Adult neurogenesis—a reality check

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Abstract It is established beyond doubt that new neurons are born in discrete areas of the adult brain throughout the lifetime of most mammals. Recent findings have shed new light on the regional limitations, regulation, and possible function of adult neurogenesis. This article aims to look critically at the existence and relevance of adult neurogenesis under physiological conditions, based on recent advances in the field. We also evaluate the therapeutic potential of adult neurogenesis and what is realistic to expect from the future. We conclude that, to date, little is known with certainty about why new neurons are generated in the adult brain. Until there is more causal evidence at hand, assumptions about the potential functions of new neurons remain hypothetical. Provided we learn how to safely regulate proliferation, migration, and proper maturation of new neurons, endogenous neurogenesis could be a promising source of new cells for replacement therapies.

Keywords neurogenesis · hippocampus · olfactory bulb · function · therapeutic

Introduction

The existence and prospects of adult neurogenesis have stimulated the imaginations of neuroscientists for more than four decades. Initially criticized to be an artifact, it is now considered a fact that adult mammals including rodents and primates produce new neurons from dividing progenitor cells. Adult neurogenesis has been established beyond doubt in two brain regions, the hippocampal dentate gyrus and the subventricular zone (SVZ) of the lateral ventricle wall, through the use of multiple detection methods, such as thymidine labeling, retroviral labeling, and stage specific antibodies. With the development of novel detection techniques, a considerable increase in the amount of studies on various aspects of neurogenesis has emerged during the last 15 years. Numerous experiments have examined whether certain interventions, be it altered gene expression, hormone levels, pharmacological treatments, lesions, or CNS diseases, lead to a change in the numbers of newborn neurons by affecting proliferation, differentiation, and/or survival of the newly generated cells. A number of experiments have focused on how behavioral and environmental variables such as physical exercise, learning paradigms, and enriched environment affect the rate of neurogenesis. Other studies have explored the specific functional characteristics of stem cells, progenitor cells, and new neurons. Several studies have also collected evidence for a wider occurrence of adult neurogenesis in brain regions other than the hippocampus and SVZ and disease situations. This final group of studies has been criticized for their limited methodological repertoire and we will critically evaluate the evidence for neurogenesis outside of the hippocampus and SVZ. We also address the paucity of causal evidence linking new neurons to the potential function(s). Whether new neurons are crucial mediators of information or an irrelevant side effect of

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hippocampal activation remains an open question. What do we really know about the relevance of adult neurogenesis, and can this knowledge be used for the benefit of mankind? Another article in this issue of “Debates in Neuroscience” presents an optimistic perspective on the potentials of adult neurogenesis. Our role in this discussion is to evaluate critically the existence, possible relevance, and therapeutic potential of adult neurogenesis, based on the findings that are at hand to date.

Neurogenesis—where and when?

At present, only two regions of the adult mammalian brain are generally accepted to harbor endogenous neuronal stem cells; the hippocampal dentate gyrus and the SVZ of the lateral ventricles [1, 2]. New hippocampal neurons originate from the border between the hilus region and the granule cell layer to form glutamatergic granule cells. Newly formed progenitors from the SVZ migrate to the olfactory bulb to become GABAergic granule cells and GABAergic/dopaminergic periglomerular interneurons [3]. Beyond these two regions the situation is more controversial. Using *in vitro* differentiation or transplantation to a neurogenic region, precursor cells with a neurogenic potential have been isolated from the neocortex, septum, striatum, corpus callosum, hypothalamus, substantia nigra, and spinal cord [4–6]. However, *in vitro* evidence can hardly be used as an argument for actual neurogenesis in the brain, as even the isolated optic nerve or pure astrocyte cultures seem to contain multipotent cells or the ability to be converted to multipotent cells *in vitro* [6]. We can only infer that cells in these areas have the potential rather than the *in vivo* function of neural stem cells. The *in vivo* production of new neurons in the neocortex and amygdala of adult primates [7, 8] is also a matter of dispute [9–11]. Recent studies using postmortem human tissue found no signs of neurogenesis in the adult neocortex [12, 13]. As the SVZ harbors a high quantity of proliferative neuronal precursors that readily migrate all the way to the olfactory bulb, what is stopping them from also migrating to other areas of the brain? Several studies suggest attractant molecules released from the olfactory bulb [14] and repellent factors in the surrounding tissue [15]. Manipulations such as experimental stroke and growth factor stimulation are suggested to induce migration and neuronal differentiation of SVZ-derived progenitors to anatomically close regions including the striatum, septum, and hypothalamus [16–18]. In this study, stem cell homing factors such as SDF-1 might be involved in directing the migration to the lesion site [19].

