

Adult neurogenesis and functional plasticity in neuronal circuits

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Abstract | The adult brain is a plastic place. To ensure that the mature nervous system's control of behaviour is flexible in the face of a varying environment, morphological and physiological changes are possible at many levels, including that of the entire cell. In two areas of the adult brain — the olfactory bulb and the dentate gyrus — new neurons are generated throughout life and form an integral part of the normal functional circuitry. This process is not fixed, but highly modulated, revealing a plastic mechanism by which the brain's performance can be optimized for a given environment. The functional benefits of this whole-cell plasticity, however, remain a matter for debate.

Adult neurogenesis

The entire set of events leading to the production of new neurons in the adult brain, from precursor cell division to functionally integrated survival.

Precursors

CNS stem cells and all progenitors are generally referred to as precursor cells.

New neurons are continually being generated in the adult brain. Two regions — the olfactory bulb and the dentate gyrus of the hippocampus — receive and integrate newborn neurons throughout adult life. In these regions, the addition of new neurons represents another means, further to molecular, synaptic or morphological alterations in individual cells, by which the brain can make changes to its own functional circuitry. Indeed, this cell-level renovation is not static or merely restorative — instead, adult neurogenesis constitutes an adaptive response to challenges imposed by an animal's environment and/or its internal state. This raises some important questions about the role of neurogenesis in mature neuronal circuits. Owing to space constraints, we concentrate on the neurogenic systems of vertebrates, and primarily those of mammals.

Neurogenesis and plasticity in the adult brain

Brain plasticity refers to the brain's ability to change its structure and function during maturation, learning, environmental challenges or pathology. Multiple dissociable plastic changes in the adult brain involve many levels of organization, ranging from molecules to systems, with changes in neural elements occurring concomitantly with changes in supportive tissue elements such as glia and blood vessels. In restricted areas of the mammalian brain, new functional neurons are constitutively generated from endogenous pools of neural stem cells throughout life. So, the possibility of adding entire new neurons to existing network circuitry must be added to the list of structural changes possible in the adult brain. The potential functional implications of such changes are fascinating, but before addressing such issues it is important that we outline how adult neurogenesis proceeds, and how it is regulated.

Mechanisms of adult neurogenesis

Post-developmental neurogenesis is conserved across evolutionary boundaries from crustaceans¹ to higher vertebrates, including birds², rodents³, primates^{4,5} and humans⁶. The degree of postnatal neurogenesis decreases with increasing brain complexity, with adult neurogenesis in lower vertebrates, such as lizards, providing an additional supply of neurons capable of regenerating entire brain parts, whereas in mammals adult neurogenesis is restricted to only a few regions, where it provides neuronal replacement. The degree of post-developmental neurogenesis in a given species might depend on a trade-off between the benefits accrued from newborn neurons and the problems they generate for the network circuitry into which they integrate⁷. It seems that more complex brains have been influenced to a greater extent by the latter issue, as, in mammals, adult neurogenesis under normal conditions is probably confined to just two regions: the subgranular zone (SGZ) of the hippocampal dentate gyrus and the subventricular zone (SVZ), which contributes interneurons to the olfactory bulb^{8,9}. Although there is evidence to suggest the presence of constitutive neurogenesis in other regions of the adult brain^{10–17} (but for an alternative view, see REFS 18–21), here, we concentrate on the two regions where the presence of constitutive adult neurogenesis is uncontroversial.

Producing new neurons. The dominant hypothesis is that astrocytes in the adult SVZ, which lines the border between the striatum and the lateral ventricle, act as slow-dividing neural stem cells, capable of generating a progeny of neuroblast precursors^{22–24}. These neuroblasts

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proceed towards the olfactory bulb along an intricate path of migration known as the rostral migratory stream (RMS). More than 30,000 neuroblasts exit the rodent SVZ for the RMS each day²⁵, where they are not guided by radial glia, but migrate tangentially^{26,27} in chains through tubular structures formed by specialized astrocytes. After detaching from these chains and migrating radially from the RMS into the olfactory bulb, adult-born cells from the SVZ mature into olfactory inhibitory interneurons of two main types — granule cells and periglomerular cells — in their respective olfactory bulb layers. Both cell types make only local contacts in the bulb, directly or indirectly modulating the processing of sensory information by the olfactory bulb's projection neurons, the mitral and tufted cells.

The SGZ of the hippocampus, where the adult progenitors of the dentate gyrus are found, lines the hilar side of the granule cell layer of the dentate gyrus. There, SGZ astrocytes give rise to intermediate progenitors, with ~9,000 new cells being produced per day in young adult rats²⁸, although this number seems to be smaller in the macaque hippocampus⁵. These progenitors mature locally into granule neurons of the dentate gyrus²⁹, sending axonal projections to area CA3 and dendritic arbour into the molecular layer^{30,31}. The hippocampal stem cell lineages and microenvironment that support neurogenesis have been extensively reviewed elsewhere (for examples, see REFS 32–34).

Maturation and functional integration. As they differentiate, the dendrites of newborn dentate gyrus cells become progressively more complex and extend deeper into the molecular cell layer³⁵ (FIG. 1). The new neurons express a series of transient markers, such as doublecortin, collapsin response mediator protein 4 (CRMP4; also known as TUC4), polysialic acid–neuronal cell adhesion molecule (PSA–NCAM) and calretinin^{36–38}, which are also characteristic of immature neurons during development (BOX 1). Physiological studies of maturing granule cells have recently been carried out using transgenic mice that selectively, and transiently, express enhanced green fluorescent protein (GFP) under the transcriptional control of particular genomic sequences. In nestin–GFP-positive type II precursor cells, although the expression of functional glutamatergic synapses has been detected³⁹, spontaneous and evoked synaptic input comes only from GABA (γ -aminobutyric acid)-mediated transmission^{39,40}. This GABA transmission is depolarizing²¹³, as is the case in early developing hippocampal cells⁴¹, and, possibly through the generation of calcium transients, might control the proliferation and differentiation of neuronal precursor cells^{40,42}. This situation contrasts strongly with that in the SVZ, where stem cells themselves are influenced by extrasynaptic GABA release⁴³. In addition, whereas the GABA-releasing neuroblast progeny of SVZ stem cells release the transmitter that controls the division of their ancestors⁴³, in the SGZ the GABA that affects type II cell proliferation comes from activity in local mature circuitry^{39,40,213}.

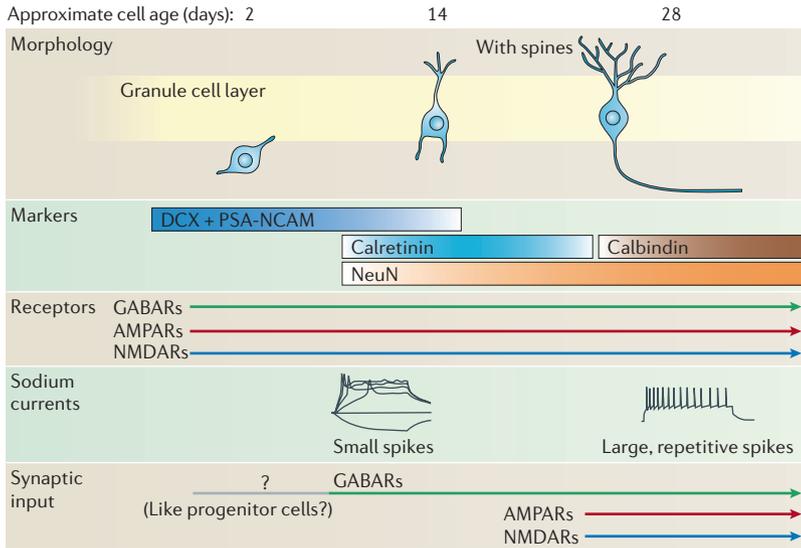
Progenitor

A mitotic cell with a fast cell-division cycle that retains the ability to proliferate and to give rise to terminally differentiated cells but that is not capable of indefinite self-renewal.

