quicker in *Tbr2* KO mice than WT mice[238]. On the other hand, depletion of adult-born neurons using GFAP-tk mice showed opposite effects[131]. In this study, animals with higher neurogenesis also had improved recovery from an acute stressor than animals with low neurogenesis[131]. These discrepancies may derive from methodological differences, and adult-born DGCs may contribute to mood regulation in a context-dependent manner. Thus, although adult-born DGCs seem to be involved in sensing and responding to stress, further studies are required to clarify how the context affects the functionality of adult neurogenesis.

The impairment of adult hippocampal neurogenesis may thus have prolonged effects on both cognitive and emotional function. Importantly, depression and cognitive impairments are also common symptoms in aged adults and patients with AD/PD. Of interest, pattern separation, the computational process associated with the DG, is impaired with aging and AD as well[188, 244, 245]. Thus, dysregulation of adult hippocampal neurogenesis may contribute to functional deficits of DG-specific information processing in humans. In addition, patients undergoing cancer treatments, which can eliminate dividing cells including adult neural stem cells, experience depression and cognitive impairment[246]. Understanding the common mechanisms underlying the dysregulation of adult hippocampal neurogenesis in pathological conditions could impact a large population of patients suffering from several diseases and the side effects of treatments.

Epilepsy

Although most of the pathological conditions discussed thus far reduce the number of adult neural stem cells and neurogenesis, seizure activity in mesial temporal lobe epilepsy (mTLE) dramatically increases aberrant neurogenesis in rodent models and human subjects soon after seizure[247–251]. Consequently, chronic seizure damages and exhausts adult neural

stem cells and eventually decreases adult neurogenesis a few months after the induction of seizures[95, 252]. In addition to cell proliferation, adult-born neurons generated by seizure activity exhibit aberrant cell migration, morphogenesis and synaptic integration through several signaling pathways and eventually establish recurrent networks[247, 253–260]. Thus, seizure-induced enhanced adult neurogenesis substantially reorganizes the local neural network in the DG and may impair cognitive functions. In fact, a recent report has shown that reducing adult neurogenesis using nestin-tk mice prior to the induction of seizure reduces the frequency of spontaneous recurrent seizures, and reducing aberrant neurogenesis by seizure also has some benefits for cognitive abilities[261]. Further investigation of how and to what extent seizure-induced adult-born neurons contribute to the etiology of mTLE will be interesting.

Summary and future directions

As summarized in this review, significant progress in our understanding of adult hippocampal neurogenesis has been made in rodent models using advanced transgenic mice, viral circuit tracing, next generation sequencing, and imaging. However, since most of our knowledge comes from research using rodent models, it is still not clear how adult hippocampal neurogenesis is regulated and contributes to cognitive abilities in humans and if impairment of adult neurogenesis contributes to the pathophysiology of human diseases. Human lifetimes are much longer than those of rodents, and it is unclear whether the time course of maturation and integration of adult-born DGCs in rodents and their functional contribution to local network activity and behavior are comparable in humans. Recent progress in non-invasive imaging of adult neurogenesis with MRI and PET may allow us to address these questions. One major limitation of studying adult hippocampal neurogenesis in humans is the inability to access live samples, which makes it difficult to characterize and manipulate adult hippocampal neurogenesis. However, recent advances in 3D culture systems derived from human pluripotent cells called organoids may provide a good model system to study several aspects of human development and disease [262]. The advantage of such systems is that they preserve some cytoarchitectural and organizational aspects of sub-regions of the human brain. Development of such systems specified toward hippocampal and DG fates may provide a good model system to study adult neurogenesis *in vitro*. While several studies have already developed organoid systems that resemble different human brain regions, including hippocampus [263], these organoids in general seems to recapitulate only prenatal stages. Some remaining challenges include differentiating organoid DGs and achieving postnatal stages that resemble quiescent and multi-potent neural stem cells.

