Neurogenesis in the Adult Mammalian Brain: How Much Do We Need, How Much Do We Have?

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Abstract The last two decades cytogenic processes (both neurogenic and gliogenic) driven by neural stem cells surviving within the adult mammalian brain have been extensively investigated. It is now well established that within at least two cytogenic niches, the subependymal zone of the lateral ventricles and the subgranular zone in the dentate gyrus, new neurons are born everyday with a fraction of them being finally incorporated into established neuronal networks in the olfactory bulb and the hippocampus, respectively. But how significant is adult neurogenesis in the context of the mature brain and what are the possibilities that these niches can contribute significantly in tissue repair after degenerative insults, or in the restoration of normal hippocampal function in the context of mental and cognitive disorders? Here, we summarise the available data on the normal behaviour of adult neural stem cells in the young and the aged brain and on their response to degeneration. Focus will be given, whenever possible, to numbers: how many stem cells survive in the adult brain, how many cells they can generate and at what ratios do they produce neurons and glia?

Keywords Neurogenesis · Gliogenesis · Neural stem cells · Progenitors · Subependymal zone/subventricular zone · Subgranural zone · Regeneration · Memory · Hippocampus

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1 Numbers Matter and Two Cautions

During the long process of evolution the brain has—on average—increased in size, but most importantly in complexity of structure (emergence of neocortex and subsequently of gyrencephalia) and of connectivity, with the latter—among mammals—being correlated to the emergence of more complex patterns of behaviour (Herculano-Houzel 2009). The striking increase in the size of the brain has been underlined by the appearance of new neurogenic progenitor populations, such that the "ancient" neuroepithelial cells that (early in evolution and in embryogenesis) form the primitive embryonic neural tube are transformed to radial glial cells when the tube becomes thicker and these are subsequently complimented by subventricular zone progenitors (for the neocortex to appear) and by outer subventricular zone progenitors (for gyrencephalia to appear) (Fietz et al. 2010; Stancik et al. 2010). Interestingly, the emergence of larger and more complicated brains has been accompanied by a marked decrease in the number of neurogenic progenitors surviving within the adult, mature tissue. Not only certain adult neurogenic areas (or niches) disappeared during evolution but also the absolute numbers of neuronal progenitors per area has decreased (Ferretti 2011; Kazanis and ffrench-Constant 2012). This has resulted in a significant weakening of the neuroregenerative capacity of the adult brain; thus, to a higher susceptibility to injury. But why has that happened? Intuitively, we believe that the increased complexity of the brain, with the emergence of very specialised neuronal types that are interconnected via numerous axonal networks, is not compatible with efficient cell-replacement machineries. The additional observation that cell replacement of glial cells—cells considered to be only supportive to neurons and more homogeneous in morphology and function—has won the battle of survival during evolution turned this intuitive belief to a "dogma" that dominated developmental neurobiology to such a degree that for many decades the first indications of persistent neurogenic activity in the adult rodent brain by Altman (1969) were dismissed. On the other hand, why would a neuronal progenitor, located within a specialised and protective microenvironment in the brain, be worried about what happens to its progeny? How can an inefficient cell-replacement process impact directly on the progenitor cell, since the vast majority of stem cell progeny

normally die before reaching maturity and before being incorporated in existing networks even in the adult neurogenic systems that survived the forces of evolution (Morshead and van der Kooy 1992; Lu et al. 2011)? A possible explanation could be that the enlargement of the brain required more space for mature tissue, leading to a gradual reduction in the size and number of niches, especially since this did not incur any serious functional defects. Another explanation could be sought in energy efficiency pressures, with brains spending less energy for maintaining a futile neurogenic process being positively selected. Finally, recently published data indicate that the cell cycle kinetics of progenitors depend on real time, rather than on developmental time (i.e. a progenitor can keep dividing for a certain number of days/weeks irrespective of whether this means old age in a rodent and infancy in humans) (Amrein et al. 2011). This—among many other possibilities—indicates that the decrease in the numbers of surviving progenitors is a function of time, with organisms with long life duration spending most of their adult lives with small pools of progenitors.

Nevertheless, one of the most important messages stemming from the discovery of persistent neurogenic activity in the adult mammalian brain is that replacement of neurons is not a process completely lost during evolution; and this has great implications in regenerative medicine. It is much easier to exogenously influence an existing cellular process rather than to attempt to re-introduce it after it has vanished. In that context, the discovery that neurogenesis has a direct role in the function of the hippocampus, involving memory and learning (Deng et al. 2010), added a new promising experimental target in the field of mental health disorders and of cognitive biology. Importantly, though, we should not forget that in regenerative and rehabilitation medicine numbers matter: not only the numbers of progenitors surviving in the adult brain, but also the numbers of cells that are affected during degeneration or disease. In this review, I will attempt to summarise the available information on persistent neurogenesis in the adult brain with a focus given, whenever possible, to numbers. Most of the evidence stems from experiments carried out in animals, especially rodents, but whenever appropriate I will discuss findings from the primate (including the human) brain.

Before proceeding further, though, two cautions have to be stated regarding “adult neurogenesis”. The first one has to do with the definition of the term “adult”. One possible way to define adulthood in the context of a tissue is as “the stage in which the tissue has reached a stable anatomical structure, with no further addition or elimination of subdivisions and which can only be altered by degenerative processes (injury or aging)”. In that sense, the brain—or at least some specific structures such as the corpus callosum (Sturrock 1980)—might be reaching adulthood much later than generally considered in rodents and much earlier in humans. In the same direction, recent evidence from the human and rodent brain suggest that the gradual decrease in postnatal neurogenic activity might not be a degenerative process of the adult brain but rather the end of a “prolonged developmental process” with the system in rodents reaching the adult steady state at around 6 months post natally (Ben Abdallah et al. 2010; Knoth et al. 2010; Amrein et al. 2011). In that case, a large volume of experimental work in

