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Young and excitable: the function of new neurons in the adult mammalian brain

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Adult neurogenesis occurs in most species and is regulated by a wide variety of environmental and pharmacological challenges. The functional integration of neurons generated in the adult was first demonstrated in songbirds more than two decades ago. In the adult mammalian brain, neurons are continuously generated in two structures, the olfactory bulb and the hippocampus. Current evidence suggests that adult-born immature neurons have distinct electrophysiological properties from old neurons, and proposed roles in a variety of functions including olfaction, learning and mood regulation.

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Introduction

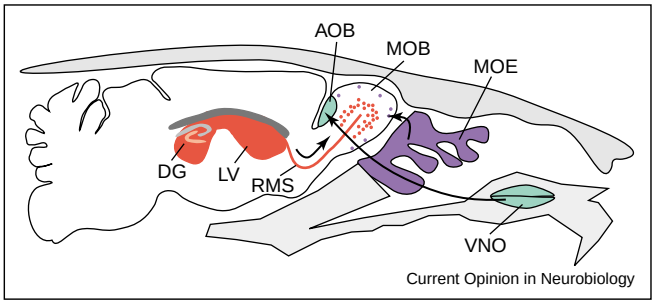
Stem cells residing in specialized niches in the adult brain continuously generate new neurons. In mammals, neurons are born in two germinal regions, in the subventricular zone (SVZ), which lies adjacent to the lateral wall of the lateral ventricle and generates olfactory bulb neurons, and in the subgranular zone (SGZ) of the hippocampal formation (Figure 1). In both the SVZ and the SGZ, the stem cells for adult neurogenesis are a subset of astrocytes, that is, glial cells classically associated with support functions in the brain [1]. In the SVZ, stem cell astrocytes divide to generate neuroblasts through rapidly dividing, transit-amplifying progenitors. From their site of origin in the SVZ, the newly generated neuroblasts migrate along the rostral migratory stream (RMS) as chains to reach the core of the olfactory bulb, where they turn radially and differentiate into granule and periglomerular inhibitory neurons (Figures 1, 2). In contrast to the long-distance migration of olfactory bulb neurons, in the hippocampus, SGZ astrocytes give rise to intermediate progenitors, which mature locally into granule neurons of the dentate gyrus (Figure 3). The stem cell lineages and microenvironment supporting adult neurogenesis, as well as factors which modulate them, have recently been reviewed elsewhere [1–3]. Here, we focus on recent insights into the function of adult neurogenesis in mammals. We review the population dynamics and functional properties of new neurons and their potential roles in brain plasticity.

Function of new neurons in the olfactory bulb

Odorants and pheromones are detected by the olfactory system (Figure 1). Volatile odorants in the environment bind to olfactory sensory neurons (OSNs) in the main olfactory epithelium, the axons of which project to the main olfactory bulb (MOB) (Figures 1, 2). OSNs expressing the same receptor converge onto one of two glomeruli in the MOB, where they synapse with the apical dendrites of mitral and tufted cells, the principal olfactory bulb output cells, which in turn project to olfactory cortex (Figure 2). Mitral and tufted cells also have lateral dendrites that radiate up to 1mm within the external plexiform layer (Figure 2). The spatial and temporal coding of mitral and tufted cells is regulated by two kinds of inhibitory interneurons, periglomerular cells and granule cells [4]. Periglomerular neurons are located in the glomerular layer and form dendro–dendritic synapses with mitral and tufted cell apical dendrites and OSNs. Periglomerular cells can act within a single glomerulus or can interconnect different glomeruli. Granule neurons, which do not have axons, form reciprocal dendro–dendritic synapses with the lateral dendrites of mitral and tufted cells. Upon stimulation, a mitral (or tufted) cell releases glutamate, exciting the granule cell and causing it to release γ-aminobutyric acid (GABA), which, in turn, inhibits the mitral cell (Figure 2). These dendro–dendritic synapses are the source of recurrent and lateral inhibition of mitral and tufted cells [4,5]. Interneurons thus have a crucial role in olfactory processing by mediating the spatial contrast and temporal coding of olfactory inputs and outputs. They are also the target of most centrifugal inputs, including serotonergic, noradrenergic and cholinergic systems, in addition to those from the olfactory cortex and the contralateral olfactory bulb [4].