Because of its clinical relevance in Parkinson’s disease, the adult substantia nigra has been studied in detail with regard to potential production of new neurons. In the adult

intact substantia nigra, a few studies found newborn cells with a dopaminergic phenotype in the range of two to ten new dopamine neurons per bilateral substantia nigra per animal [20–22]. On the other hand, several other studies using similar methods found no newborn dopamine neurons in the adult substantia nigra [4, 23, 24].

In summary, most reports on generation of new neurons in areas other than the SVZ/olfactory bulb and hippocampus show a very low rate of neurogenesis. A major critique has been that these studies have exclusively relied on thymidine labeling for the detection of new neurons. Thymidine analogs such as bromo-deoxyuridine (BrdU) are incorporated during DNA synthesis, which occurs during cell division, and also during DNA repair. Therefore, cells undergoing DNA repair while exposed to BrdU may be mistakenly classified by the experimenter as “new cells.” Whether the amount of BrdU incorporated during DNA repair is sufficient to be detected by immunohistochemistry is under debate, but it is clearly dependent on the amount of DNA damage in relation to the concentration of BrdU used. At the most commonly used concentration of 50 mg/kg BrdU, the risk of BrdU uptake into cells undergoing cell death is relatively low in intact tissue, but it increases, for example, after lesions of the nigrostriatal pathway [25].

The best evidence for ongoing neurogenesis is retroviral labeling, as a retrovirus only integrates into the host DNA after nuclear membrane breakdown, which occurs in viable cells only during cell division. The method has the advantage to label all progeny of an infected cell and allows for stable expression of marker proteins such as GFP. It is therefore not only possible to colabel with neuronal markers, but also to prove the functionality of the new neurons using electrophysiological methods [26, 27]. Disadvantages of retroviral labeling include: (1) nonquantitative labeling, (2) invasive intracranial injections, and (3) low frequency of labeling, which makes it a difficult tool to analyze the reportedly rare occurrence of neurogenesis in areas outside the dentate gyrus and SVZ/olfactory bulb.

It is therefore crucial to improve immunohistochemical detection of neurogenesis with BrdU. Prerequisites are proper neuronal markers and the correct use of the confocal microscope to colocalize the immunohistochemical signals, i.e., controlling for bleed-through and optical slice thickness.

What are the best criteria to unmask false colabeling of BrdU with a mature neuronal marker? So far, neurogenesis has been shown to require the cell division of an immature cell, be it a stem cell or a progenitor cell. The maturation into a neuron requires several days in which the cell undergoes frequent morphological and molecular changes, including the expression of stage-specific markers [28]. Hence, one of the key elements in proving neurogenesis in a new region could be the demonstration of this development from an immature cell to a mature neuron. If an experimental paradigm

includes multiple time points for perfusion after BrdU administration, ranging from a few hours to several weeks, one can determine whether a BrdU signal is detected immediately after BrdU labeling in mature neurons (which would indicate labeling via DNA repair) or whether initially immature marker combinations such as nestin/GFAP or doublecortin colabel with BrdU [29]. The progression through multiple developmental stages is the best proof that neurogenesis is in progress. In conclusion, before a consensus can be reached about the neurogenic potential of different brain areas, we suggest the methodological repertoire for neurogenesis labeling and detection should be verified by at least two independent research groups to meet with well-defined criteria for the definition of an adult-born neuron. Further, we suggest these criteria include at least two out of the following three criteria: 1) detection using retroviral labeling, 2) thymidine analog labeling, and 3) progression through multiple developmental stages using stage-specific markers in combination with proper confocal microscopy.