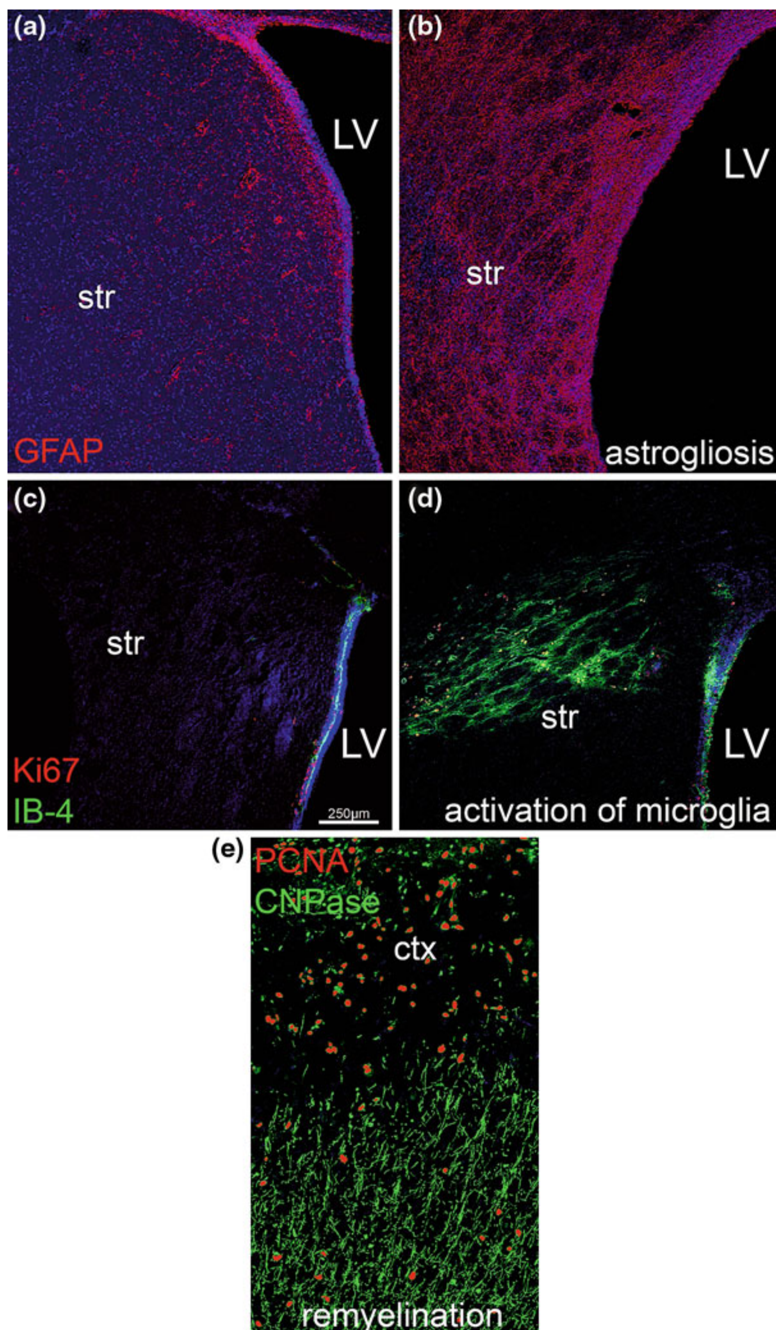
"adult neurogenesis" in the rodents has been performed in a non-adult neurogenic system. Moreover, if the numbers of persisting progenitors are a function of time, then an additional caution has to be made regarding the extrapolation of experimental results from adult rodents (e.g. 3 month old) to the adult human brain (e.g. 30 years old) (Amrein et al. 2011; Sanai et al. 2011).

The second caution has to do with the fact that experiments in the laboratory are performed in animals kept in captivity and in very controlled, stereotypic and stable conditions. Recent data suggest that in mice captured in the wild neurogenesis in the hippocampus is not directly dependent on exercise, as has been shown in laboratory-kept mice (Klaus and Amrein 2012; Klaus et al. 2012). A possible explanation for this discrepancy could be that in experimental conditions the levels of homeostatic neurogenesis are low due to the minimal exposure of animals to stimuli. This would therefore mean that it is "relatively easy" to induce increases in neurogenesis in the hypo-active laboratory animals. Other studies have also showed that specific features of progenitor behaviour (such as cell cycle kinetics) show a rather genetic regulation, while others (such as the rate of differentiation and the rate of survival) are more influenced by the environment (Amrein et al. 2011; Roth et al. 2012). In that sense, the caution regards the extrapolation of results regarding the effects of the administration of chemical substances or of the manipulation of the environment in the levels of neurogenesis in animals kept in captivity to animals living in the wild, such as humans (Hauser et al. 2009).

2 Cellular Plasticity in the Adult Brain; When New Cells are Required?

2.1 Gliogenesis in the Parenchyma of the Brain

Although the brain is widely perceived to be a structurally non-plastic organ, apart from the micro-level of the synapse and of the dendrite, the truth is that whenever appropriately stimulated, brain tissue can host robust proliferative and migratory events. If an area is injured by mechanical forces, cytotoxic substances or hypoxia, the widely spread astrocytes react immediately. They change their morphology by increasing in size and extending processes, they proliferate and they also migrate at the site of lesion. This is called astrogliosis (Fig. 1a, b) and in many cases results in the formation of permanent scars in the tissue (Fawcett and Asher 1999). In exactly the same instances another pool of cells becomes equally activated: microglial cells (Fig. 1c, d). Microglia comprise the innate immune system of the brain and in many cases their response is complimented by blood-borne macrophages that invade the tissue, often through the broken blood–brain barrier (Perry et al. 2010). More impressively, if the insulating and protective myelin sheaths that cover neuronal axons are destroyed due to chemotoxic or autoimmune reasons (a


(a)
LV
str
GFAP
(b)
LV
str
astrogliosis
(c)
str
LV
Ki67
IB-4
250μm
(d)
str
LV
activation of microglia
(e)
PCNA
CNPase
ctx
remyelination