The olfactory system exhibits a remarkable amount of neuronal turnover in the adult. OSNs are continuously generated by dividing basal precursors in the MOE and subsequently project their axons to appropriate glomeruli. Within the olfactory bulb itself, granule and periglomerular interneurons, most of which are produced in the first

Figure 1



Schema of a sagittal section depicting the sites of adult neurogenesis in the adult rodent brain. New neurons in the dentate gyrus are born locally in the SGZ. By contrast, neurons destined for the olfactory bulb are born along the wall of the lateral ventricle (red) in the SVZ and migrate along the RMS to reach the olfactory bulb where they differentiate into interneurons. OSNs, which detect volatile odorants, project axons to individual glomeruli in the main olfactory bulb. OSNs are also constantly generated by precursors in the MOE. Pheromones are detected by vomeronasal organ neurons, which project to the accessory olfactory bulb. Abbreviations: AOB, accessory olfactory bulb; DG, dentate gyrus; LV, lateral ventricle; MOB, main olfactory bulb; MOE, main olfactory epithelium; RMS, rostral migratory stream; VNO, vomeronasal organ.

two weeks after birth [6,7], continue to be generated throughout adult life [8]. The continual elimination and integration of newly generated neurons in the olfactory system might have a profound effect on olfactory bulb function.

Integration of adult-generated neurons into the olfactory system

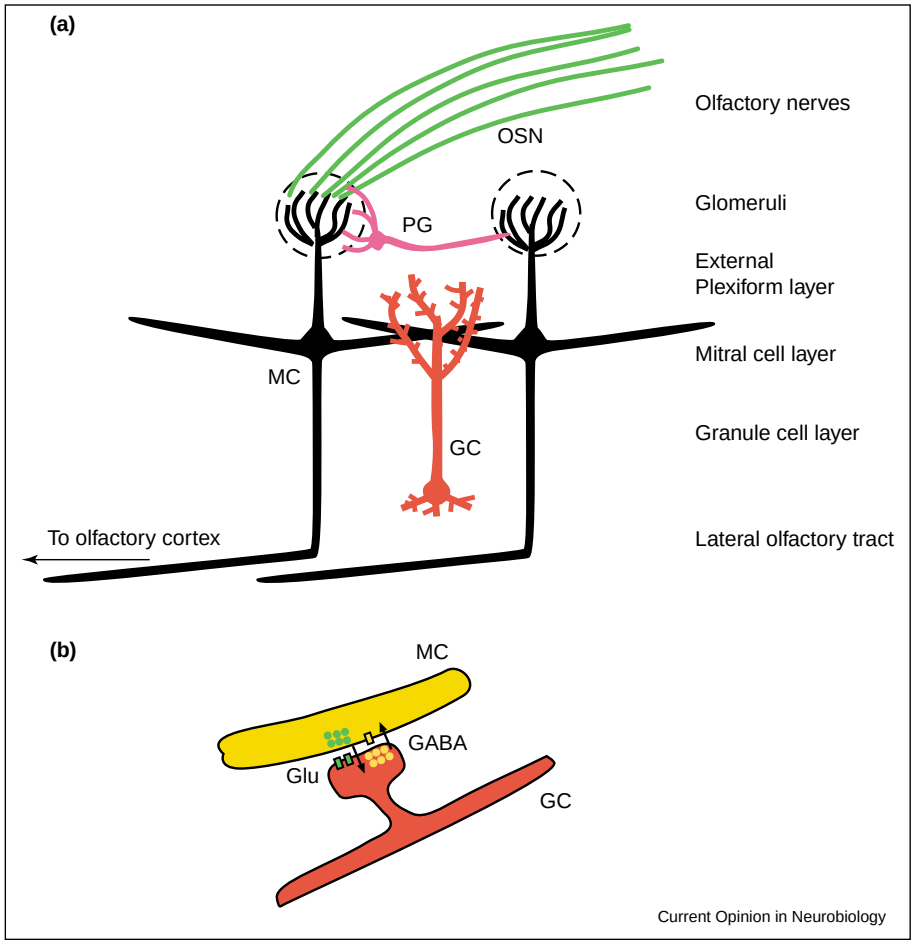
Approximately 1% of total olfactory bulb interneurons are added each day in the adult. Almost all become granule cells, with less than 3% differentiating into periglomerular cells [6,9–11]. One-half of the adult-generated interneurons die between 15 and 45 days after their birth [10,11], after they have elaborated complex dendritic morphology and spines. This early wave of cell death is activity-dependent, in contrast to neurogenesis. In mice, in which the cyclic nucleotide gated channel required for transduction of electric impulses from afferent OSNs is inactive, the production, migration and differentiation of new-born neurons are unaffected, but the newly generated neurons die in greater numbers during the early wave of cell death [11]. Those neurons that survive persist for at least one year. Defining the population dynamics of olfactory bulb interneurons emerging at different stages of development is now of key importance. Are those born during the first two postnatal weeks stable throughout life, or are they replaced by adult-generated neurons? Alternatively, are only adult-generated neurons turned over?