The analysis of human tissue from postmortem material or surgical resection faces the additional problem that neither BrdU nor retroviral labeling can be routinely performed for ethical reasons, as they have to be administered several weeks or months before tissue collection. Studies have made use of stage-specific markers to prove cell division and immature progenitor cells in similar locations as the nonhuman primate and rodent brain [30–34]. So far, only a single study generated postmortem tissue from patients that received BrdU for *in vivo* tumor labeling and confirmed the existence of BrdU/NeuN colabeling in the human hippocampus [35]. It is apparent that beyond its existence in the hippocampus, our knowledge on human neurogenesis is limited and mostly extrapolations from primate or rodent studies. However, novel methods such as carbon dating could help answer important questions. This innovative method takes advantage of the dramatic global increase in the levels of ^{14}C in the atmosphere that took place after testing of nuclear weapons, followed by an exponential decrease after 1963 to roughly determine the DNA synthesis and thereby birth date of cells in tissue samples. The first studies using this technique indicate that there is no turnover of neurons in the adult neocortex, at least in human subjects [12, 13].

Function of new neurons in the adult brain under physiological circumstances

Why are we equipped with the ability to produce new neurons in the dentate gyrus of the adult hippocampus?

The functional relevance of hippocampal neurogenesis can be divided into two issues: (1) at the cellular level, the role

of progenitor cells and new neurons within the network and (2) at the behavioral level, the consequences of ongoing neurogenesis for cognitive processes. Numerous publications have characterized the new neurons at the cellular level. Newborn neurons have a lower threshold for eliciting action potentials and long-term potentiation and are more plastic than the existing granule neurons [36, 37]. They are also thought to be added in an activity-dependent manner [38, 39]. Adult-born granule cells follow the same maturation patterns as in embryonic development, including a transient period of being excited, rather than inhibited, by the neurotransmitter GABA the first few weeks after birth [36, 40, 41]. The new neurons in the hippocampus are born in the subgranular zone of the dentate gyrus, from where they migrate a short distance into the granule cell layer, and make dendritic connections with the molecular layer and axonal connections with the CA3 within 2 weeks [42–44]. They become functionally integrated into the existing circuitry, and at 4 to 5 months after mitosis, they appear morphologically indistinguishable from the older granule cells [26] but remain physiologically more responsive to stimulation than the older counterparts [45]. Does this mean that the new neurons can carry out processes the older ones are too “rigid” for? It has been suggested that new neurons come about to avoid “catastrophic interference” in the hippocampus [46], to form temporal links between long-term memories [47], or even to help with the clearance of memories to make room for new ones, i.e., facilitate forgetting [48]. It is also plausible that new neurons strengthen certain forms memory formation while interfering with others, depending on the timing and other factors. However, these theories are at this point hypothetical or based on circumstantial evidence.

Do the numbers matter?

It is often posited that more new neurons would be beneficial for hippocampal function, but what is the evidence speaking in favor of this assumption? Available immunohistochemical techniques such as Ki-67, PCNA, doublecortin, and thymidine labeling have made it easier to detect and quantify mitotic cells and new neurons. Approximately 9,000 new neurons are generated everyday in the dentate gyrus of a young adult male rat [49]. From this level a continued decline is observed during aging [50], but neurogenesis appears to be still present and inducible at old age [51, 52]. The steepest decline in neurogenesis occurs rather early (during the first year in rats), whereas cognitive impairment that can be associated with age has its onset rather late (after 18 months in rats). Studies attempting to link cognitive performance and numbers of newly born cells in the aged hippocampus have shown very mixed results, one negative and one positive correlation between intact memory function

and the level neurogenesis in the aged hippocampus and two studies without correlation [53–56].

Regardless of age, about half of the newborn progenitors die within the first few weeks after they are generated [3, 57, 58]. Those that survive the first critical period are likely to survive for as long as measurements have been made [2, 28].

A functional role for neurogenesis is best defined by experiments that selectively up- or downregulate neurogenesis in the adult brain. As a large number of published studies show, many different manipulations, even seemingly subtle ones such as the amount of handling or the number of BrdU injections, can dramatically reduce or increase the numbers of newborn neurons [59, 60]. Several factors associated with increased cognitive performance also increase neurogenesis, enriched environment [61], voluntary running [62], and restricted diet [63] are some examples. It is crucial to acknowledge that factors that influence the rate of neurogenesis also have a wide array of other effects on the organism, rendering it very difficult to ascertain whether the increase or decrease in neurogenesis contributes to the behavioral effects. Attempts to dissect out the role of neurogenesis in the beneficial effects seen with enriched environment, using ablation techniques, have resulted in diverging findings. One study reports that ablation of hippocampal neurogenesis reduces the beneficial effects of enriched environment on long-term recognition memory [64]. Another recent report indicates that several measures of hippocampus-dependent behavior stimulated by enriched environment occurs independently of hippocampal neurogenesis [65]. However, because of methodological discrepancies, it is difficult to interpret these data. Conversely, a correlation between hippocampus-dependent memory tasks and the numbers of new hippocampal neurons has been sought. Also in this study, the picture has been blurred by diverging results. Engagement in certain hippocampal-dependent tasks leads to increased hippocampal neurogenesis [66–69], whereas others lead to no change or even decreased numbers of new neurons [62, 70–72]. A major confounder of these studies is the stress associated with the behavioral tasks, as stress is a powerful regulator of hippocampal neurogenesis [73, 74]. Most hippocampus-dependent memory tasks for rodents involve negative or positive reinforcement, fear, or restraint. However, even if performance of the task is not accompanied by confounders of hippocampal neurogenesis, it is impossible to tell whether an effect on the numbers of new neurons is an effect of the learning *per se*, or an epiphenomenon elicited by changes in neurotransmitters, blood flow, and other responses to the task.