◀ **Fig. 1** Gliogenesis in the brain parenchyma. (Panels **a**, **b**) Microphotographs of adult rat brain tissue immunostained for glial fibrilary acidic protein (GFAP, in *red*), a marker of astrocytes. Numbers of astrocytes increase significantly in response to degeneration, in this case after an experimental model simulating stroke, a phenomenon called astrogliosis. (Panels **c**, **d**) Microphotographs of adult rat brain immunostained for isolectin B4 (IB-4, in *green*) a marker of microglial cells and Ki67 (in *red*) a marker of proliferating cells. A degenerative insult, in this case an experimental model simulating stroke, induces a massive proliferative response of microglial cells. (Panel **e**) Microphotograph of adult mouse brain immunostained for CNPase (in *green*) a marker of cells of the oligodendroglial cell lineage and PCNA (in *red*) a marker of proliferating cells. A demyelinating insult, in this case the focal infusion of lysolecithin (1 %) in the cortex, leads to the destruction of myelin sheaths (note the absence of CNPase positive processes), and to the mitotic activation of oligodendrocyte progenitors that will regenerate lost oligodendrocytes (remyelination). (*ctx* cortex, *LV* lateral ventricle, *str* striatum)

process called demyelination), then another pool of cells, the oligodendrocyte progenitors, are recruited: they proliferate (Fig. 1e), migrate and successfully regenerate myelin sheaths (remyelination) (Franklin and ffrench-Constant 2008). Importantly, in recent years evidence has appeared indicating that these processes, that were considered to be relevant only to the world of glial cells, might hide a more dynamic capacity. Astrocytes activated by a focal cortical injury were shown to be able to act as multipotent progenitors when cultured in vitro (Buffo et al. 2008), while oligodendrocyte progenitors responding to focal demyelination were found to generate cells of the peripheral nervous system (schwann cells) and neurons in vivo (Guo et al. 2010; Zawadzka et al. 2010).

2.2 Neurogenesis/Gliogenesis in Cytogenic Niches of the Brain

Surprisingly, and in contrast to the above-mentioned glial cell-replacement processes that operate in very low levels in the homeostatic adult brain and show a robust response after degeneration, neuron cell-replacement processes show a higher daily level of activity during homeostasis and serve specific functional needs. Adult neurogenesis is almost exclusively driven by pools of adult neural stem cells that survive in two specialized microenvironments in the adult brain: in the subependymal zone (SEZ/often called subventricular zone) of the lateral walls of the lateral ventricles and in the subgranular zone (SGZ) of the dentate gyrus in the hippocampus (Doetsch et al. 1997; Seri et al. 2004) (Fig. 2). The same cytogenic niches also generate glial cells (astrocytes and oligodendrocytes), though in much lower frequencies.

2.2.1 The Architecture of Cytogenic Niches

The process of cell generation is similar in the two neurogenic niches of the adult rodent brain; therefore, the main cell types located therein are also similar. NSCs of astroglial morphology that remain relatively quiescent generate precursors of

neuronal commitment that are called neuroblasts and express doublecortin and the polysialiated form of NCAM, via a cell amplification step (Fig. 2). In the SEZ, transit amplifying precursors undergo many symmetric self-renewing divisions before producing committed progenitors (Morshead et al. 1998; Doetsch et al. 1999) and express the transcription factor Mash1 (Parras et al. 2004) and the receptor for epidermal growth factor (Doetsch et al. 2002). Apart from neuron-committed progenitors few recent reports have demonstrated the generation of oligodendrocyte progenitors from the SEZ that are subsequently migrating to the corpus callosum (Jackson et al. 2006; Menn et al. 2006; Etxeberria et al. 2010; Jablonska et al. 2010). Although the process of lineage commitment remains largely unexplored the available evidence indicates both the existence of separate populations of transit amplifying progenitors (with either neuronal or glial commitment, expressing transcription factors Pax6 and Olig2, respectively) (Hack et al. 2005) and that cells of neuronal fate retain the ability to transdifferentiate into oligodendroglial progenitors upon gliogenic stimulation (Jablonska et al. 2010). Approximately 15,000 cells are born every day in each SEZ (Lois and Alvarez-Buylla 1994) and the vast majority of these are neuroblasts. The average ratio of oligodendrogenesis versus neurogenesis has been estimated to 1:20, with approximately the same number of oligodendrocytes being generated in all rostrocaudal levels of the SEZ, but neurogenesis being markedly decreased caudally (Menn et al. 2006). In the SGZ, the volume of cells generated is smaller than that of the SEZ with estimates varying from 9,000 cells (Cameron and McKay 2001) to 4,000 cells per SGZ per day (Rao and Shetty 2004). In the hippocampal niche, the amplification process is limited to 1–2 divisions and transit amplifying progenitors express doublecortin, similar to neuroblasts and immature neurons (Seri et al. 2004), although there is evidence for Mash1 and Tbr2 expression (Yoshihara et al. 2007; Hodge et al. 2008).

Another common structural feature of the two niches is the close distance between proliferating neural precursors and the vasculature (Palmer et al. 2000; Mirzadeh et al. 2008; Shen et al. 2008; Tavazoie et al. 2008). The SEZ neurogenic niche—which has been more extensively described—is preferentially rich in blood vessels as compared to other periventricular domains (Kazanis et al. 2010) with precursors contacting blood vessels in microdomains void of astrocytic endfeet and pericytes (Tavazoie et al. 2008). Regarding the SGZ, in mice subjected to exercise increased neurogenesis was correlated with an increase in vascularisation (Clark et al. 2009). A structural characteristic that is specific for the SEZ is the proximity to the lateral ventricle, from which it is separated by the monolayer of ependymal cells. The importance of ependymal cells and of the regulated communication with the cerebrospinal fluid (that fills the ventricles) in the regulation of neurogenesis is underlined by several findings. Ependymal cells express regulating factors, such as several bone morphogenetic proteins (Colak et al. 2008; Gajera et al. 2010) and pigment epithelium-derived growth factor (Ramirez-Castillejo et al. 2006), while their cilia create a gradient of factors at the ventricular side that instructs the direction of migration to neuroblasts (Sawamoto et al. 2006). Moreover, ependymal cells create specific pinwheel structures in the ventricular