Neuroanatomical tracing and patch clamp recording of adult-generated interneurons have shown that they become functionally integrated into olfactory bulb circuitry. When exposed to complex mixtures of odorants, newly generated neurons express the immediate early gene *c-fos* and can be labeled with a viral trans-synaptic tracer injected into relay neurons [12]. Granule and periglomerular cells that have been newly generated exhibit mature electrical properties [13•,14•] and periglomerular neurons yield synaptic responses when afferent nerves are stimulated [13•].

Infection of SVZ stem cells or progenitors by focal injection of a replication incompetent retrovirus encoding green fluorescent protein (GFP) results in the stable inheritance of GFP by all daughter neurons. Patch clamp recordings of GFP+ neurons at different survival times after infection have revealed the sequence of functional integration of adult generated neurons [13•,14•]. In the rostral migratory stream migrating neuroblasts show weak and delayed inwardly rectifying potassium currents, and are depolarized by GABA acting through $GABA_A$ receptors [15–17] but do not exhibit sodium or fast potassium currents. The neuroblasts then acquire α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) responsiveness and as they begin migrating radially in the olfactory bulb they express N-methyl-D-aspartate (NMDA) receptors [14•]. The delayed excitability of adult-generated neurons might enable them to integrate without disrupting the neural circuitry. Whereas periglomerular cells are able to fire action potentials before they receive synaptic inputs, granule neurons receive synaptic inputs before they develop mature sodium currents [13•,14•]. Both types of adult-generated interneurons have larger sodium currents than mature cells [13•], which might reflect a greater excitability.

Olfactory bulb interneurons differ in the combination of calcium binding proteins, neurotransmitters and neuromodulators they express [18], in the centrifugal inputs they receive from the brain and in their connectivity. Different classes of granule neurons ramify in distinct layers of the external plexiform layer and therefore might interact selectively with mitral or tufted cells [4], with different functional consequences. Periglomerular neurons can form dendro–dendritic connections with OSNs and/or mitral cells. Calretinin-positive periglomerular cells, which do not contact OSNs, and GABAergic and dopaminergic cells, which contact both OSNs and mitral cells [18], are both generated in the adult brain in approximately equal number [10]. Periglomerular cells also exhibit distinct electrophysiological properties [19]. However, among the pool of periglomerular neurons generated between postnatal day (p) 14 and 28, non-rectifying periglomerular neurons represent the vast majority [13•]. These findings highlight the importance of precisely defining the combined electrophysiological, neurochemical and morphological profiles of interneuron subtypes generated in the adult brain. Their unique