Acknowledgments

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Box

Genetic mutation, variation and retrotransposons

It is now becoming clear that the process of neurogenesis puts the neuronal genome in a state that is prone to new mutations. Developing neurons sustain genetic mutations ranging from chromosomal aneuploidy to copy number variations (CNVs), single-nucleotide polymorphisms (SNPs), and mobilized retrotransposons (RTs) [83, 264–267]. This somatic mosaicism shines a light on an additional impact of adult neurogenesis: the ability to generate an increase in genomic complexity within the brain of a single individual. However, the functional impact of these mutations is still largely unknown.

Early studies of adult-born neurons in the mouse subventricular zone revealed that chromosomal mis-segregation occurred during mitosis and, as a result, a subset of neurons experienced the complete loss or gain of a chromosome[264, 268]. Since this discovery, there has been intense debate over the degree of aneuploidy in neurons, with estimates ranging from 1–33%; the most recent high-powered study placed the degree of aneuploidy at 10% [264, 269–271]. Despite the debate over the exact frequency, aneuploidy likely has a profound impact on neuronal function, as evidenced by the common elimination of these cells when mutations arise during early development[272]. Although the specific impact of aneuploidy during adult neurogenesis is unclear, these events result in altered expression of the associated genes[268].

Human neurons also harbor a mosaic complement of CNVs residing within the kilo- and megabase range[272–274]. NPs have a propensity to generate large-scale structural rearrangements due to replication stress in actively transcribing regions[275, 276]. Importantly, the DNA damage that drives these mutations in NPs is often localized to hotspots that are focused around genes that are important for neuronal development and function[275], indicating that there might be an associated recurring functional role of repair.

An additional layer of genomic diversity imparted during neurogenesis is the amplification of RTs. RTs are expressed and mobilized in NPs both *in vitro* and *in vivo*, where they colocalize with neurogenic and non-neurogenic areas of the brain[277]. Interestingly, retrotransposition dysregulation has been associated with the diagnosis of a subset of neurological disorders. For example, MeCP2, a gene that is mutated in Rett syndrome, works to modulate RT mobilization in NPs, and brains of individuals with Rett syndrome exhibit higher levels of RTs[83]. Similarly, genomic levels of RTs are also higher in the brains of individuals diagnosed with schizophrenia[83, 278], further indicating that somatic retrotransposition may be linked to cognitive function.

It is tempting to speculate that somatic mutations during adult neurogenesis impart an additional layer of heterogeneity to the broader circuit. We know from decades of study that the above-mentioned mutations can have a profound impact on neurological phenotypes when present in the germline. Therefore, if a single new neuron harbors changes in the copy number of key neuronal genes, or perhaps a more subtle alteration in the ability to regulate those genes, it is likely that the function of that individual neuron will be modified and may even be differentially tuned in comparison to surrounding