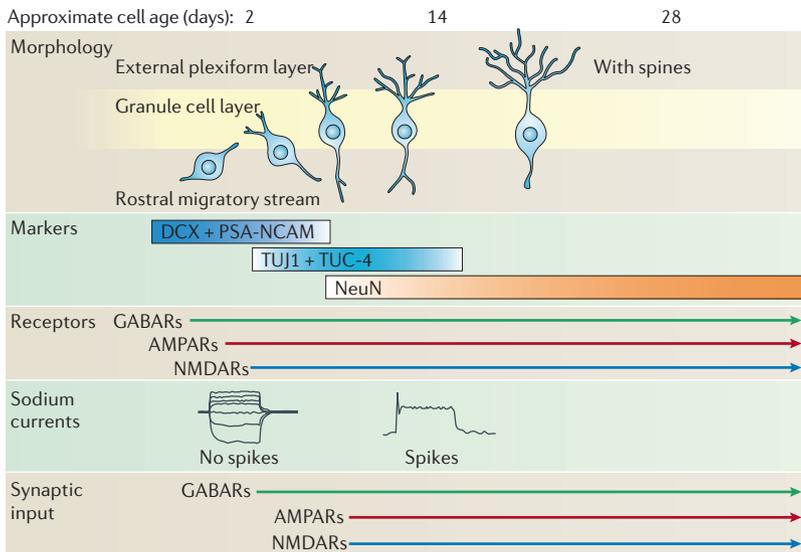
Figure 1 | Postmitotic maturation of newborn neurons in the adult brain. Shows the anatomical and functional stages through which three types of adult-born neuron progress before becoming fully mature^{35,39,40,44,47,56–59,117,213} (morphologically simplified and not to scale). This simplified state of affairs comes with a number of caveats, as the maturation of individual adult-born neurons has yet to be followed: maturation stages are likely to reflect a continuum rather than discrete steps; and maturation time points are likely to vary considerably from cell to cell. For this last reason, ages here represent the earliest age at which particular properties have been observed in a given cell type. Note also that maturation certainly does not stop at 28 days of age: arbour complexity and spine density can increase for up to 4 months after the birth of a neuron^{35,47}. Nevertheless, certain key similarities and differences between maturation of the three cell types stand out. In all three, receptor expression precedes synaptic activation, and GABA (γ -aminobutyric acid)-mediated input precedes glutamatergic input. However, olfactory bulb granule cells show atypical maturation in that they only fire sodium-based action potentials after they have begun to receive synaptic input. Olfactory bulb granule cells also appear to mature faster than the other two cell types, although the full maturation of both olfactory bulb periglomerular cells (dopaminergic phenotype) and hippocampal granule cells (spine density and dendritic arbour complexity) extends for much longer than the month-long timeframe shown here. AMPAR, α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor; DCX, doublecortin; GABAR, GABA receptor; GAD, glutamate decarboxylase; NMDAR, *N*-methyl-D-aspartate receptor; NeuN, neuronal nuclear antigen; PSA–NCAM, polysialic acid–neuronal cell adhesion molecule; TH, tyrosine hydroxylase; TUC4, collapsin response mediator protein 4; TUJ1, beta III-tubulin.

Postmitotic newborn neurons in the dentate gyrus show a similar profile of inputs to their dividing progenitors. Glutamate receptors do exist in ~2-week-old neurons that are positive for pro-opiomelanocortin (POMC)–GFP, but evoked and spontaneous synaptic currents are exclusively GABA-mediated⁴⁴. These GABA-mediated inputs show immature characteristics, including slow kinetics and depolarized reversal potentials, and are relatively insensitive to the GABA_A (GABA type A) receptor modulator zolpidem. Consistent with this, newborn granule cells isolated by fluorescent cell sorting lacked the α 1 GABA_A receptor subunit⁴⁵. The initial emergence of slow GABA-mediated synaptic input in 2-week-old cells has also been described using retroviral labelling of newborn dentate gyrus neurons⁴⁶. Initially, then, newborn granule cells receive only slow depolarizing GABA-mediated input²¹³. It is important to stress the difference between this input and the fast GABA-mediated inhibition that occurs onto more mature granule cells⁴⁶. The former might simply have a local, maturational role (perhaps in migration or neurite outgrowth^{41,213}), whereas the latter probably contributes to information processing in the dentate gyrus network.

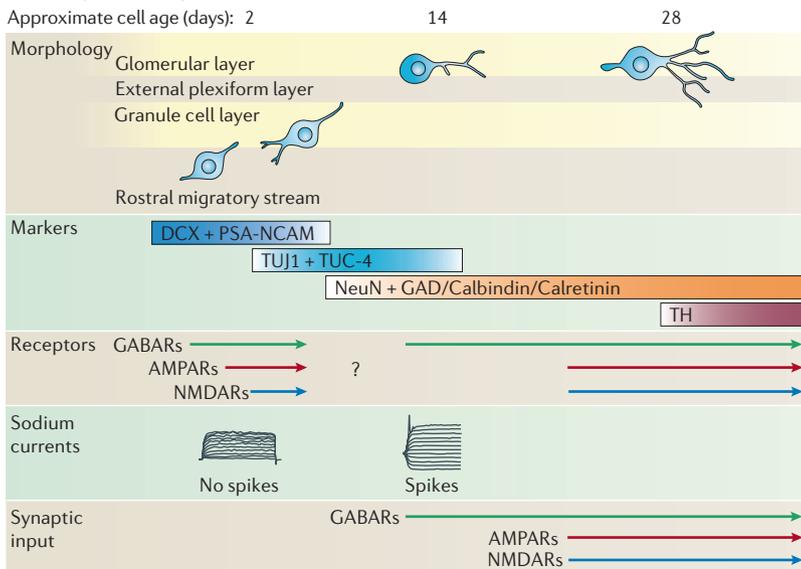
Hippocampal granule cells



Olfactory bulb granule cells



Olfactory bulb periglomerular cells



Functional glutamatergic inputs are evident as cells become more mature^{46,47} and are followed by the final step in synaptic input maturation: the presence of fast, perisomatic GABA-mediated inputs⁴⁶. Glutamatergic inputs, although late-appearing in adult-born neurons, are more easily potentiated in younger adult-born granule cells than in their fully mature neighbours^{48–50}. This effect might depend on the presence of action potential-boosting calcium spikes in immature cells⁵⁰, or on the paucity of fast inhibitory GABA-mediated input to these neurons^{48,49}. Organotypic slice cultures might be a useful preparation with which to analyse in further detail how newborn bulbar cells migrate⁵¹ and acquire neuronal properties^{52,53}, and, in particular, to provide a complete understanding of the molecular steps that lead adult neural stem cells from the SGZ to become mature neurons.

In vivo evidence shows that parvalbumin-positive inhibitory interneurons as well as excitatory granule cells are born in the adult rat dentate gyrus⁵⁴. These cells might be immature granule cells transiently expressing GABA⁵⁵. However, the absence of GABA expression in all granule cells born at the same time contradicts this possibility. Alternatively, the adult-born GABA-containing cells might be small, immature chandelier, axo-axonic or basket cells, as suggested by their location. Further studies are required to unequivocally clarify the mechanisms by which neurogenesis provides the hippocampus with granule cells and inhibitory interneurons.

Using replication-incompetent retroviruses to infect newly generated neurons in the SVZ and label them with GFP, it has been possible to characterize the morphological and electrophysiological properties of these newborn olfactory bulb neurons during their migration and differentiation^{56–58} (FIG. 1). Morphologically, newly generated cells become more complex within the first few weeks after their birth. Granule cells form more elaborate dendrites that extend into the external plexiform layer of the bulb, becoming fully morphologically mature by as early as 2 weeks of age⁵⁶. By contrast, periglomerular cells take ~4 weeks to develop their full dendritic and axonal morphology⁵⁷; a similar time course is required for the maturation of adult-born hippocampal cells⁴⁷ (FIG. 1). During this maturation, immature bulbar interneurons express transient marker proteins including TUJ1 (beta III-tubulin) and TUC4 (REF. 59). Functionally, as in the adult dentate gyrus, the first synapses made onto new cells are GABA-containing, followed only several days later by glutamatergic inputs^{57,58}. Remarkably, the developmental sequence of voltage-dependent currents and synaptic connections marks the main difference between newborn periglomerular and granule cells (and that between bulbar and hippocampal granule cells; FIG. 1). In periglomerular cells, the maturation of the voltage-dependent sodium current, and consequently the capacity of the newly generated cells to fire action potentials, seems to precede the appearance of synaptic contacts, whereas in granule cells, full development of the sodium current is observed only after synaptic connections are established^{47,58}. The delayed maturation of granule cell excitability might prevent disruption of the pre-existing adult circuitry while newborn cells insert themselves, although, as even mature granule

Box 1 | Early versus late neurogenesis — the functional perspective

To what extent do the processes of neurogenesis in the adult brain resemble the much more widespread processes of new neuron production in the developing CNS? Proliferation appears to be similar in both cases, not least in the molecular markers expressed by immature mitotic cells. However, adult stem cells have a longer cell cycle and a higher proportion of quiescent progenitors than their neonatal counterparts. In terms of migration, neuroblasts take much longer to reach the olfactory bulb in neonates¹⁹³, a difference that could be due to intrinsic features of neuroblasts in young versus old mice, or due to maturational changes in the rostral migratory stream extracellular environment. Functionally, many features of adult neurogenesis appear to recapitulate the sequence of events that occurs during neuronal development. The emergence of GABA (γ -aminobutyric acid)-mediated inputs prior to glutamatergic influences is strikingly consistent across adult-born^{39,40,44,46,57,58} (FIG. 1) and developing⁴¹ neurons. Furthermore, early GABA-mediated inputs are depolarizing in immature cells in both the developing⁴¹ and adult^{40,213} hippocampus. However, although the ability to fire action potentials develops early in olfactory bulb granule cells born in postnatal day (P)2–4 mice, this ability develops much later in adult-born neurons⁵⁸.