Different strategies of eliminating adult neurogenesis have been employed to illuminate the importance of intact neurogenesis. Modes of blocking adult neurogenesis in behavioral studies include irradiation, cytostatics, and

genetically targeting multipotent neural progenitor cells [75–80]. These studies show no clear-cut effect on cognitive function in general, but interestingly, some measures of specific hippocampus-dependent behaviors are negatively affected. However, the methods for blocking neurogenesis that are currently available are neither brain-region-specific nor cell-type-specific for hippocampal neuronal progenitors. Furthermore, all methods of ablating neurogenesis rely on the elimination of dividing progenitor cells. Even if the ablation was 100% restricted to the progenitor cells, it should be noted that these progenitor cells are multipotent and thus also give rise to cell types other than neurons, such as astrocytes. Realistically, the effects of ablation may just as well be attributable to the loss of other cell types or factors secreted by them. Development of genetic approaches to conditionally and locally turn down, off, or up neurogenesis in a restricted area could prove to be a more suitable method to study effects on behavior. The different markers used for quantification of new neurons all have their inherent advantages and pitfalls (as discussed above); moreover, they only allow us to study the presence of these markers at one time point, post mortem. Hence, the fate of the new cells cannot be studied over time. There are elegant techniques to study a smaller number of cells using prelabeling of newborn cells in acute hippocampal slices [36, 43, 81]. This makes it possible to study electrophysiological properties and observe development of neuronal processes. However, as the slice is “cut out” of its complete context, it is impossible to study the firing patterns in correlation with the animal’s behavior. As discussed above, several studies indicate that interventions that increase hippocampal neurogenesis are paralleled by enhanced cognitive performance. However, as most of these studies acknowledge, the evidence is merely correlational. Taken together, these studies speak in favor of the probability that neurogenesis is a positive modulator of cognition; however, it cannot be ruled out that neurogenesis has nothing to do with the behavioral effects. In conclusion, to date there is no undisputed evidence that links new hippocampal neurons with any changed behavior, mainly because of the fact that there are no techniques available to tease out the exact function of the new neuron. Labeling techniques that allow for *in vivo* visualization of new cells [82–84] as well as advancements in imaging may provide better tools to study the function of new cells with respect to cognition and behavior.

Are other features more important?

As mentioned above, newly added hippocampal neurons receive and elicit electrical input and seem to participate in the existing circuitry. They also seem to have properties (other than being more recently added to the network) that

make them different from their older counterparts. Furthermore, the number of new cells born each day make up about 1% of the total number of granule cells in an adult rat [49, 85]. However, should all these cells survive, the number of cells in the dentate gyrus would double in just a few months. As most of the newborn cells die within the first 2 weeks after birth, and most of the dying cells in the granule cell layer are newborn [58, 86], the major event is new cells competing for survival rather than new cells replacing older ones. Indeed, most recent theories assume that the function of newborn neurons is based on their being new and different from mature cells [47, 87]. So, is the number of new neurons relevant or is it the quality, or “what you do with them” that matters? Are all new neurons the same, or does it matter how they differentiate in terms of dendritic connections, spine formation, axonal projections, phenotype, and receptor expression? The earliest signs and time points of dendritic and axonal projections have been mapped out in a study using real-time confocal imaging [43]. In the same study, it is shown that mice that are allowed to engage in voluntary running develop a richer dendritic arborization faster than nonrunners. In general, newborn neurons are shown to carry receptors for and respond to both GABA and, at a later stage, glutamate [36, 88, 89]. Further, estrogen receptors have been found on only a subset of neurons expressing the early neuronal marker doublecortin [90].