Figure 2



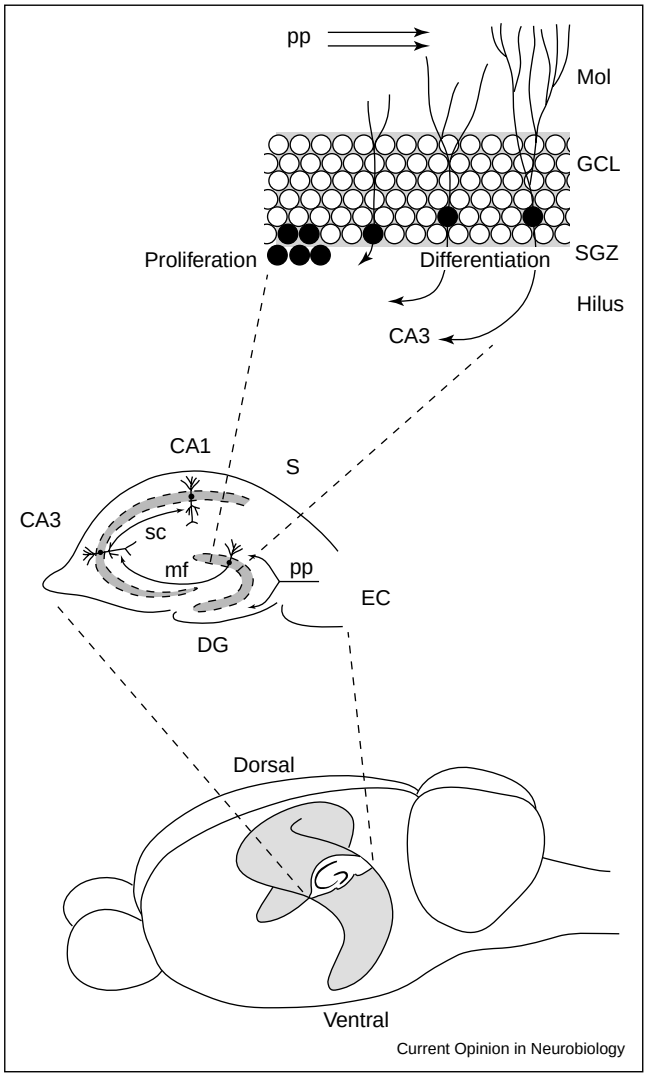
Olfactory bulb circuitry. **(a)** OSNs expressing the same receptor converge onto a single glomerulus and synapse with mitral cells, the principal output cells of the olfactory bulb. Mitral cells send a single apical dendrite up to the glomerulus and extend numerous lateral dendrites in the external plexiform layer. Tufted cells are not depicted for simplicity. Periglomerular neurons and granule neurons are inhibitory interneurons. Periglomerular neurons (PGs) are found in the glomerular layer and make dendro–dentritic synapses with mitral cell apical dendrites and OSNs. Granule neurons (GCs) make dendro–dendritic synapses with mitral cell (MC) lateral dendrites and mediate lateral inhibition. **(b)** Dendro–dendritic synapse between a granule cell and a mitral cell. Glutamate released from mitral cells activates granule cells, which in turn release GABA that inhibits mitral cells. The continual addition of granule and periglomerular neurons to the adult olfactory bulb might modulate spatial and temporal coding of odor processing.

connectivity and excitability properties might have distinct functional consequences on the processing of olfactory information.

The role of new olfactory bulb neurons

Olfactory cues are essential for survival, mediating reproductive and maternal behaviors, social cues, exploration, foraging for food and predator detection. Olfactory discrimination and learning and memory have been attributed to changes at reciprocal dendro–dendritic synapses between mitral/tufted cells and interneurons. The continual addition of interneurons, which modulate the spatial and temporal coding of olfactory information through lateral inhibition and synchronization of firing of the mitral/tufted cells [5,20], might provide a novel substrate for adapting to complex, changing environments. Cell death, which is prominent in the olfactory bulb [10,11,21,22], may also effect rapid changes in neural circuits. The first experiments investigating the role of new neurons in the olfactory system have evaluated whether increasing or decreasing the number of interneurons has effects on olfactory discrimination and memory. Modelling studies have suggested that activity-dependent survival of adult-generated neurons can redistribute the representation of odorants to maximize olfactory discrimination [23]. Enriched olfactory environments increase the survival of adult-generated neurons, which is accompanied by improved performance on olfactory memory tasks [24], although it is unclear if this improvement is due to the new neurons or enhanced

Figure 3



The hippocampal formation extends longitudinally along a dorso–ventral axis in the rodent brain. A transverse section reveals the characteristic tri-synaptic circuit that is enlarged in a separate panel. The perforant path (PP) comes from the entorhinal cortex (EC) and innervates the dendrites of granule cells in the molecular layer (Mol) of the dentate gyrus (DG). Granule cells send axons to CA3 pyramidal neurons that constitute the mossy fibers (mf). Schaffer collaterals (sc) are the projections of CA3 pyramidal neurons toward CA1 pyramidal neurons, which in turn project to the subiculum (S). The dentate gyrus is composed of the molecular layer containing the dendrites of the granule cells, the granule cell layer (GCL) containing the cell bodies of the granule cells, and the subgranular zone (SGZ) containing the proliferating progenitor cells. As these progenitors differentiate into mature granule cells they migrate within the inner third of the GCL and extend progressively longer and more complex dendrites in the molecular layer.

activity of existing cells. Conversely, mice that have impaired production of new neurons, such as in neural cell adhesion molecule and transforming growth factor α null mice and aged mice, have deficits in fine olfactory discrimination [25,26]. However, these mutations are not selective for olfactory bulb interneurons. Pregnancy induces an increase in neurogenesis specifically at gestation day 7 and at post-partum day 7 in female mice, in part through circulating prolactin [27•]. This results in an increased number of new olfactory bulb neurons maturing two weeks to one month later at birth and at weaning, raising the untested possibility that they play a role in pup recognition or in other olfactory processes occurring at these times. The relationship between newly generated OSNs that project to glomeruli and newly generated olfactory bulb interneurons, which mediate the output of mitral cells, remains unknown.