Furthermore, newborn neurons in neonatal mice tend to occupy more external positions in the granule cell layer, and are much more likely to survive over long periods of time than their adult-born counterparts. The two cell populations might also subservise different forms of olfactory learning¹⁹³. Whether such large differences exist between early- and late-born neurons in the hippocampus, and whether newborn cells have entirely different roles in the same circuits depending on when they enter the network, remain to be investigated.

cells lack an axon, it could be due to morphological differences between granule and periglomerular neurons. To unequivocally demonstrate their integration into adult networks, future studies will need to determine whether newborn neurons make functional synapses with their downstream target neurons and whether they release appropriate neurotransmitters.

Factors regulating adult neurogenesis

If it were a static, merely restorative process, adult neurogenesis could not be regarded as a mechanism for adult brain plasticity. However, as detailed below, we know that every aspect of adult-born cell production is tightly regulated and modulated (FIGS 2,3). This strongly suggests that the adult brain can tailor its production of new neurons to match the demands of its environment.

Stem cells and cellular niches. Stem cells constantly interact with their environment, occupying a particular neurogenic niche in the adult brain. In ecological terms, an organism's niche refers to where it lives, what it does, and how it interacts with its close environment. Altering an ecosystem (or neurogenic environment) can produce disastrous consequences for an organism (or stem cell). In the two neurogenic areas of the adult brain, neural stem cells occupy niches formed by both astrocytes and endothelial cells. In general, endothelial cells encourage stem cells to renew themselves⁶⁰, and astrocytes instruct them to become neurons⁶¹. More surprisingly, mammalian neural stem cells are not passive elements of their microenvironment: they can, under certain conditions, give rise to endothelial cells⁶². This suggests that, if the need arises, stem cells can populate their niche with the features that they need to thrive. In other words, complex bidirectional interactions between intrinsic programmes and extrinsic cues take place in the two niches. We define intrinsic programmes here as the ensembles of factors expressed by stem cells and progenitors that control different neurogenic phases. By contrast, external factors are produced by surrounding tissues to act on stem cells and progenitors.

Intrinsic programmes. Given that multipotent precursor cells can give rise to neuronal and glial cell types in a characteristic order of birth, it is clear that precursor cell proliferation must be precisely regulated. Indeed, at present much research is focused on teasing apart the biochemical signalling that controls the proliferation of adult stem cells and their progeny (FIGS 2,3).

Retinoblastoma, along with its relatives *neccin* and the E2F family of transcription factors, are important cell cycle factors in the regulation of proliferative activity⁶³. Adult mice lacking **E2F1**, for example, show a lower level of cell proliferation and a reduction in the number of neurons generated in adult neurogenic areas⁶⁴. Recent interest has concentrated on the ephrins and their Eph receptors, which are well known for their roles in axon guidance, as possible controllers of cell proliferation. The receptor tyrosine kinases **EphB1–3** and **EphA4** are expressed in the SVZ, where their ephrin-B ligands are associated with astrocytes, and infusing either EphB2 or ephrin-B2 into the lateral ventricle has been shown to disrupt the migration of neuroblasts and increase cell proliferation⁶⁵. Ephrin-A2 might also be a key player in the control of proliferation, as adult mice lacking this protein have a shorter SVZ cell cycle, higher proliferation rates and more neurons in the olfactory bulb⁶⁶. Disrupting the interaction between ephrin-A2 and its receptor **EphA7** in the adult brain of wild-type mice disinhibits proliferation and results in increased neurogenesis⁶⁶.

Like Eph–ephrin signalling, the sonic hedgehog (**SHH**) signalling pathway is not only required for many aspects of development (for more information, see REF. 67), but is also involved in progenitor cell maintenance during adulthood. Loss of hedgehog signalling results in abnormalities in the dentate gyrus and olfactory bulb, and stimulation of the hedgehog pathway in the mature brain results in elevated proliferation in adult progenitors⁶⁸. Furthermore, adeno-associated viral vector delivery of SHH cDNA to the hippocampus increases cell proliferation, whereas pharmacological inhibition of SHH signalling reduces hippocampal neural progenitor

Retrovirus

An RNA virus that uses reverse transcriptase to convert its RNA into DNA.

Neurogenic niche

Regions where the degree of neurogenesis depends on the interaction of the microenvironment with precursor cells that have neurogenic potential.

proliferation *in vivo*⁶⁹. Another extremely important signalling system during development, the WNT system, also augments neurogenic proliferation in the adult dentate gyrus⁷⁰.

Two adhesion molecules are involved in the control of proliferation rates. First, neural cell adhesion molecule (NCAM) facilitates hippocampal neurogenesis proliferation and the differentiation of neuronal cells through regulation of proneurogenic transcription factors⁷¹. Second, mice deficient in CD24, a glycosylphosphatidylinositol-anchored, highly glycosylated molecule that is expressed in both neurogenic niches in the adult brain, show a significant increase in the number of rapidly (in the SVZ and the dentate gyrus) and slowly (in the SVZ) proliferating cells⁷². Even large protein signals can regulate progenitor proliferation. The SVZ is a major binding site for the soluble secreted form of amyloid precursor protein (sAPP), and this binding occurs on progenitor cells expressing the epidermal growth factor (EGF) receptor. *In vivo*, sAPP infusions increase the number of EGF-responsive progenitors through their increased proliferation. Conversely, blocking sAPP secretion, or downregulating APP synthesis, decreases the proliferation of EGF-responsive cells, thereby reducing the pool of progenitors⁷³. It is possible that sAPPs in adult neurogenesis provide a link between aberrant APP processing and some of the cognitive impairments that are associated with Alzheimer's disease. Finally, as discussed above, GABA signalling between neuroblasts and astrocytes limits stem cell proliferation and might, therefore, contribute to maintaining a balance between the amplification and mobilization of progenitors⁴³.

The results of recent studies suggest that cell fate specification is also under the complex, yet stringent, control of a multitude of molecular signals. Most of the neurogenic factors that have so far been identified are associated with a specific population of local astrocytes in the SVZ and SGZ, which indicates that they specifically instruct the neurogenesis of adult neural stem cells in their respective niches. For instance, neural stem cells express members of the bone morphogenetic protein (BMP) family and their receptors in the adult SVZ. The BMP family instructs adult neural stem cells to adopt a glial fate, and, therefore, possibly to adopt the 'default path' as astrocytes⁷⁴. Antagonizing BMP signalling causes neurogenesis 1 (NG1), a secreted factor from astrocytes, to prevent the adoption of a glial fate but to promote differentiation of adult neural stem cells⁷⁵. Similarly, ependymal cells, another type of glial cell, secrete a distinct BMP antagonist, **noggin**, and therefore divert stem cells from a glial to a neuronal fate. Antisense oligodeoxynucleotides against **noggin** decrease cell proliferation in the dentate gyrus of adult rats, which indicates that endogenous **noggin** is important for naturally occurring cell proliferation in the structure⁷⁶. However, although **noggin** blocks gliogenic signals, alone it is insufficient to induce the neuronal differentiation of precursors. WNT signalling might also instruct stem cells to adopt a neuronal fate. In the adult dentate gyrus, the WNT inhibitors sFRP2 and 3 (secreted frizzled-related proteins 2 and 3) partially block astroglial-induced neurogenesis of adult

stem cells, whereas **WNT3** promotes neurogenesis of adult neural stem cells⁷⁰. Together, these studies identify astroglial-derived WNT signalling as a key pathway promoting neurogenesis in adult neural stem cells.