Learning more about the special features of new neurons is necessary to understand whether multiple types of new neurons exist that could contribute to hippocampal processes.

Why neurogenesis in the adult olfactory bulb?

In the intact rodent brain, newly generated cells from the subventricular zone migrate along the rostral migratory stream toward the olfactory bulb. After reaching the bulb, neuroblasts differentiate into amacrine (axonless) interneurons, mainly GABAergic granule cells. Some adult-born cells can be found in the periglomerular layer. They are GABAergic, but about half of them coexpress tyrosine hydroxylase and are also considered dopaminergic [3]. Functionally, it is well established that olfactory deprivation by naris closure decreases neurogenesis in the olfactory bulb, whereas olfactory enrichment increases the generation of new neurons [91, 92]. The effect is mediated through differential survival of newly generated cells in the olfactory bulb [93]. The SVZ proliferation is largely unaffected by olfactory stimulation. From functional analysis in gene knockout studies, which showed altered olfactory neurogenesis, it was concluded that adult neurogenesis is needed for discrimination learning of new odors [92–95]. However,

similar to hippocampal studies, whether functional changes are caused by altered olfactory neurogenesis is at this point largely speculative, as a variety of other mechanisms are altered in these knockout models.

At the cellular level the situation is clearer. The new neurons are very much dependent on sensory input and the majority of dying cells in the olfactory bulb appear to be young neurons with dendritic arborization. Olfactory deprivation alters the milieu in the olfactory bulb, for example, by downregulating tenascin-R, which in turn leads to reduced recruitment of new neurons [96]. In conclusion, olfactory neurogenesis is clearly olfaction-dependent, but the reverse relation that proper olfactory function needs adult neurogenesis is not fully established. As for the occurrence in higher mammals, it is established that primates also have a rostral migratory stream and olfactory neurogenesis [10, 97, 98]. In humans, the discussion is still open because of conflicting data on new neurons in the olfactory bulb. Although neurogenesis might occur in the olfactory bulb [30], another study reported no structural evidence of a migratory pathway from the ventricle wall [99]. It is therefore too early to postulate the existence of olfactory neurogenesis in humans at this point. Functional speculations on altered olfaction in neurodegenerative diseases as a result of changes in olfactory neurogenesis are therefore also highly speculative.

Adult neurogenesis as a therapeutic tool

Neural cell transplantation studies have paved the way by showing that lost neurons can be functionally replaced by new ones [100–102]. Endogenous neural stem cells may be a potential source for new neurons. Such an avenue circumvents some of the problems that have plagued tissue transplantation, such as difficulties associated with obtaining donor tissue, surgery, and immunosuppression. In theory, adult neurogenesis promises almost unlimited potential to replace lost cells during neurodegenerative disorders, stroke, and spinal cord injury. After almost two decades of intense research on the regulation of adult neurogenesis, how close are we to taking advantage of endogenous neurogenesis as a therapeutic tool?

One of the most suitable targets for stimulating endogenous neurogenesis is the substantia nigra, as the main neuropathology leading to motor deficits is loss of dopaminergic neurons in the substantia nigra, a single cell type and a single target. Hence, enhancing proliferation and dopaminergic differentiation of local progenitors could be a very attractive means of replacing cells lost in Parkinson’s disease. The adult substantia nigra, like many other brain areas, appears to harbor precursor cells that can be coaxed

into a dopaminergic fate *in vitro* [4]. The challenge is to develop strategies to induce this potential *in vivo* to a great enough extent to compensate for the high number of neurons lost in Parkinson's disease. Transcription factors that trigger dopaminergic neurons in the normal immature mesencephalon [103] have recently been identified and could potentially be used to lure immature cells into a dopaminergic phenotype. Then remains the challenging task of ensuring that the newborn dopaminergic neurons make the necessary axonal connection with the striatum to safely deliver the neurotransmitter.