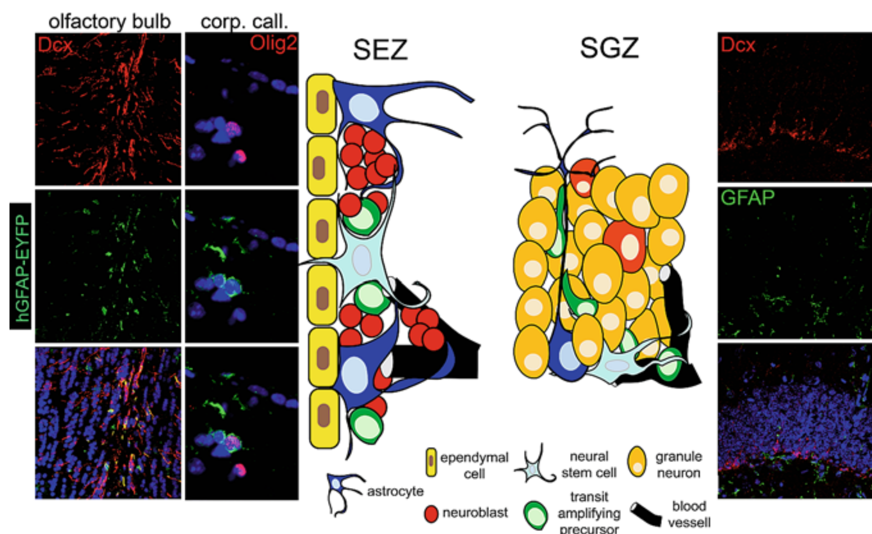


Fig. 2 The cytogenic niches of the adult mammalian brain. Graphic illustration of the cytoarchitecture of the subependymal zone (SEZ/*centtre left*) and the subgranular zone (SGZ/*centre right*) neurogenic niches. Note the common features: adult neural stem cells are of astroglial morphology (*light blue* cells), neurogenesis occurs through an intermediate precursor stage (*green* cells) leading to the generation of immature neurons (*red* cells) and is closely related to the presence of blood vessels (in *black*). Note also the ependymal cell layer that forms the wall of the lateral ventricle at the side of the SEZ and the process of the NSC that intercalates among ependymal cells and contacts the content of the ventricle. In the panels at the *left* side are shown microphotographs of adult mouse brain tissue immunostained for EYFP expressed via the human promoter of GFAP (in *green*, marking astrocytes—including adult NSCs—and their progeny) and either doublecortin (Dcx/in *red*, marking new neurons) or Olig2 (in *red*, marking oligodendrocyte progenitors). Double positive cells (*yellow*) within the olfactory bulbs are SEZ-generated new neurons and within the corpus callosum are SEZ-generated oligodendrocyte progenitors. In the panels, at the *right* side are shown microphotographs of adult mouse brain tissue immunostained for GFAP (in *green*, marking astrocytes) and Dcx (in *red*, marking new neurons). Note the coexistence of astrocytes (some of which are NSCs) and Dcx-positive cells within the thin SGZ at the base of the dentate gyrus. (This figure is an adaptation from Kazanis et al. 2008 published under the Creative Commons Attribution 3.0 Unported License http://creativecommons.org/licenses/by/3.0/)

wall, allowing the regulated intercalation of monociliated processes extended by astrocytes (potentially the NSCs) that contact the content of the ventricles (Doetsch et al. 2002; Mirzadeh et al. 2008) (Fig. 2). Interestingly, such cilium-bearing processes have also been identified on SGZ stem cells (that are not positioned near the ventricle) and are important for adult neurogenesis mainly through regulation of sonic hedgehog signalling (Han et al. 2008). Finally, when comparing the neurogenic and non-neurogenic parts of the ventricular walls two more—possibly important—features can be observed: first, the neurogenic side is rich in myelinated axons (Fig. 3) and second, at the non-neurogenic side an astrocytic layer appears below the ependymal cell layer as if insulating the subependymal area

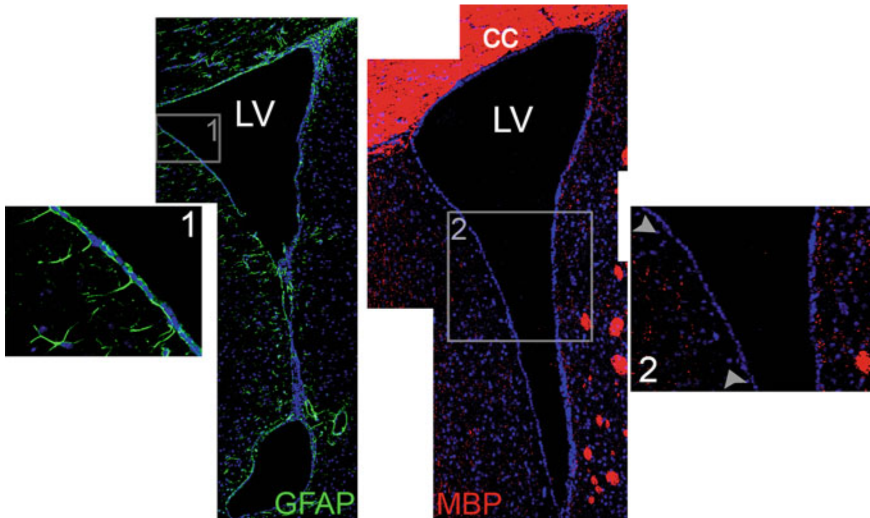


Fig. 3 Structural hallmarks of the SEZ. Microphotographs of adult mouse brain tissue, at the area around the lateral ventricle (LV) immunostained either for GFAP (*left* panels, in *green*, marking astrocytes) or for myelin basic protein (MBP/*right* panels, in *red*, marking myelin sheaths surrounding axons). Note that the neurogenic side (the SEZ niche) is located at the lateral wall of the lateral ventricle (here at the *right* walls of the LV). Also, note the astrocytic layer that is found next to the ventricular wall at the non-neurogenic side (inset 1) and the high density of myelinated axons found adjacent to the ventricular wall only at the neurogenic side (inset 2, with *arrowheads* indicating the axon-poor non-neurogenic side of the LV). (*cc* corpus callosum. The figure is an adaptation from Kazanis et al. 2010)

from the content of the ventricle (Kazanis et al. 2010) (Fig. 3). Another major element in the architecture of the niche is the extracellular matrix. The SEZ, more similar to the embryonic CNS than to mature neural tissue, is rich in laminins, tenascin-C and sulphated proteoglycans (Kazanis et al. 2007, 2010; Akita et al. 2008) with fractones (extensions of the blood vessel basal lamina) contacting almost all the different cellular elements of the niche (Mercier et al. 2002). Various components of this matrix have been shown to be important for the post-natal formation of the niche (Peretto et al. 2005; Kazanis et al. 2007), and the modulation of growth factor activity (von Holst et al. 2006; Kerever et al. 2007; Sirko et al. 2007). Importantly, the interaction between extracellular matrix molecules and their receptors on cells, such as the laminin-integrin interactions, are crucial for regulating the proliferation of progenitors (Shen et al. 2008) and possibly the activation of NSCs (Kazanis et al. 2010).