In vitro studies have shown that activation of Ca²⁺ channels and NMDA (*N*-methyl-D-aspartate) receptors in adult neural stem cells profoundly biases their fate towards neuronal specification, which suggests that Ca²⁺ signalling has an important role in neurogenesis⁴². In some cases, stem cells are anchored to their support cells; here, biochemical signalling might require physical contact between cell-surface receptors. This concerns the Notch pathway, which encourages stem cells to keep dividing to renew themselves. **Notch 1**, the effectors of which repress neuronal determination and differentiation in cells not destined to become neuroblasts, is a crucial regulator of neural stem maintenance and self-renewal in the SVZ niche⁷⁷. Consistent with this, Notch is involved in determining glial fate⁷⁸. In addition, it was shown recently that BMI1 (polycomb family transcriptional repressor) is required for the self-renewal of stem cells in the gut and SVZ, but not for their survival or differentiation⁷⁹, whereas knockout of the orphan nuclear receptor TLX produces a loss of cell proliferation and reduced labelling of nestin in neurogenic areas in the adult brain⁸⁰. TLX can silence glial-specific expression of the astrocyte marker glial fibrillary acidic protein (**GFAP**) in neural stem cells, which suggests that transcriptional repression is crucial in maintaining the undifferentiated state of these cells⁸⁰.

Finally, recent work has started to unravel the molecular mechanisms that determine how and when the fate of newborn cells is specified along the SVZ-olfactory bulb pathway⁸¹. Two transcription factors, paired box 6 (**PAX6**) and oligodendrocyte transcription factor 2 (**OLIG2**), are expressed in the SVZ in adulthood, with OLIG2 being exclusively expressed in SVZ transit-amplifying precursor cells. Viral vector-mediated overexpression of mouse OLIG2 in the SVZ facilitated oligodendrocyte maturation, thereby repressing neuronal development. By contrast, PAX6 was scarce in the SVZ but more abundant in neuroblasts that migrate along the RMS, and viral vector-mediated repression⁸¹ and genetic deletion⁸² of PAX6 in the SVZ led to a substantial reduction in the proportion of neuronal precursors. These results, which have been extended to adult hippocampal neurogenesis⁸³, point to an important role for PAX6 in promoting neurogenesis, which it might achieve together with the ventral telencephalic proneural protein mammalian achaete-scute homologue 1 (**MASH1**) (REF. 84). Interestingly, the neuronal commitment and subtype-specification functions of PAX6 can be experimentally uncoupled⁸¹, which indicates that these two operations are distinct, although they are mechanistically linked by common transcriptional regulators.

We understand little about the intrinsic factors that regulate the route of neuroblast migration in the RMS. However, neuroblasts are known to express functional GABA_A receptors, and respond to ambient GABA (controlled by the action of astrocyte transporters) with changes in migration speed⁸⁵.

Antisense oligodeoxynucleotide

A small deoxynucleotide that is complementary to a select region of the mRNA that encodes the protein of interest. It can potentially interfere with transcription and translation, thereby decreasing gene expression. These molecules have been used *in vivo* to selectively inhibit the expression of peptides and proteins in the brain. This provides a simple way of studying the effects of the absence of a gene product in simple organisms and in cells.

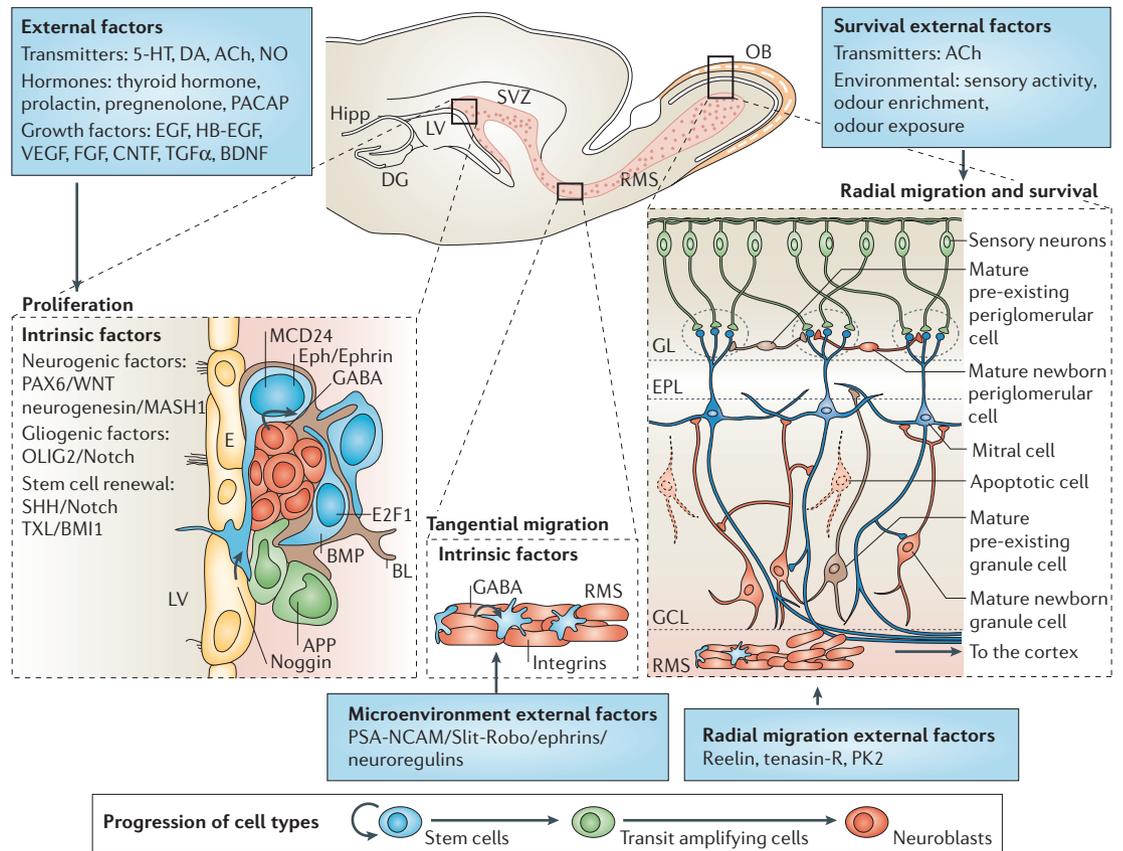


Figure 2 | Intrinsic programmes and external factors controlling adult neurogenesis in the subventricular zone. Proliferation in the subventricular zone (SVZ) takes place in the medial wall of the lateral ventricle (LV), where stem cells divide to generate transit amplifying cells, which, in turn, give rise to neuroblasts that migrate in the rostral migratory stream (RMS) to their final destination in the olfactory bulb (OB). Several intrinsic factors expressed by stem cells and progenitors control both proliferation rates and the fate of newborn cells. In addition, external factors such as neurotransmitters, hormones and growth factors might cooperate with intrinsic programmes to modulate these processes. Tangential migration along the RMS is regulated by interactions between neuroblasts and the local RMS microenvironment, which involves different receptors and proteins that are necessary for contact-mediated repulsion or attraction. After reaching the core of the olfactory bulb, chain detachment and radial migration of neuroblasts is regulated by the external factors reelin, tenascin-R, and prokineticin 2 (PK2). When cells detach from chains, they invade the overlaying layers, where they differentiate into two local interneuron subtypes: granule cells (located in the deeper layer of the olfactory bulb) and periglomerular neurons (located in the most superficial layer). Newborn cell survival then depends on sensory input. 5-HT, 5-hydroxytryptamine (serotonin); ACh, acetylcholine; APP, amyloid precursor protein; BDNF, brain-derived neurotrophic factor; BL, basal lamina; BMI1, polycomb family transcriptional repressor; BMP, bone morphogenetic protein; CNTF, ciliary neurotrophic factor; DA, dopamine; DG, dentate gyrus; E, epidermal cell; E2F1, E2F transcription factor 1; EGF, epidermal growth factor; EPL, external plexiform layer; FGF, fibroblast growth factor; GABA, γ -aminobutyric acid; GCL, granular cell layer; GL, glomerular layer; HB-EGF, heparin-binding EGF; Hipp, hippocampus; MASH1, mammalian achaete-scute homologue 1; MCD24, glycosylphosphatidyl-inositol-anchored highly glycosylated molecule; NO, nitric oxide; OLIG2, oligodendrocyte transcription factor 2; PACAP, pituitary adenylate cyclase-activating polypeptide; PAX6, paired box 6; PSA-NCAM, polysialic acid-neuronal cell adhesion molecule; SHH, sonic hedgehog; TGF α , transforming growth factor- α ; TXL, thioredoxin-like 1; VEGF, vascular endothelial growth factor.