neurons that have their own, but different, sets of somatic mutations (Fig. 2). To move towards a deeper understanding of the true impact of somatic mutations, the Brain Somatic Mosaicism Network was recently formed with the goal of exhaustively characterizing such mutations within the human brain[266]. As we begin to refine strategies for identifying somatic variants in neurons, the next few years should prove to be an exciting time to study how mutations that arise in adult-born neurons impact neural function and potentially generate increased diversity within a single human brain.
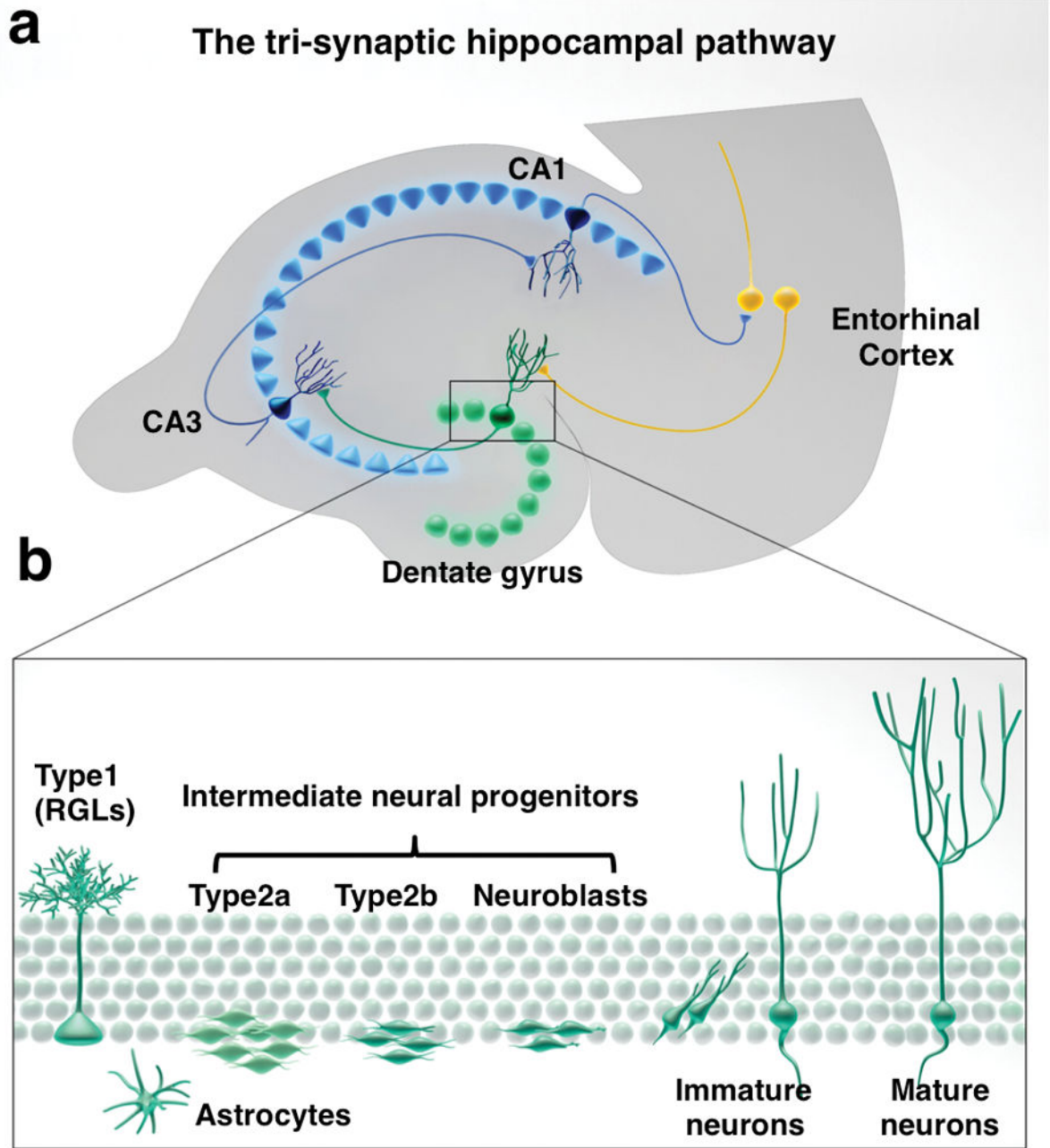
Figure 1. Development of adult-born DGCs and the trisynaptic circuit in the hippocampus
(**a**) The trisynaptic neural circuit in the hippocampus from the entorhinal cortex through the dentate gyrus, CA3 and CA1. (**b**) Developmental processes of adult hippocampal neurogenesis. Adult neural stem cells in the hippocampus (radial glia-like cells, Type 1 cells) and their differentiation through intermediate progenitors to mature DG neurons.