In addition to cells of the adult NSC lineage and blood vessels, experimental work has also revealed the presence of cells of the innate (in homeostasis) and the blood-borne (after injury) immune system within cytogenic niches in the brain. These cells have been shown to exert important regulatory roles, in vitro (Walton et al. 2006; Thored et al. 2009) but data from in vivo experiments still remain inconclusive. For example, after stroke, the activation of microglial cells can be

both pro-neurogenic (Walton et al. 2006) and anti-neurogenic (Hoehn et al. 2005), while a recent study failed to find any significant impact caused by their ablation (Heldmann et al. 2011). An interesting finding has been generated from animal models of Huntington's disease. Increased neurogenesis was observed only in animal models in which the disease was mimicked by the use of cytotoxic substances, inducing inflammatory reactions, while no change was observed in transgenic models, in which cell loss is minimal (Phillips et al. 2005). In addition, recent experimental work in an animal model of demyelination indicated impaired proliferation caused by the inflammatory microenvironment (Pluchino et al. 2008), while examination of tissue from patients suffering from multiple sclerosis indicated sustained activation of the SEZ within the inflammatory microenvironment created by the disease (Nait-Oumesmar et al. 2007). Nevertheless, locally residing microglial cells are likely to be important in the accurate buffering of cell numbers and local migratory events, as they participate in the removal of dying progenitors (Sierra et al. 2010), surprisingly aided by neuronal progenitors (Lu et al. 2011). Furthermore, niche microglia were shown to have distinct properties from those residing outside, such as the ability for indefinite expansion in vitro (Marshall et al. 2008).

The above presented description of the cytoarchitecture of the niches refers to the rodent brain (most data are derived from experiments in the mouse but they largely apply to the rat). Recent ultrastructural and immunohistochemical analyses of the human and non-human primate brains have revealed the existence of similar neurogenic areas at the SEZ of the lateral walls of the lateral ventricles (Jackson et al. 2006; Fancy et al. 2009) and in the hippocampus (Eriksson et al. 1998). The main differences between the rodent and the human SEZ are: the existence of a hypocellular (gap) area underneath the ependymal cell layer that is followed—deeper in the tissue—by an astrocyte-rich ribbon-like zone, the existence of displaced ependymal cells, the absence of chains of migrating neuroblasts and the absence of transit amplifying precursors (Sanai et al. 2004; Quinones-Hinojosa et al. 2006; Wang et al. 2011). Notably, the human SEZ acquires this distinct, mature architecture as soon as cytogenic activity is drastically reduced, at around 18 months after birth (Sanai et al. 2011). On the other hand, NSCs are of similar astroglial morphology—often in contact with the content of the ventricles—and clusters of neuroblasts are found within the hypocellular zone (Jackson et al. 2006; Fancy et al. 2009). In the Macaque brain, the structure of the SEZ neurogenic niche is similar to that of the human brain, albeit chains of migrating neuroblasts are observed similarly to the rodent SEZ (Jackson et al. 2006).

2.2.2 Focusing on Adult NSCs: How Many—How Plastic?

Two of the factors that determine the regenerative capacity of adult cytogenic niches are the numbers of available NSCs and their differentiation potential. In the absence of an absolute marker for adult NSCs, it is very difficult to estimate their numbers in the adult brain. Three such attempts have been published, all focusing

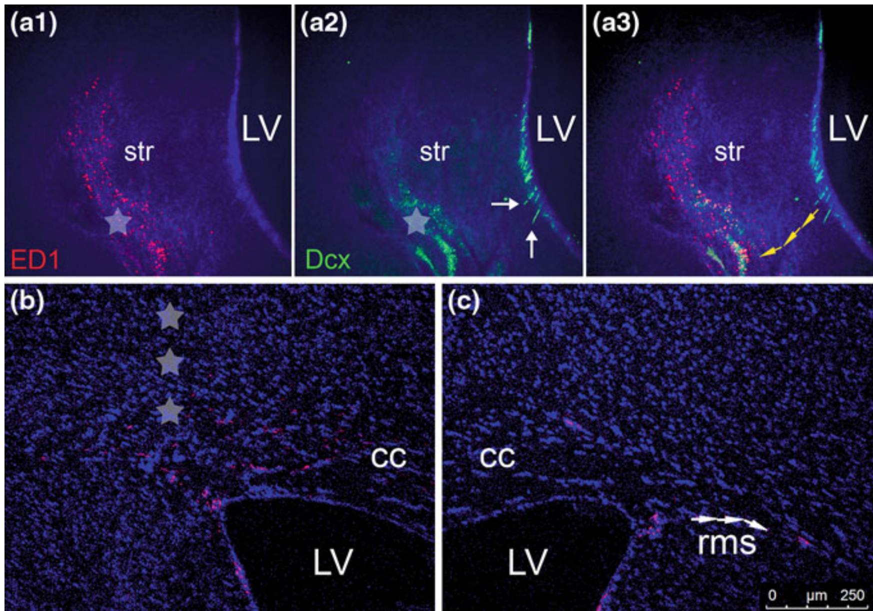


Fig. 4 Activation of the SEZ after degeneration. (Panel **a**) Microphotographs of adult rat brain tissue immunostained for ED1 (in *red*, marking activated macrophages) and Dcx (in *green*, marking newborn neurons). The tissue is taken from a rat subjected to a focal ischaemic insult (unilateral middle cerebral artery occlusion for 1 h). Note that neurons generated in the SEZ form chains (*white arrows*) with a direction towards the core of the lesion (*asterisk*) which is rich in activated macrophages and immature neurons. *Yellow* arrows indicate the possible route of SEZ-generated cells towards the lesion. (Panels **b**, **c**) Microphotographs of adult mouse brain tissue immunostained for Dcx (in *red*, marking neuronal progenitors). Note that although the normal migratory route of SEZ-born progenitors is the rostral migratory stream (rms/indicated with *white arrows* in **c**), which drives them to the olfactory bulb, after a focal demyelinating insult (induced by 1 % lysolecithin, the stars mark the site of demyelination) progenitors are diverted towards the lesion (in **b**). (*cc* corpus callosum, *LV* lateral ventricle, *str* striatum)

in the SEZ and producing a range of values. Two of the studies are more comparable because they are based on the analysis of the regenerating niche, i.e. the NSC-driven repopulation of the niche after the exogenously induced ablation of their downstream daughter cells (transit amplifying progenitors and committed progenitors are actively dividing cells, thus, very sensitive to cytostatic drugs such as AraC or to tritiated thymidine). According to these studies approximately 600 (Morshead et al. 1998), or 300 (Kazanis and ffrench-Constant 2012) NSCs reside within each SEZ. The third study (Golmohammadi et al. 2008) used a combination of in vitro colony-formation assays and in vivo labelling-retention experiments and estimated a much lower number of potential NSCs per SEZ (approximately 50), that is closer to the number of active NSCs at any random time estimated by Kazanis and ffrench-Constant (2012). Interestingly, when the mouse and rat SEZs were compared, the latter was found to contain approximately three times more