Extrinsic factors. The processes of newborn neuron production, migration, maturation and survival are all subject to modulation by environmental changes (FIGS 2,3). Neurotransmitters, hormonal status, growth factors and injuries are known to influence proliferation, with most of the evidence so far coming from studies in the hippocampus.

Many *in vivo* manipulations that influence electrical activity affect the production of neurons from neural stem cells and/or progenitor cells in the adult forebrain

(for a review, see REF. 86). Recent evidence suggests that hippocampal activity itself can act directly on proliferating progenitors, giving rise to a computationally intriguing scenario in which network activity controls the insertion of new network elements^{40,42}. In terms of fast neurotransmitters, glutamate appears to have complex effects on proliferation, acting through NMDA⁸⁷⁻⁸⁹ and metabotropic⁹⁰ receptors to inhibit division, but causing an increase in proliferation when acting through AMPA (α -amino-3-hydroxy-5-methyl-4-isoxazole

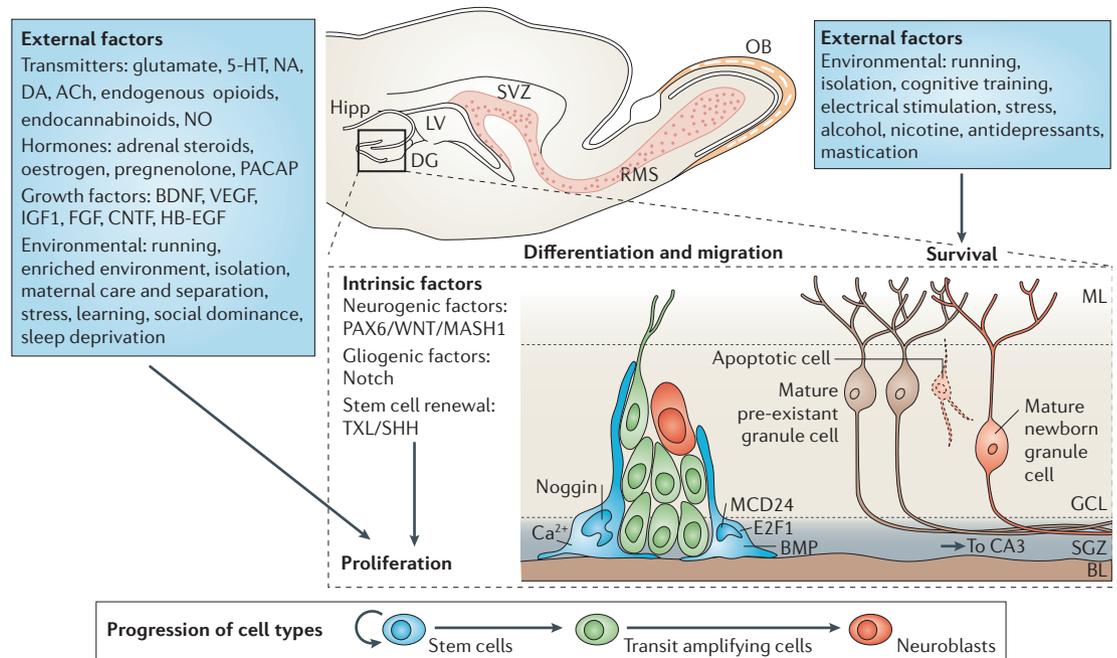


Figure 3 | Intrinsic programmes and external factors controlling adult neurogenesis in the dentate gyrus. In the hippocampus (Hipp), stem cells located in the subgranular zone (SGZ) of the dentate gyrus (DG) produce neuroblasts (but for an alternative view, see REF. 212), which function as transient precursors, and give rise to new granule neurons (type A cells, or neuroblasts). The proliferation of newborn cells in this niche has been studied extensively, revealing many external and internal factors — including transcription factors, neurotransmitters, hormones, growth factors and environmental stimuli — that are involved in regulating the process. In addition, many external factors modulate newborn neuron survival in the granular cell layer (GCL). 5-HT, 5-hydroxytryptamine (serotonin); ACh, acetylcholine; BDNF, brain-derived neurotrophic factor; BL, basal lamina; BMP, bone morphogenetic protein; CNTF, ciliary neurotrophic factor; DA, dopamine; E2F1, E2F transcription factor 1; FGF, fibroblast growth factor; HB-EGF, heparin-binding epidermal growth factor; IGF1, insulin growth factor 1; LV, lateral ventricle; MASH1, mammalian achaete-scute homologue 1; MCD24, glycosylphosphatidyl-inositol-anchored highly glycosylated molecule; ML, molecular layer; NA, noradrenaline; NO, nitric oxide; OB, olfactory bulb; PACAP, pituitary adenylate cyclase-activating polypeptide; PAX6, paired box 6; RMS, rostral migratory stream; SHH, sonic hedgehog; SVZ, subventricular zone; TXL, thioredoxin-like 1; VEGF, vascular endothelial growth factor.

propionic acid) receptors⁹¹. GABA_A receptors, acting through GABA_A receptors, appears to decrease proliferation in both the SVZ and dentate gyrus^{40,43}. Many slower transmitters can also regulate neurogenic proliferation in the adult brain. Although it is clear that dopamine signalling affects proliferation, it is not entirely clear how; the effects of selective agonist and antagonist substances suggest that dopamine decreases proliferation^{92–94}, but conditions that decrease the number of dopaminergic neurons in the brain also appear to decrease proliferation^{95,96}. Serotonin (or 5-hydroxytryptamine, 5-HT), acting through 5-HT_{2A} receptors in the dentate gyrus, 5-HT_{2C} receptors in the SVZ⁹⁷ and 5-HT_{1A} receptors in both regions^{97,98}, upregulates cell proliferation^{99–101}, whereas cholinergic and noradrenergic activation in the hippocampus facilitate dentate gyrus neurogenesis^{102,103,214}. Finally, nitric oxide signalling reduces proliferation in the SVZ^{104,105}.

Chronic administration of morphine and heroin, drugs that act on the opioid signalling system, decreases neurogenesis in the adult rat hippocampus¹⁰⁶. Consistent with this, *in vitro* experiments have shown that reduced signalling through μ - and δ -opioid receptors decreases proliferation in rat adult hippocampal progenitors¹⁰⁷.

Endocannabinoids and ethanol are newcomers in the field of research into addictive drugs that control progenitor cell proliferation and differentiation^{108–111}, although their precise mechanisms of action remain to be elucidated.

Growth factors can also regulate adult neurogenic proliferation. Stimulating brain-derived neurotrophic factor (BDNF) production enhances hippocampal proliferation, an effect that is blocked by BDNF-specific antibodies¹¹². Chronic ventricular infusion of BDNF has also been shown to increase bromodeoxyuridine (BrdU)-labelled cells in the SVZ and olfactory bulb¹¹³. Other growth factors known to increase either dentate gyrus or SVZ proliferation (or both) include ciliary neurotrophic factor (CNTF)^{114,115}, heparin-binding epidermal growth factor (HB-EGF)¹¹⁶, basic fibroblast growth factor 2 (FGF2)^{117,118}, EGF¹¹⁸, insulin growth factor 1 (IGF1)¹¹⁹, transforming growth factor (TGF)^{120,121} and vascular endothelial growth factor (VEGF)^{122–124}. VEGF is also an angiogenic protein, and might constitute an important link between the two processes of blood vessel and neuron formation (see above). Indeed, not only are stem cells and endothelial precursors found in close physical proximity, but this contact also appears to govern astrocyte precursor behaviour (for more information, see

Box 2 | Adult neurogenesis under pathological conditions

Pathological conditions can produce dual and concerted actions on adult neurogenesis. Not only do several factors that promote neurogenesis act in neurogenic regions, but non-neurogenic regions also respond to injury or pathological stimuli by allowing newborn neurons to invade and integrate into the lesioned area¹⁹⁴. Following ischaemia or brain trauma, proliferation is increased in the dentate gyrus and subventricular zone (SVZ)^{195–198}, but newborn neurons can also be found in the striatum and neocortex^{195,197–200}. These latter effects have been attributed to the atypical migration of SVZ neuronal precursors towards damaged areas²⁰¹. Intriguingly, however, the presence of newborn cell clusters in cortical areas in the vicinity of blood vessels also suggests the recruitment of resident quiescent stem-like cells, or the infiltration of blood-borne cells²⁰². Pathological conditions might therefore trigger processes of endogenous neurogenesis in regions where adult neurogenesis is usually non-existent (for more information, see REF. 34).