New granule and periglomerular neurons are also added to the accessory olfactory bulb (AOB) [28], the first relay of the vomeronasal organ, which mediates pheromone detection in addition to sexual and aggressive behaviours (Figure 1; [29,30]). However, the population dynamics, functional properties and possible contribution of AOB interneurons to memory formation during mating and to aggressive behaviours are uncharacterized. Ultimately, definitive experiments elucidating the functional significance of adult neurogenesis for olfactory processing and memory formation will require the selective genetic ablation of newborn neurons combined with ethologically relevant behavioural experiments.

Function of the new neurons in the dentate gyrus of the hippocampus

The hippocampus is involved in the learning and memory of explicit information [31]. In addition, the hippocampal formation is very sensitive to stress and decreases in hippocampal volume have been observed in rodents after chronic stress and in humans afflicted with mood and anxiety disorders [32,33]. The hippocampus extends along the septo–temporal axis (dorso–ventral in rodents and posterior–anterior in primates; Figure 3). Neurons from the entorhinal cortex project to the granule cells of the dentate gyrus (perforant path), which project to the CA3 pyramidal neurons (mossy fibers), which in turn project to the CA1 pyramidal neurons (Schaffer collaterals; Figure 3). The SGZ where the adult progenitors are found lines the hilar side of the granule cell layer of the dentate gyrus (Figure 3).

The neurons produced in the dentate gyrus during adulthood integrate into the existing circuitry of the hippocampus as evidenced by the development of functional synaptic inputs provided by the medial perforant path and growth of axons to target cells in CA3 [34,35]. Adult generated neurons populate the inner third of the granule cell layer [36]. As they differentiate, their dendrites become progressively more complex and extend progressively deeper into the molecular cell layer. The new neurons express a series of transient markers such as doublecortin, collapsin response mediator protein 4

(CRMP4), polysialylated neural cell adhesion molecule (PSA-NCAM) and calretinin [37–40] that are also found on immature neurons during development.

Electrophysiological properties of young neurons

Single cell recordings of young neurons have revealed that their electrophysiological properties are distinct from those of mature neurons but resemble those of immature neurons formed during development. GABA is an excitatory neurotransmitter for immature neurons [41]. New neurons can be depolarized using currents of very small amplitude, a feature probably attributable to the activity of low threshold calcium channels [42•]. Possibly as a result of this increased excitability, long-term potentiation (LTP) can be elicited more readily in young neurons than in old ones [36,42•]. These altered properties are specific to immature neurons that, based on doublecortin or CRMP4 expression [37], could correspond to around 10% of all the granule cells of the dentate gyrus. New neurons might therefore have impact on the entire hippocampal circuitry. Field recordings have identified a form of LTP that can be elicited in the dentate gyrus upon weak stimulation of the medial perforant path [37]. Gamma-ray irradiation, a procedure that kills the progenitor cells and within three weeks results in the disappearance of most immature neurons, eliminates this form of LTP. We have recently confirmed these findings using both X-ray-irradiation [43•] and a genetic ablation procedure that also kills the progenitor cells [44,45].

Impact of the young neurons on behavior

Attempts to assess the functional significance of adult hippocampal neurogenesis on behavior have relied on various ablation strategies. The first such study employed the methylation agent methylazoxymethanol (MAM) that when used at moderate doses kills dividing cells. Gould and co-workers [46,47] showed that mice treated with MAM and therefore lacking hippocampal neurogenesis displayed a learning impairment in trace fear conditioning, a specific hippocampal-dependent learning paradigm. Interestingly, no deficit was found in the Morris water maze, another hippocampus-dependent task that is used to assess spatial learning. However, these studies were difficult to replicate in other animal models because MAM is toxic and, it is difficult to find a dose that ablates neurogenesis without making the animal sick. The next strategy to be employed was selective irradiation of the region of the brain containing the hippocampus [43•]. This strategy is less toxic than MAM and is restricted to the subgranular zone while sparing the subventricular zone. Irradiated mice are essentially undistinguishable from normal mice in most behavioral paradigms including learning-related tests such as the Morris water maze, as well as anxiety-related paradigms such as the open field, elevated plus maze and cued fear conditioning. However, irradiated mice become unresponsive to chronic treatment with antidepressants [43•]. These findings, together with the fact that antidepressant treatments increase neurogenesis specifically in the dentate gyrus, have led to the suggestion that an increase in the number of young neurons contributes to the mechanism of action of antidepressants and could explain at least in part their delayed onset of therapeutic efficacy [48]. However, irradiation has also been shown to induce inflammatory responses that might in turn also have various behavioral and physiologic effects [49]. Therefore, it is crucial that the findings derived from irradiated animals be replicated with independent ablation strategies [44].