NSCs, although its volume was five times bigger (Kazanis and ffrench-Constant 2012). Moreover, it was shown that the size of the neurogenic area was determined by the scale of the whole brain, while the number of NSCs was limited by the number of ependymal cells. This suggests that during evolution the enlargement of the brain (leading to a higher demand for cell-replacement events in the case of degeneration) is not isometrically followed by the enlargement of the NSC pool. This could potentially underline the emergence of the gap zone in the even larger primate brain although more comparative analyses have to be performed in order to test this hypothesis. Notably, both adult brain cytogenic niches are not populated by NSCs in their full (volumetric) capacity. Detailed analyses of the SEZ have revealed areas of high and low density of astrocytic endfeet projecting in the ventricle (interpreted as areas of high and low abundance of NSCs, respectively) (Mirzadeh et al. 2008) and similar results have been obtained by investigating the presence of NSCs in serial coronal vibratome-cut sections (Golmohammadi et al. 2008). In the rat hippocampus, quiescent domains have also been identified within the SGZ of the upper blade of the dorsal dentate gyrus (Gil-Mohapel et al. 2010). Nevertheless, the absolute number of NSCs is only one of the parameters potentially affecting the cytogenic capacity of adult brain niches. Another parameter is the ability of these NSCs to become activated when necessary. Again by investigating the regenerating SEZ, it was estimated that only the mitotic activation of almost the whole NSC population can explain the fast repopulation of the transit amplifying progenitor pool (Kazanis et al. 2007), but only limited data exist directly showing activation of NSCs after degeneration (Zhang et al. 2004).

Adult NSCs retain the cardinal property of all stem cells that is the capacity for inexhaustible self-renewal for the duration of the life span of the organism (Ahlenius et al. 2009). They also retain the multipotentiality of embryonic NSCs, as indicated by their ability to generate—in vivo and in vitro—the three main CNS cell types: neurons, astrocytes and oligodendrocytes (Suh et al. 2007; Jessberger et al. 2008; Scott et al. 2010) (Fig. 5). Amazingly, isolated adult NSCs not only can act as embryonic NSCs when re-introduced in a host neural tube (Neumeister et al. 2009) but can also contribute to all germ layers in chimeric chick and mouse embryos (Clarke et al. 2000). Additional experimental studies showed that SEZ-derived NSCs can differentiate into cells of the hematopoietic lineage when transplanted in the bone marrow of irradiated mice (Bjornson et al. 1999) as well as into muscle cells both in vitro and in vivo (Galli et al. 2000; Rietze et al. 2001). The differentiation potential of SGZ-derived NSCs has not been directly explored, although transplantation experiments have demonstrated that SGZ progenitors can behave similar to SEZ progenitors when grafted in this neurogenic system, suggesting that NSCs of the two distinct niches might be fundamentally analogous (Suhonen et al. 1996).

The differentiation repertoire of adult NSCs is normally restricted, although it is altered in abnormal conditions (such as after injury, or genetic and chemical manipulation) as will be discussed later in this review. NSCs of the SEZ give rise mainly to GABAergic periglomerular and granule cell interneurons (Doetsch et al. 2002) and possibly interneurons of the external plexiform layer (Yang 2008) and

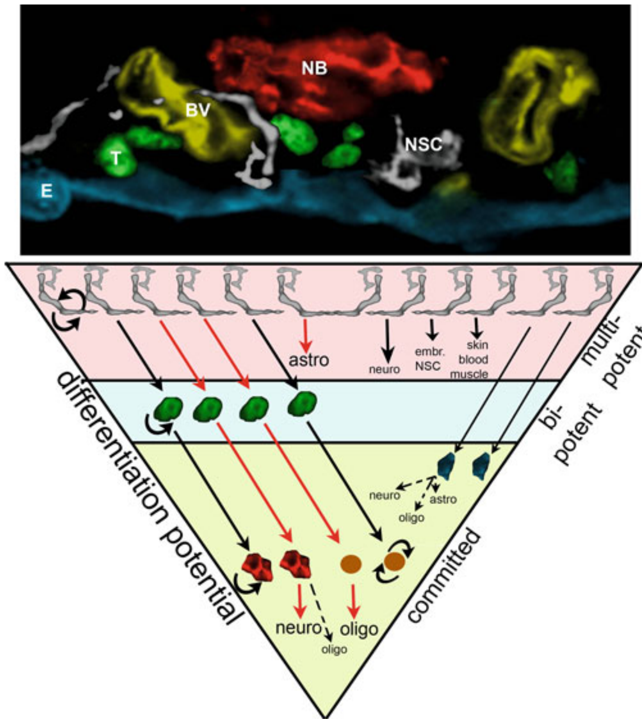


Fig. 5 Differentiation potential of NSCs and of their progeny. (*Top* panel) A collage of microphotographs illustarting the main cellular elements of the cytogenic niche of the SEZ. Ependymal cells (E, *blue*) form the wall of the ventricle (which is at the bottom of the image), adjacent are found the astrocyte-like NSCs (*white*), the transit amplifying progenitors (T, *green*), the neuroblasts (NB, *red*) and multiple blood vessels (BV, *yellow*). (*Lower* panel) Illustration depicting the known differentiation potential of the different cells of the adult NSC lineage (following the colours of the *top* panel). Note that the only cell type not shown in the *top* panel is the SEZ-generated oligodendrocyte progenitor (shown as a *brown circle* in the *lower* panel) that has not been clearly identified so far. The differentiation potential of progenitors follows the shape of a pyramid, with NSCs being at the base (thus exhibiting the widest differentiation potential). The *red* arrows indicate the normal routes of generation of the main three cell types of the central nervous system (neurons, astrocytes, oligodendrocytes) from adult NSCs. Interrupted lines indicate differentiation processes that occur only after degeneration

glutamatergic juxtaglomerular neurons (Colak et al. 2008). The limited plasticity of SEZ NSCs is even more dramatically revealed by the fact that they generate only specific subpopulations of periglomerular cells: those expressing calretinin and tyrosine hydroxylase (Peretto et al. 2004). The other major cell types homeostatically generated by SEZ progenitors are oligodendrocyte precursors and oligodendrocytes (Jackson et al. 2006; Menn et al. 2006; Etxeberria et al. 2010; Jablonska et al. 2010) that migrate short distances and then become stationary within the corpus callosum. SEZ progenitors have also been reported to generate astrocytes (Chmielnicki et al. 2004). However, most of the published cell fate

experiments have not identified SEZ-derived astrocytes outside the niche (Merkle et al. 2007; Havrda et al. 2008; Scott et al. 2010); thus, the level of SEZ astrogliogenesis remains controversial. No data exist regarding the generation of microglial cells from adult NSCs. The plasticity potential of SGZ progenitors is also normally limited; they generate almost exclusively granule neurons, very low numbers of astrocytes (less than 10 % of generated cells) (Suh et al. 2007) and extremely low numbers of early oligodendrocyte progenitors (approximately 3 %) that do not mature efficiently (Jessberger et al. 2008).