Despite the presence of neural stem cells in the adult mammalian brain, neurons are not replaced in most regions after injury. New data indicate that oligodendrocyte transcription factor 2 (OLIG2) is a natural repressor of neurogenesis in cells reacting to brain injury²⁰³. Unsurprisingly, evidence of neurogenic upregulation in the damaged brain has led to interest in therapeutic strategies that exploit naturally existing responses. Such approaches could prove fruitful, not only for stroke and trauma patients, but also in patients with degenerative brain diseases for which there is evidence of an increase in neuronal proliferation^{204,205}. Work has concentrated on the mechanisms that produce pathological increases in neurogenesis, showing that activation of glutamate receptors⁸⁹, mitotic factors such as basic fibroblast growth factor (bFGF)²⁰⁶ and inflammatory metabolites such as nitric oxide synthase²⁰⁷ or leukotrienes²⁰⁸ are all involved. Furthermore, in a recent study enhancing bFGF and epidermal growth factor (EGF) activity greatly increased the proliferation of endogenous progenitors following ischaemia, produced newly generated neurons that integrated into neuronal circuitry and was associated with reversals of ischaemia-produced cognitive deficits²⁰⁹. Although grafts of neural tissue into infarcted areas have been associated with symptomatic improvement²¹⁰, it might be more productive for reconstruction therapies to take advantage of endogenous adult neurogenesis. Indeed, single astrocytes taken from the human SVZ can generate *in vitro* neurospheres that differentiate into astrocytes, oligodendrocytes and neurons²¹¹. However, the same study found no evidence in the human brain for the presence of either a rostral migratory stream or precursors organized into clusters of migrating chains, even though rare individual cells expressing specific markers of immature neurons were reported. These findings raise crucial questions about the destination, fate and functions of human SVZ astrocytes, and about their potential interest for auto-transplantation in brain regions of clinical relevance.

REF. 33). Owing to this unique microenvironment, adult stem cell division can be self-replicating: usually at least one of a stem cell's two descendents is a stem cell itself³³. All species studied so far have shown this capacity for long-term self-renewal in the adult brain (for an example, see REF. 125), a feature that could potentially have huge clinical importance for humans (BOX 2).

Among hormones, corticosteroids were the first to be implicated in hippocampal neurogenesis, with evidence coming from various approaches including adrenalectomy, acute administration and stress^{88,126–129}. However, suppression of corticosterone does not affect the SVZ niche¹³⁰. Moreover, stereological analyses of newborn cell numbers have shown that females produce more cells than males in the dentate gyrus but not in the SVZ. This seems to be affected by ovarian hormone levels, as ovariectomy diminishes the number of BrdU-labelled cells, an effect that is reversed by oestrogen replacement¹²⁷. Conversely, the production of neuronal progenitors is stimulated in the SVZ, but not in the dentate gyrus, during pregnancy through the control of prolactin¹³¹ (see below). More recently, thyroid hormone was found to be crucial for neurogenesis in the SVZ¹³². Finally, both *in vivo* pregnenolone administration¹³³ and ventricular infusion of pituitary adenylate cyclase-activating polypeptide (PACAP) increase cell proliferation in the SVZ and the dentate gyrus²¹⁵.

With regard to environmental influences on neurogenesis, physical activity is one of the most reliable promoters of dentate gyrus cell proliferation^{134,135}, and

might predict successful acquisition of new spatial information. Interestingly, physical activity promotes both vascularization and the production of growth factors¹³⁶. Housing in an 'enriched' environment can also significantly increase new neuron production in the dentate gyrus¹³⁷, although this effect is not seen in all mouse strains¹³⁸. By contrast, isolated rearing reduces dentate gyrus proliferation²¹⁶. In addition, adverse experience early in life, in the form of maternal separation, produces a decrease in cell proliferation and immature neuron production in the dentate gyrus of adult rats¹³⁹. Behavioural stress reduces dentate gyrus neurogenesis, mainly through glucocorticoid hormones, whereas social status leads to greater production of new neurons in the dentate gyrus of dominant males in a social hierarchy¹⁴⁰. Finally, sleep deprivation also reduces the proliferation of cells in the adult dentate gyrus¹⁴¹. The strong, if complex, links between learning and neurogenesis are discussed below.

Among the molecular mechanisms involved in tangential migration along the RMS, PSA-NCAM seems to be crucial^{142,143}. An as yet unidentified chemorepulsive signal that acts through SLIT-ROBO signalling also controls tangential migration, with SLIT1 and SLIT2 expressed in the septum and ventricular zone possibly repelling migrating neuroblasts^{144,145}. Ephrins⁶⁵ and the receptor tyrosine kinase ErbB4¹⁴⁶ also seem to direct migration through the RMS, whereas integrins might be crucial in making the RMS a migration-permissive substrate¹⁴⁷. Finally, long-range attractants generated in

Stereological analyses

Classic stereology microscopy has developed along independent pathways as a methodology to provide a quantitative understanding of the structure of the brain. This type of analysis has concentrated on the unbiased numerical estimation of parameters such as length, area, volume and population size that characterize entire regions of the brain as well as individual elements within them, for example, cell volume.

Box 3 | Is there a critical period in the olfactory bulb circuit?

Most neuronal circuits are shaped by their activity in critical periods during development¹⁹⁰. However, olfactory plasticity seems to extend throughout life: removal of afferent input by naris closure causes the deprived olfactory bulb to atrophy¹⁹¹. Moreover, strong olfactory plasticity in adulthood is behaviourally adaptive. Female mice form an olfactory memory at the time of mating that programmes spontaneous abortion when a novel male intruder appears (the Bruce effect; for more information, see REF. 192), and offspring recognition from olfactory cues occurs within 4 hours after parturition in sheep. Could such adult olfactory plasticity be related to ongoing neurogenesis in the mature system? Certainly, the ability of a mother rodent to recognize and nurture her young is associated with an increase in newborn neurons that are integrated into olfactory bulb circuitry¹³¹. But whether large-scale morphological changes¹⁹¹ or specific olfactory behaviours depend on adult neurogenesis remains unclear.

In contrast to the idea of a critical period for plasticity with regard to the life of an organism, critical periods for changes within the brain can also exist with regard to the life of individual cells. The results of a recent study that used naris occlusion at various time points suggest that the survival of newly born olfactory bulb granule cells is affected by sensory experience, but only when those cells are between 14 and 28 days of age¹⁶⁰. These two ideas of organism-based and cell-based critical periods might not be independent, as newborn neurons in the olfactory bulb show distinct survival rates depending on their postnatal time of production¹⁹³. In the olfactory system, then, early experience remains crucial in shaping brain development, but processes of adult neurogenesis might cause this influence of sensory activity to persist for an unusually long time.

the olfactory bulb have been proposed to be involved in neuroblast migration¹⁴⁸, although the results on which this idea is based are still controversial¹⁴⁹.

After reaching the core of the olfactory bulb, neuroblasts detach from their chains and turn radially to reach the outer layers. Chain detachment is promoted by reelin expressed by mitral cells¹⁵⁰, while the extracellular matrix glycoprotein tenascin-R initiates both the detachment of neuroblasts from chains and their radial migration¹⁵¹. Interestingly, the expression of tenascin-R is activity-dependent¹⁵¹, and it might act with secreted prokineticin 2 (PK2), which functions as a chain-detachment signal and a chemoattractant for SVZ-derived neuronal progenitors¹⁵².

Adult neurogenesis is a wasteful process — of the newborn cells that migrate, differentiate and mature successfully, only ~50% survive for longer than a month^{56,59,153}. Despite the clear importance of this survival process, only a comparatively limited number of external cues have been shown to affect the survival rate of newly generated neurons in the dentate gyrus — namely, physical activity, enriched rearing and housing, spatial learning (see below), mossy fibre stimulation, antidepressants and alcohol (for examples, see REFS 134, 135, 138, 154, 155, 217–219).

In the olfactory bulb, mice lacking the $\beta 2$ -subunit of the nicotinic acetylcholine receptor show an increased survival of newborn granule cells, but not of newborn periglomerular neurons¹⁵⁶, and several studies have shown that the survival of newborn bulbar granule cells depends on sensory input^{56,157–161} (BOX 3). This influence of sensory input does not appear to be long-lasting: the increased survival of newborn neurons produced by an enriched environment ceases immediately after animals are returned to standard raising conditions¹⁶². Increased newborn cell survival with augmented sensory input might occur through the actions of the anti-apoptotic protein BCL2: although odour presentation induces an increase in bulbar BCL2 expression¹⁶¹, mice that over-express the protein show enhanced survival of newborn hippocampal neurons¹⁶³.