In the adult striatum, neurogenesis has been observed after experimental stroke [16]. Progenitor cells migrate from the SVZ toward the damaged tissue. To a low percentage, differentiation into medium spiny interneurons is observed, a neuronal population which is affected in large numbers by the stroke lesion. This progenitor migration is surprisingly long lasting. Up to 1 year after lesion, the SVZ is still producing a higher number of progenitor cells that enter the striatal parenchyma [19]. However, it is again too early to say whether functional recovery after stroke or trauma is a direct consequence of striatal neurogenesis being present, as no conclusive neurogenesis-ablation studies in combination with stroke lesion have been performed. Moreover, the new neurons only make up about 0.2% of the numbers of dead neurons after experimental stroke [16], and it has been debated how these few new neurons could significantly impact motor function [104, 105]. However, the extensive progenitor migration to the lesion site could indicate a separate functional role of the progenitor cells, as these cells are likely to produce a variety of growth factors and trophic factors. This might benefit the resident neurons in surviving and in forming new circuitry after a lesion.

Similar to experimental stroke, animal models of epilepsy also increase neurogenesis, particularly in the hippocampus [106, 107]. It has been suggested that seizure-induced neurogenesis is implicated in the pathological progression of epilepsy [108]. However, another recent study indicates that new neurons generated after seizures show reduced excitability and thus could counteract pathologic epileptic hyperexcitability [109]. Hence, the question of whether generation of new neurons is a detrimental side-effect or a compensatory mechanism to epileptic seizures has to be resolved before adequate therapeutic modulations can be designed.

Similarly, it is unclear whether there is a role for hippocampal neurogenesis in neurodegenerative diseases affecting cognitive function, such as Alzheimer's disease. The characteristic neurodegeneration in Alzheimer's disease is widespread, and cell loss in the hippocampus mainly affects the CA1 region. Therefore, hippocampal neurogenesis cannot provide a source of neurons primarily to replace lost cell populations. However, as a few newborn hippocampal neurons may change the properties of the entire circuitry,

lowering the threshold for excitation, manipulations aimed at enhancing neurogenesis could still be beneficial for cognition. Some studies indicate impaired hippocampal neurogenesis in models for Alzheimer's disease [110–114], and several treatments associated with cognitive improvement have been shown to stimulate hippocampal neurogenesis [115, 116]. One can therefore speculate, if a cognitive function for neurogenesis exists, a significant loss of neurogenesis during the progression of Alzheimer's disease could contribute to the deterioration of hippocampal function. But again, a causal link between neurogenesis and cognitive function in models of Alzheimer's disease needs to be experimentally established.

Similar to cognition, behavioral effects of antidepressants have been suggested to be dependent on hippocampal neurogenesis [117, 118]. The strongest evidence comes from a study using selective radiation of the hippocampus to demonstrate that the anxiolytic effects of antidepressants are not detectable when hippocampal neurogenesis is eliminated [119]. This study is open to the above-mentioned critique of specificity of the neurogenesis-ablating technique. Nevertheless, it is intriguing that so far most antidepressants tested have neurogenesis-elevating effects when given chronically. But even if behavioral effects of antidepressants require neurogenesis, it is another big step to assume that neurogenesis is involved in the etiology of depression [120]. Here, timing of onset of depression episodes and other variables seem unlikely to be caused by acute dysregulation of hippocampal neurogenesis and further experimental data are needed to provide insight.

Conclusions

The majority of published work thus far reports that neurogenesis is regulated by an incredible variety of factors. Why is adult neurogenesis so reactive to changes in the internal and external milieu? A possible explanation is that we are observing a large number of developmental processes from proliferation and fate decision, to migration, differentiation, integration, and survival of new neurons. These mechanisms are very sensitive to environmental changes, and this is likely one of the reasons why the largest part of mammalian brain development takes place in the protected environment of the uterus, separated even from the mother by the placenta. Adult neurogenesis is rather exposed and therefore more susceptible to external signals.

Too little is known with certainty about why new neurons are generated in adult brains, how they function, and what their relevance is. The main challenge is to develop techniques to selectively study the function of adult neurogenesis. Before there is more causal evidence at hand, assumptions about the potential functions of new neurons should be made with caution.

The neurogenic regions could be a source of new cells for cell replacement therapies. Overexpression of factors that drive neuronal differentiation could potentially be used to entice newborn or uncommitted cells located in different brain areas to adopt a neuronal fate. Hence, the therapeutic promise of adult neurogenesis is vast. However, to fully capitalize on the endogenous precursors, signals that trigger cell division, migration, differentiation, and long-term survival have to be controllable from the outside, ideally by pharmacological regulation of these processes.

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