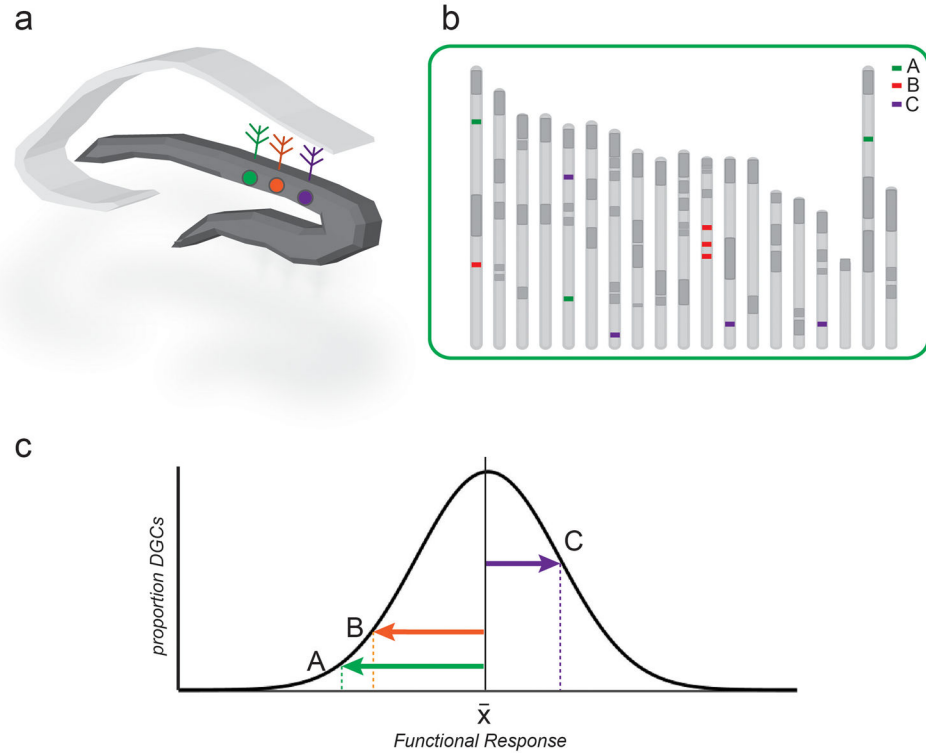
Figure 2. Somatic mosaicism during adult neurogenesis drives functional heterogeneity
(**a**) Adult-born neurons are generated in the subgranular zone of the dentate gyrus; during this period of maturation they are prone to DNA damage, replication stress, and retrotransposition. Neuron A (green), B (purple), and C (orange) represent three distinct adult-born neurons. (**b**) Each newborn neuron will have a unique complement of neurogenesis-driven mutations. Each tick mark represents a unique mutation in the respective neuron such as an aneuploidy event, a CNV, or a newly inserted retrotransposon. (**c**) Depending on the complement of mutations, the neuron may be shifted further away from the mean function of all dentate granule neurons, thereby increasing diversity within the DG.