Functions of neurogenesis during adulthood

It is clear that many factors regulate the production, transport, development and life-death decisions of adult-born neurons. But once a newborn cell has reached its target, has become a mature neuron and has survived, what does it do then? Why is it there?

Cellular, network and systems levels. Taking an abstract, fundamental approach, newborn neurons might be able to contribute to adult brain function at the cellular, network and systems levels⁷. At the cellular level, the function of newborn neurons might seem straightforward — they are neurons. But are they special types of neuron? Work on the maturation of newborn cells suggests that their cellular function might differ from that of their older counterparts, at least transiently (FIG. 1). Young granule cells in the adult dentate gyrus, for example, show a greater propensity for synaptic plasticity compared with older granule cells^{48,50}, whereas newborn granule and periglomerular cells in the olfactory bulb show markedly different active membrane properties compared with the existing neurons around them^{57,58}, and show greater plasticity in response to sensory deprivation¹⁵⁹. Adult-born olfactory bulb cells also show different early-gene responses to odours¹⁶⁴. Functions of adult neurogenesis at the cellular level might also depend on the cells that are replaced by newborn neurons. We do not yet know whether adult-born cells constitute a specialized, specific population of neurons that replace each other, or whether newborn cells fulfil a more general role by replacing the function(s) of much older neurons (FIG. 4).

At the network level, newborn neurons might contribute to properties that are produced by the concerted activity of groups of cells. In the olfactory bulb and hippocampus, oscillations and synchrony of neuronal activity represent two obvious and important network phenomena that might be influenced by adult neurogenesis. Individual networks are also capable of a wide range of information coding and storage operations, and models of adult neurogenesis have begun to suggest that

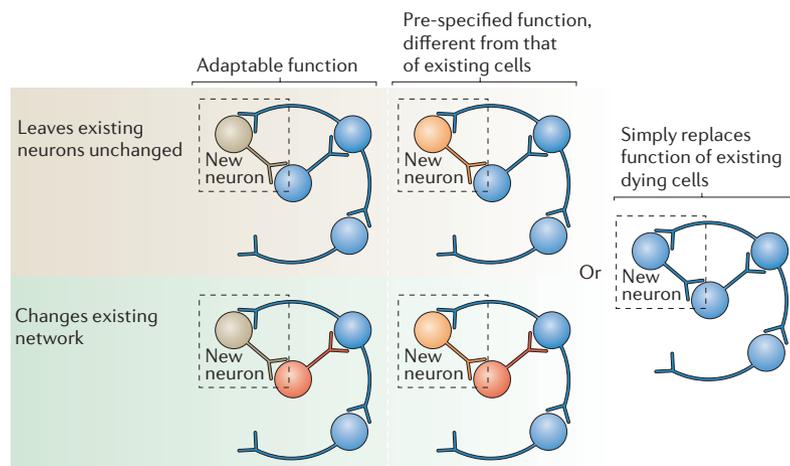


Figure 4 | Possible functions of newborn neurons at the cellular and network levels. We offer a basic scheme of the functional possibilities that newborn neurons might bring to the networks they join. New neurons might have an unspecified, flexible function, or they might have a specific, predetermined role in information processing. In addition, they might simply ‘slot in’ to the pre-existing network, playing their part without causing any other changes, or they could alter the characteristics of existing neurons. This alteration could depend crucially on the types of neuron with which newborn cells form connections. Do newborn granule cells, for example, preferentially make contacts with other granule cells, or do they have a preference for excitatory projection neurons? Finally, newborn neurons might do nothing functionally special at all, and could simply replace the function of existing, but dying cells. Note that these functions need not be mutually exclusive, or individually exclusive to a given neuron: a single newborn cell, for example, might possess a pre-specified specialist function early in its maturation, but then assume a role similar to that of existing cells once it matures fully. Furthermore, it is entirely possible that each stage of maturation shown in FIG. 1 could be associated with its own unique functional role.

Trace eyeblink conditioning

A hippocampus-dependent task in which animals must associate a conditioned stimulus with an eyeblink-producing unconditioned stimulus. The key ‘trace’ aspect comes from the fact that the two stimuli are separated in time.

Morris water maze

In its most common form, a test of spatial learning and memory, in which animals must use spatial cues to locate a hidden platform in a pool of opaque water.

Long-term potentiation (LTP)

An enduring increase in the amplitude of excitatory postsynaptic potentials as a result of high-frequency (tetanic) stimulation of afferent pathways. LTP is often considered to be the cellular basis of learning and memory in vertebrates.

newborn cells might be vital to some of these functions (see below). Finally, in terms of functional plasticity, neurogenesis at the network level should be considered from the viewpoint of permissiveness versus instruction. It is not clear whether, through pre-specified roles, newborn cells instruct changes in the networks that they join, or whether, through a general alterable role, they simply permit changes to occur in those circuits (FIG. 4). It is, however, at the systems level that most work into the functions of adult neurogenesis has taken place. The role of the hippocampus in learning and memory, and the perceptual and mnemonic functions of the olfactory bulb have understandably led to investigations into the importance of adult neurogenesis in these processes. Although the gap between cell generation and cognitive processes is large, we are beginning to understand how the plasticity afforded by adult neurogenesis might contribute to an animal’s behaviour.

Roles in information processing and storage. As a first step towards identifying a systems function to which adult neurogenesis contributes, it might seem sensible to ask whether individual performance levels of that function correlate with individual levels of newborn cell production and/or survival. In the hippocampus, individual performance on tasks known to depend on the structure is positively correlated with adult neurogenesis:

trace eyeblink conditioning performance correlates with measures of newborn cell survival¹⁵⁵ and reactions to novelty correlate with levels of proliferation¹⁶⁵. However, performance on another hippocampus-dependent task, the Morris water maze, varies much less robustly with indices of neurogenesis. No correlations have been found between individual spatial learning and neurogenesis in young rats (for an example, see REF. 166), and whereas some reports found water maze learning to vary with newborn cell proliferation and survival in aged rats¹⁶⁶, other studies failed to find similar correlations¹⁶⁷. Other studies still have found complex relationships between neurogenesis and water maze performance that depend on stages of training and the maturity of newborn cells¹⁶⁸. A precise knowledge of the functions tested by various stages and aspects of training coupled with a precise knowledge of the neurogenesis features measured will be essential to resolving these inconsistencies.

Many studies have reported parallel effects of a particular manipulation on both neurogenesis and function, providing further indirect evidence for a link between the two processes. At the cellular/network level, manipulations that increase (running¹³⁴) or decrease (methyl-CpG binding domain protein 1 (MBD1) knock-out¹⁶⁹) adult neurogenesis cause either increases or decreases, respectively, in levels of dentate gyrus long-term potentiation (LTP). At the systems level, physical activity¹³⁴ and environmental enrichment¹⁵⁴ increase both neurogenesis and performance on hippocampus-dependent learning tasks, whereas age¹⁶⁶, stress¹³³, cholinergic lesions¹⁰³ and knockout of the *Mbd1* gene¹⁶⁹ are associated with deficits in both phenomena. In addition, acquisition of spatial memory in the water maze correlates with the proliferation and survival of newborn dentate gyrus neurons across different inbred mouse strains¹⁷⁰, and the negative effects of environmental enrichment on the retention of contextual fear conditioning are reduced in presenilin 1-knockout mice that concomitantly lack enrichment-induced increases in hippocampal neurogenesis¹⁷¹. In the olfactory bulb, olfactory enrichment links increased newborn cell survival with improvements in olfactory memory¹⁵⁸. By contrast, olfactory discrimination is decreased by genetic manipulations that reduce the number of newborn cells in the adult bulb^{121,172}. These correlative observations suggest that adult neurogenesis might contribute to the learning and memory functions subserved by the hippocampus, and to the perceptual and memory functions performed by the bulb. However, there are instances in which manipulation-induced changes in neurogenesis are not matched by parallel changes in hippocampal- or bulbar-dependent cognitive function^{156,173,174}.

Instead of looking for correlations between neurogenesis and function, a more direct approach would be to determine whether a particular function regulates neurogenesis. In the female mouse olfactory system, for example, the proliferation of adult newborn cells increases after mating, during gestation and during lactation¹³¹. This suggests that adult neurogenesis might be important for the high olfactory perceptual and memory demands associated with reproduction (for

more information, see REF. 175). Efforts have been made to influence neurogenesis in the hippocampus by training on learning and memory paradigms that are known to require this structure. However, results have been confusing and contradictory. Overall, the simple story is that spatial learning tasks do not influence newborn cell proliferation^{134,176} but do enhance newborn cell survival^{155,168,176}. The full story, however, suggests that the influence of spatial learning tasks on hippocampal neurogenesis depends crucially on the specific demands of particular task elements and the precise maturation stage of newborn neurons present during particular learning phases^{168,177}. Therefore, the exact role of hippocampal neurogenesis in spatial learning and memory, if any, remains far from clear.