The lack of immature hippocampal neurons in rodents results in two seemingly unrelated behavioral consequences: a deficit in a hippocampal-dependent fear learning paradigm and a lack of response to antidepressants in a series of tests related to mood or anxiety [43•,46,47]. In both cases emotional responses are altered in mice or rats lacking hippocampal neurogenesis, highlighting an emerging role for the hippocampus in mood and anxiety, in addition to its classic role in learning and memory. In recent years, lesion studies have suggested a functional differentiation of the hippocampus along the dorso–ventral (septo–temporal) axis (Figure 3; [50,51]). Specifically, lesions of the dorsal hippocampus result in impaired spatial learning, without affecting anxiety-related measures, whereas ventral lesions affect anxiety-related behaviors without affecting spatial navigation. Furthermore, anatomical studies show that the dorsal and ventral regions receive different inputs and send their projections to distinct targets [52].

The mood-related impact of hippocampal neurogenesis might be due to neurogenesis in the ventral part of the dentate gyrus. However, neurogenesis also takes place in the dorsal part of the dentate gyrus. It is therefore likely that hippocampal neurogenesis will also have consequences on cognitive functions mediated by the dorsal hippocampus. To date, irradiation has been shown to elicit deficits in two spatial learning paradigms, the Barnes maze [53] and a long-term memory version of the Morris water maze [54]. A better understanding of the specific function of the dentate gyrus within the hippocampal circuitry might enable the design of behavioral paradigms that demonstrate deficits in the behavior of animals with disrupted neurogenesis. For example, alterations in the activity of CA1 pyramidal neurons can be readily detected in the Morris water maze, whereas alterations in CA3 neuronal activity require more subtle tests that involve fast learning of one-time experience [55].

Impact of behavior on young neurons

Neurogenesis can be modulated both positively and negatively by environmental factors such as enriched

environment, learning and stress (reviewed by Schinder and Gage [56]). Recent behavioral manipulations suggest a link between hippocampal activity and neurogenesis. Specifically, an intense hippocampal-dependent learning paradigm increases the survival of newly formed dentate gyrus neurons [57]. By contrast, a non-hippocampal paradigm had no effect on survival. Furthermore, glutamate can act directly on hippocampal progenitor cells to promote neurogenesis and neuronal differentiation [58•]. An emerging concept is that the type of activity in which the animal is engaged influences the rate of survival of hippocampal neurons (80% of the immature neurons die within a month in base line conditions [59]) and possibly the fate of the progenitors (glia versus different neuronal types) [60].

This 'use it or lose it' rule suggests that hippocampal neurogenesis might be a form of adaptation to novel or enriched environments. Coping with a challenging environment might require additional plasticity within the hippocampal circuitry, which in turn might enable more efficient learning and possibly forgetting [61]. Recent modeling studies have indeed suggested that neurogenesis increases the capacity for learning new information and forgetting old information [62].

Conclusions and future directions

Although great strides have been made into characterizing the integration of new neurons into adult neural circuits, the functional significance of adult neurogenesis remains elusive. New animal models are still needed, such as transgenic mice expressing GFP at various stages of differentiation of adult-generated neurons [63], as well as conditional mutants that enable the selective, inducible and reversible ablation of adult-generated neurons in the SVZ or SGZ [44,64].

A better understanding of the function of adult neurogenesis might also prompt the development of strategies aimed at increasing neurogenesis in specific brain regions. Pharmacological agents might be identified that can stimulate the proliferation or differentiation of neuronal progenitors to treat cognitive impairments or mood disorders. Finally, it might be possible to harness dormant progenitors in non-neurogenic regions of the brain such as the substantia nigra and the cortex [65,66]. Pharmacological strategies aimed at waking up these dormant cells might hold promise for the treatment of a variety of neurodegenerative disorders.

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