Table 1

Signals regulating adult hippocampal neurogenesis

	Stages	Regulators
Secreted factors and downstream effectors (Morphogens, growth factors, cytokines, etc)	Type 1 (RGLs)	*Maintenance of RGLs* BMPs [11–14], VEGF[15], Shh[16–19] *Proliferation of RGLs/NPs* IGF2[20]
	Type2a, 2b	*Proliferation of NPs* FGF2[21], IGF-2[20], EGF[22, 23], ERK5 [24], estrogen[25] *Promoting differentiation* Wnt[26–28], IGF-1[29, 30], VEGF[15], BDNF/NT-3[31], BMPs[14, 32] *Inhibition of proliferation* Cortisol[33–35], Chronic Opioid Use [36], ApoE4[37]
	Neuroblasts & immature neurons	*Promoting neuronal maturation* Wnt/PCP [28, 38], BDNF/NT-3[39, 40], TIMP2[41] *Inhibition of proliferation* CCL11[42], β2M[43]
Adhesion molecules	Type 1, 2a & 2b	*Maintenance of RGLs* Notch[44–46] *Inhibition of proliferation* Integrin [47, 48] *Promoting differentiation* Eph-Ephrin[49],
	Neuroblasts & immature neurons	*Neuronal migration and synaptogenesis* Semaphorin/Plexin [50, 51] *Inhibition of proliferation* Tenasin-R[52]
Transcription factors	Type 1	*Maintenance of RGLs* REST[53, 54], Sox2[55], Hes5[46], FoxO[56], NFIX[13], NFIB[57] *Activation of RGLs* Ascl1[58, 59]
	Type 2a	*Maintenance of NPs* Sox2[55, 60], TLX1 [61–63], REST [53, 64] *Differentiation of NPs* Ascl1[65]
	Type 2b	*Differentiation into intermediate progenitors* Tbr2[66] *Neuronal differentiation* Neurog2 [67, 68], NeuroD1[26, 27]
	Neuroblasts	*Neuronal differentiation* NeuroD1[26, 27]
	Immature neurons	*Neuronal maturation* Prox1[28, 69, 70], CREB[71, 72], Klf9[73]
Epigenetic modifiers	Type 1, 2a & 2b	*Proliferation of RGLs/NPs* GADD45b[74], TET1[75], miR-137[76], miR-17-92[77], Nup153[78] *Differentiation of RGLs/NPs* MBD1[79–82], HDAC1[27, 83], HDAC2[84], MeCP2 [76, 83, 85–87], miR-184[80], miR-199 [87]
	Immature neurons	*Synaptogenesis* MeCP2 [88], HDAC2 [84, 87] *Neuronal migration/dendritic growth* miR19[89], miR-132[90]
Neurotransmitters	Type 1	*Activation of RGLs* GABA [91–93], Glutamate[94, 95]
	Type2a, 2b & neuroblasts	*Proliferation of NPs* GABA[93, 96–98], Dopamine[99], Serotonin [31, 99, 100], Norepinephrine[101], Acetylcholine [102–105] *Inhibition of proliferation*

	Stages	Regulators
		Chronic opioid use[106]
	Immature neurons	*Activation of immature neurons* GABA[107–114], Glutamate[108, 112, 114–116], Acetylcholine[112, 117, 118], Dopamine[119]

Table 2

The effects of manipulation of adult neurogenesis on hippocampus-dependent behavio

Reference	Method	Direction of Manipulation	Age at treatment onset	Behavioral testing start relative to treatment onset	Behavioral Task	Phenotype
Saxe 2006	X-IRR; GFAP-tk	Down	12–25 weeks for IRR; 12–20 weeks for GFAP-tk	12 weeks for IRR; 6 weeks for GFAP-tk	CFC, MWM, Y-maze	impaired acquisition of contextual but not cued FC; IRR had no effect on other tasks
Meshi 2006	X-IRR +/– enrichment	Both	10 weeks for IRR; 22 weeks for enrichment	6 weeks after enrichment	MWM; novelty-suppressed feeding	improved MWM probe performance and reduced latency to feed in enriched mice regardless of IRR
Kitamura 2009	X-IRR	Down	5 weeks	5 weeks	CFC	no effect on remote memory at 28 days; minimal impairment of recent memory at 1 day depending on strain
Clelland 2009	X-IRR	Down	8 weeks	8 weeks	Radial arm maze; touchscreen location discrimination task	impairment discriminating small but not large separations on both tasks
Deng 2009	nestin-tk	Down	8 weeks	3 weeks	MWM, CFC	no change in MWM acquisition but poor long-term retention 1 week later; normal CFC acquisition but impaired extinction
Garthe 2009	TMZ	Down	6–8 weeks	8 weeks	MWM	transiently impaired acquisition and impaired reversal learning
Creer 2010	Running	Up	4 mo, 23 mo	1 week	touchscreen location discrimination task	improvement on small separations in young mice only
Sahay 2011	Bax KO (iBaxNes)	Up	8+ weeks	8 weeks	novel object; MWM; active avoidance; CFC; open field; novelty-suppressed feeding; forced swim test	only impact is improved CFC discrimination of similar contexts; no effect on CFC extinction; no effect on MWM reversal
Tronel 2012	Bax overexpression (Tet-Bax × nestin-rtta)	Down	8 weeks	9 weeks	CFC; odor discrimination	impaired CFC discrimination between similar contexts; odor discrimination unaffected
Burghardt 2012	X-IRR; GFAP-tk	Down	10 weeks for IRR; 6–8 weeks for GFAP-tk	12–16 weeks for IRR; 8–11 weeks for GFAP-tk	active place avoidance	normal learning of initial shock zone, but impaired reversal and learning of an additional zone
Denny 2012	X-IRR, GFAP-tk	Down	9–15 weeks for IRR; 6 weeks for GFAP-tk	2–8 weeks for IRR; 6 weeks for GFAP-tk	novel object; CFC	impairment on one-shock CFC at 6 weeks; hyperactivity to novel object at 6 weeks