2.2.3 Neurogenesis in Homeostasis and the Effects of Ageing

In rodents, the immature neurons generated in the SEZ migrate a long distance in order to reach the olfactory bulb (Lois and Alvarez-Buylla 1994) where they differentiate mainly in interneurons (Fig. 2). Augmenting evidence indicates that the addition of these newborn neurons is essential for odour recognition (Doetsch et al. 2002; Breton-Provencher et al. 2009; Mouret et al. 2009). What still remains unclear is whether these cells replace old neurons (having been generated during embryonic development) or only other neurons previously born in the SEZ (Lemasson et al. 2005; Ninkovic et al. 2007). To have a sense of magnitude, approximately 170,000 cells arrive in the OB from the SEZ in a period of 10 days and 40% of these survive for more than 3 months (Winner et al. 2002). Recent experimental work has shown that the newly incorporated cells behave differently to the old neurons, by for example being more sensitive to plasticity with the expression of long-term potentiation (LTP) (Nissant et al. 2009) and are necessary for short-term olfactory memory (Breton-Provencher et al. 2009). Notably, proper olfactory functionality depends not only to the arrival and integration of new cells, but also to the efficient removal of older cells, as it is disturbed upon inhibition of cell death (Mouret et al. 2009). The NSCs that reside in the SGZ generate new granule neurons; thus, progenitors migrate only short distances (Fig. 2) from the niche until their final destination. As in the olfactory bulb, newly born neurons behave differently from already established "old" cells. Importantly, it takes a few weeks for SGZ-generated neurons to mature; initially, they are not responsive to neuronal activity (Snyder et al. 2009) and gradually start to receive only GABAergic inputs from local interneurons (Esposito et al. 2005; Ge et al. 2006). Subsequently—similar to what happens during development—this GABAergic input becomes inhibitory and glutamatergic input starts to appear. Although these adult-born neurons gradually become morphologically identical to older cells, they exhibit lower threshold for the induction of LTP, thus are more plastic (Ge et al. 2006, 2007) and seem to be more responsive to stimuli generated by animal's experiences (Deng et al. 2010). Many computational models have indicated that the integration of new neurons is compatible—and even necessary—for the efficient functioning of the dentate gurus and the hippocampus (Kempermann et al. 2004); however, the issue of whether new neurons replace older ones (Becker 2005) or are added to the network (Aimone et al. 2009; Weisz and Argibay 2009)

remains unresolved. A recent quantitative analysis of post-natal neurogenesis in the macaque monkey dentate gyrus revealed that approximately 40% of granule neurons in a mature adult macaque are born post natally, with the 25% within the first 3 months after birth. In the same study, it was found that the size of the dentate gyrus keeps increasing even in mature animals (Jabes et al. 2010). Finally, two interesting aspects of the SGZ are that its activity is affected by gender, with females having higher basal levels of neurogenesis and showing fluctuations depending on the reproductive state (Galea and McEwen 1999; Westenbroek et al. 2004; Barker and Galea 2008) and by corticoid rhythms (Pinnock et al. 2007; Pinnock and Herbert 2008).

Homeostatic neurogenesis is significantly altered in the aged brain. In terms of structure, the ventral domains of the SEZ are gradually disappearing with ageing, leading to a smaller niche and lower numbers of generated cells (Luo et al. 2006; Blackmore et al. 2009). Similarly, the volume of the human hippocampus is reduced in the elderly (Small et al. 2002) and levels of neurogenesis in the SGZ are markedly decreased in the aged rodent and human brain (Heine et al. 2004; Lucassen et al. 2010). The decline in normal neurogenesis has been correlated with deficits in fine olfactory discrimination (Enwere et al. 2004) and cognitive deficits (Drapeau et al. 2003; Bizon et al. 2004). Very little is known about the mechanisms that underline this age-related decline in neurogenesis. It could be caused by a gradual exhaustion of the intrinsic self-renewal potential of NSCs (Amrein et al. 2011), to aberrant NSC maintenance signalling (affecting molecules such as leukaemia-inhibitory factor, wnt and notch signalling) (Lie et al. 2005; Bauer and Patterson 2006; Ferron et al. 2011), or to defects in cell cycle regulation (Kippin et al. 2005; Molofsky et al. 2006). Surprisingly, recent experimental work has revealed that NSCs within the aged SEZ retain their cardinal properties and behave similar to young NSCs in vitro (Ahlenius et al. 2009), that exercise can partially reverse the decrease in neurogenesis (van Praag et al. 2005; Blackmore et al. 2009) and that exposure to a young milieu (such as in parabiosis experiments) can rejuvenate adult progenitors either located within cytogenic niches (Villeda et al. 2011), or in the parenchyma (Ruckh et al. 2012).

2.2.4 Plasticity of Cytogenic Niches: Exploring the Limits

Under abnormal conditions, such as in response to degeneration or to external stimuli (as during episodes of stress or exercise), cell production in the SEZ and the SGZ can be significantly altered. This is manifested as changes in the numbers of cells generated and in the balance between neurogenesis and gliogenesis. The plasticity of these systems has also been tested—probably to the extreme—by exogenous manipulations, such as genetic interference or administration of growth factors and morphogens. Intracerebroventricular (i.cv.) infusion of epidermal growth factor increases astrogliogenesis not only in the SEZ and the adjacent striatum (Doetsch et al. 2002), but also within the olfactory bulb (Kuhn et al. 1997), while i.cv. infusion of fibroblast growth factor-2 enhances neurogenesis.