The most direct approaches to investigating the functions of adult neurogenesis have involved attempts to specifically abolish the process. Administration of the antimetabolic agent methylazoxymethanol acetate (MAM) over 2 weeks considerably reduces the number of newborn neurons present in the dentate gyrus, and produces deficits in hippocampal-dependent trace conditioning^{178,179}. Moreover, at the right concentration, MAM reduces newborn cell proliferation without affecting an animal's general health, standard measures of hippocampal physiology or performance on non-hippocampus-dependent learning tasks¹⁷⁸. Despite this, however, the drug is far from specific, and a dependence of learning deficits on non-neurogenic hippocampal influences cannot be completely ruled out. In addition, problems of intervention completeness are raised by the fact that MAM treatment only reduces newborn neurons to 20% of their normal level, and does not impair learning on all hippocampus-dependent tasks¹⁷⁹. Either certain hippocampus-dependent learning tasks depend more on adult neurogenesis than others, or the hippocampal side effects of MAM are specific to only certain functions performed by the structure.

Adult neurogenesis is almost completely compromised by irradiation of the brain. At the network/cellular level, a severe reduction in newborn neurons produced by clinical levels of irradiation is associated with a complete lack of a particular form of dentate gyrus LTP⁴⁹. This form of synaptic plasticity, which is independent of GABA-mediated inhibition, might be particularly important during active behavioural exploration, when it is known that inhibition in the hippocampus is at a high level¹⁸⁰. At the systems level, irradiation produces deficits in spatial memory retention in the water maze¹⁸¹, and on spatial learning in the Barnes maze¹⁸² without affecting water maze learning^{181,182} or non-hippocampus-dependent learning tasks. It also prevents hippocampus-dependent behavioural responses to antidepressant treatment¹⁰¹. However, the specificity of the effects of radiation has been questioned. Irradiation has been shown to decrease neurogenesis owing to effects on the SGZ microenvironment rather than specific effects on dividing cells¹⁸³.

So, correlational and intervention evidence converge, in the most part, to suggest that neurogenesis in the adult olfactory bulb and hippocampus is important for the very functions — spatial learning and memory

in the hippocampus, and olfactory discrimination and memory in the olfactory bulb — for which the structures themselves are believed to be important. This is not surprising, although the possible discrepancies between hippocampus-dependent learning tasks and hippocampal neurogenesis-dependent learning tasks (for an example, see REFS 179,181) are intriguing. What is certain is that specifically and completely halting adult neurogenesis, as might soon be offered by conditional knockout approaches, should offer the opportunity to more rigorously investigate the functions of adult neurogenesis at the systems level, provided that our approaches to behavioural characterization are extremely well considered.

Of course, one way to specifically and completely manipulate adult neurogenesis is to use simulated computational models. In a model of olfactory bulb circuitry, introducing activity-dependent survival of newborn neurons produces better orthogonalization of sensory representations, which are indicative of better olfactory discrimination in changing environmental conditions¹⁸⁴. Similarly, neuronal turnover in the dentate gyrus layer of a simulated hippocampal network improves the recall of information by minimizing interference between similar stored items¹⁸⁵. In terms of learning, simply adding new neurons to a network can threaten the fidelity of both newly and previously stored information¹⁸⁶. However, if a network possesses homeostatic mechanisms to compensate for increased excitability, adding new excitatory neurons can aid the storage of new information, while simultaneously facilitating the forgetting of old memories^{42,186,187}. Interestingly, these effects of neurogenesis appear similar whether the homeostatic mechanisms involve turnover of existing excitatory neurons or processes to reduce activity in pre-existing connections¹⁸⁶.

These models represent perhaps the best current evidence for a commonly proposed function of adult neurogenesis: that, rather than (or as well as) participating in the storage of new information, it endows a network with the ability to adapt to future changes in input¹⁸⁸. Therefore, adult neurogenesis could represent a form of metaplasticity — a change in the brain that facilitates further changes in the brain. It would certainly be interesting to investigate whether increased neurogenesis produced by one form of learning facilitates the retention of a different future task.

Concluding remarks

The two faces of Janus: stability and flexibility. The job of the adult brain is to guide the organism through a changing world, a job that involves being able to adapt to new challenges without compromising the ability to respond to familiar situations. This is simple if the brain possesses unlimited learning and storage capacity, but if we recognize the likely case that learning everything is not possible, it is clear that the twin demands of stability and flexibility are contradictory: learning new information when your memory is full must involve some forgetting. At first glance, neurogenesis in the adult brain would seem to bias a system in favour of flexibility;

Barnes maze

In its most common form, a challenging test of spatial learning and memory. Animals must locate a single escape tunnel hidden under one of 40 possible entrance holes.

after all, it is a drastic step to introduce a completely new cell to an already functional circuit, or to remove an existing neuron from that network. However, certain features of the maturation of adult-born neurons might minimize the instability produced by their addition. In particular, the fact that newborn cells always receive GABA-mediated synaptic input before glutamatergic influences^{39,40,44,57,58,213} (FIG. 1) might allow their integration into existing networks without running the risk of excitation-induced neurotoxicity. In addition, the late development of sodium spikes by maturing olfactory bulb granule cells might allow them to integrate 'silently' into the existing network, only contributing to network activity when they are fully mature⁵⁸ (FIG. 1).

Computational models suggest that adult neurogenesis, rather than introducing drastic flexibility to a network, might actually stabilize an already plastic network in the face of a large volume of new incoming information (see above, and REF. 186). However, it is also possible that in a system with limited capacity that needs to forget old information, producing a large degree of plasticity through adult neurogenesis might represent an ideal solution^{42,171,186,187}. Neurogenesis might therefore favour flexibility, stability, or both, in the adult brain.

Why only a few brain areas? Those looking for the functional meaning of adult neurogenesis might be inspired by its extremely limited spatial distribution. What is so special about adult neurogenic regions that they alone possess adult-born neurons? Or, the question could be turned around to ask why, given the relative abundance of neurogenesis in the adult brain of reptiles and birds, do so many regions of the adult mammalian brain not receive newborn neurons? The olfactory bulb and hippocampus certainly share many similar features, any or all of which could be related to adult neurogenesis. They are both evolutionarily old areas of the brain, and, during development, both are populated by cells arising from neurogenic zones adjacent to the lateral ventricle. From a functional point of view, it is intriguing that both structures appear to be vital in the temporary storage of information¹⁸⁹, a role that fits well, if rather vaguely, with the functions of adult

neurogenesis discussed above. It has also been suggested that both the olfactory bulb and hippocampus might deal with particularly large amounts of information¹⁸⁷ or use specific coding strategies to deal with that information¹⁸⁴. However, for every similarity between the olfactory bulb and hippocampus there are large differences, not least in terms of adult neurogenesis (FIG. 1). Moreover, for every proposed shared function between these two regions, there are other, non-neurogenic regions of the adult brain that have the same attribute. Whether neurogenesis in the adult olfactory bulb and hippocampus has a particular, common role will await more precise investigation of its function. In the meantime, a simple answer to the question above might be that the olfactory bulb and hippocampus are two regions of the mammalian brain in which mutations preventing adult neurogenesis were never beneficial, or simply never occurred.

Note added in proof

In a recent paper, Sawamoto *et al.* report that the planar polarity of ciliated ependymal cells of the lateral ventricles is essential for the formation of chemorepulsive factor gradients that guide neuroblast migration in the adult brain. They show that polarized epithelia and motile cilia in the brain serve as important conveyors of directional information for neuroblast migration²²⁰.

Ziv and colleagues have identified CNS-specific autoimmune T cells as being important to adult brain plasticity. They found that their involvement occurs, at least in part, by means of crosstalk with resident microglia. This new and important finding suggests that CNS-specific T cells affect adult neurogenesis, both in the dentate gyrus and in the SVZ, primarily through their effect on progenitor cell proliferation²²¹.

Götz and Huttner cover recent data that shows how neural stem cells and their derivative progenitor cells generate neurons by asymmetric and symmetric divisions during the development of the mammalian CNS. The authors discuss the molecular mechanisms that evolve during development from neuroepithelial to radial glial cells, and how this transition affects cell fate and neurogenesis²²².

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Competing interests statement

The authors declare no competing financial interests.

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