Reference	Method	Direction of Manipulation	Age at treatment onset	Behavioral testing start relative to treatment onset	Behavioral Task	Phenotype
Nakashiba 2012	X-IRR	Down	9–12 weeks	6 weeks post	CFC	impaired CFC discrimination between similar contexts
Bekinschtein 2014	dnWnt	Down	7–8 weeks	5 weeks	spontaneous location recognition	impaired discrimination of small but not large separations
Swan 2014	GFAP-tk	Down	6–8 weeks	4 weeks	touchscreen location discrimination; nonspatial brightness discrimination	reduction in location discrimination, but only after a reversal, not related to size of separation; no effect on brightness discrimination
Denny 2014	X-IRR	Down	9 weeks	6 weeks	CFC	impaired acquisition of one-shock but not 3-shock CFC
Wang 2014	Constitutively active MEK5	Up	8–10 weeks	7–8 weeks	MWM; novel object recognition; open field	improved MWM acquisition, probe, and reversal; improved novel object recognition at 24–48hr
Zou 2015	ERK5 KO	Down	10–12 weeks	7–8 weeks	CFC; open field; elevated plus maze; light-dark test; novelty-suppressed feeding; novelty-induced hypophagia; sucrose splash test; sucrose preference test; forced swim test; tail suspension test	impaired remote fear memory at 5 weeks; but no impact on any anxiety or mood tests
Clemenson 2015	Running; enrichment; x-IRR	Both	8 weeks	4 weeks post-RUN; 3 weeks post EE; 9 weeks post-IRR	CFC	enrichment, but not running, rescues immediate shock deficit and is blocked by irradiation; enrichment alone leads to loss of CFC discrimination if animals are pre-exposed to shock context
Park 2015	X-IRR	Down	10 weeks	12–16 weeks	active place avoidance	normal learning of initial shock zone, but impaired reversal
Tsai 2015	Tbr2 KO; X-IRR	Down	7 weeks	12 weeks	elevated plus maze; novelty-suppressed feeding; forced swim test; sucrose preference test	reduction in anxiety during dark cycle only; no change in depressive-like behavior at any time
McAoy 2016	Klf9 overexpression	Up	3, 11, or 17months	6 weeks	MWM; CFC; open field; light-dark test; novel object recognition	improvements in MWM probe after reversal, remote CFC discrimination, and novel object recognition with no effect on anxiety tests in young; improved remote CFC discrimination in middle aged and old
Danielson 2016	optogenetic silencing	Down	8 weeks	6 weeks	CFC	inactivation of <6-week old DGCs during training impairs

Reference	Method	Direction of Manipulation	Age at treatment onset	Behavioral testing start relative to treatment onset	Behavioral Task	Phenotype
						test performance 24hr later; inactivation during test phase results in impairment when silenced in the similar but not training context
Zhuo 2016	optogenetic silencing	Down	10–11 weeks	5–10 weeks; 14–18 weeks	touchscreen location discrimination task	inactivation of 5–10 week old DGCs impairs discrimination of small separations during acquisition phase but not after reaching asymptotic performance; inactivating 14–18 week old DGCs has no effect

Abbreviations: IRR = IRR; MWM = Morris water maze; CFC = contextual fear conditioning