Both growth factors lead to significant increases in the size of the SEZ (Kuhn et al. 1997) an effect also elicited by i.cv. infusions of vessel endothelial growth factor (Jin et al. 2002). Pigment epithelium-derived growth factor and leukaemia inhibitory factor induce the self-renewal activity of NSCs (Bauer and Patterson 2006; Ramirez-Castillejo et al. 2006) while treatment with platelet-derived growth factor leads in increased oligodendrogenesis (Jackson et al. 2006). Interesting, albeit in many cases conflicting, results have also been generated by manipulating availability of brain-derived neurotrophic factor in the SEZ (reviewed in (Bath et al. 2012) and nitric oxide can be acting both to enhance or restrict neurogenesis depending on the context (reviewed in (Estrada and Murillo-Carretero 2005). The balance between neuro- and gliogenesis can also be altered by interfering with the molecular machinery of progenitors. Overexpression of transcription factors Pax6 and Olig2 enhances the generation of neurons and oligodendrocytes, respectively (Hack et al. 2005). Disruption of BMP signalling favours oligodendroglial over neuronal fate (Colak et al. 2008), while the transcription factor Sox9 was recently shown to promote self-renewal of NSCs and to regulate the balance in the generation of divergent cell fates (Scott et al. 2010). Moreover, disruption of microRNAs and of epigenetic modifications also result in changes in the level of neurogenesis (Liu et al. 2010; Szulwach et al. 2010).

In the SGZ neurogenic niche, even though the primary output is neurogenic, gliogenesis can be significantly enhanced by overexpressing the transcription factor Mash1 (Asc1) (Jessberger et al. 2008) and astrogliogenesis by knocking out reelin (Zhao et al. 2007). Infusion (i.cv.) of either fibroblast or epidermal growth factors does not induce proliferation in the hippocampus, but the latter results in a bias in differentiation in favour of gliogenesis (Kuhn et al. 1997). On the other hand, i.cv. administration of vessel endothelial growth factor leads to strong increase in proliferative activity within the SGZ (Jin et al. 2002).

2.2.5 Plasticity of Cytogenic Niches: Disease

Importantly, degenerative phenomena in the brain have been shown to induce the generation of neuronal subtypes not normally produced by SEZ progenitors, such as striatal spiny interneurons ectopically found in the striatum after stroke (Chmielnicki et al. 2004) and glutamatergic neurons in the injured cortex (Colak et al. 2008). In addition, astrogliogenesis has been reported to be enhanced after stroke (Li et al. 2010) and recent experimental work showed that migrating neuroblasts are diverted toward oligodendrogenic fate in areas of demyelination (Jablonska et al. 2010), thus widening the plasticity potential of SEZ progenitors to cells having exited the microenvironment of the niche that were previously thought to be almost irreversibly committed (Hack et al. 2005) (Figs. 4, 5). Another novel and surprising potential of NSCs residing in the SEZ that was recently demonstrated is the generation of ependymal cells either after their controlled chemotoxic ablation, or after their ageing-related destruction (Luo et al. 2008) (Fig. 5). This property of adult NSCs becomes even more interesting in light

of the evidence that after ischaemic injury, ependymal cells behave as progenitors; they migrate out of the niche and into the penumbra where they generate neurons and glia (Fushiki et al. 2003), a property that has also been attributed to ependymal cells lining the wall of the central canal in the spinal cord (Barnabe-Heider et al. 2010).

Experimental studies have shown that proliferation is significantly increased in the SEZ in response to traumatic brain injury (Gotts and Chesselet 2005; Ramaswamy et al. 2005) and focal ischaemic lesions that model stroke in humans (Li et al. 2001, 2010; Zhang et al. 2004) with many of these newly generated cells migrating towards the infracted areas (Arvidsson et al. 2002; Yamashita et al. 2006; Thored et al. 2007; Pluchino et al. 2008; Jin et al. 2010; Li et al. 2010). Stereological analysis of the rat SEZ after a focal cortical injury revealed that cell numbers in the niche increased from a total of 300,000 cells to a total of 450,000 cells in a 2 days time frame (Gotts and Chesselet 2005). Enhanced proliferation in the SEZ has also been observed in patients suffering from epileptic seizures (Grote and Hannan 2007) and multiple sclerosis (Picard-Riera et al. 2002; Nait-Oumesmar et al. 2007). Neurogenesis is increased in human cases and animal models of Huntington's disease (reviewed in (Curtis et al. 2011) while it is decreased in patients and animal models of Alzheimer's and Parkinson's disease (Hoglinger et al. 2004; Elder et al. 2006; Ziabreva et al. 2006; Curtis et al. 2007). The effects of exercise or environmental enrichment in SEZ activity are not still clear (Komitova et al. 2005a, b; Blackmore et al. 2009) but these external conditions seem to influence its response to ischaemia (Komitova et al. 2005a, b).

Status epilepticus strongly increases SGZ proliferation in short term, while leading to decreased activity long term (reviewed by (Parent et al. 2007) and ischaemia enhances proliferation but only of neurogenic progenitors (Tureyen et al. 2004). Importantly, the plasticity of the SGZ neurogenic system is demonstrated either as changes in proliferation, or in cell survival. Traumatic injury and enhanced physical activity significantly induce the proliferation of progenitors (van Praag et al. 2005; Urbach et al. 2008), but hippocampus-dependent learning promotes the survival of newly born cells (Leuner et al. 2004; Epp et al. 2007). A critical finding stemming from experimental work in animals was that antidepressants increase neurogenesis in the SGZ and that by either inhibiting this effect, or by depleting neurogenesis, the efficacy of the drugs is markedly decreased (Santarelli et al. 2003). Nevertheless, a recent study failed to reveal any effect of antidepressants in SGZ neurogenesis in elderly human patients (Lucassen et al. 2010). This observation highlights the difficulty in extrapolating experimental results to human conditions; difficulty that might be even bigger in the case of SGZ neurogenesis due to the effects of the endocrine system, as reflected in the role of the hypothalamic–pituitary–adrenal axis (Snyder et al. 2011) and of the gender (Barker and Galea 2008). Importantly, augmenting evidence indicates that the plasticity of hippocampal neurogenesis is tightly regulated by epigenetic modifications (Zhao et al. 2003; Parent et al. 2007; Ma et al. 2009).

3 Conclusions: Requirements—Limitations—Opportunities

Experimental animal work and descriptive studies in the human brain performed during the last two decades have clearly demonstrated that persistent neurogenesis in the adult brain is essential for normal functions, such as olfactory discrimination, learning and memory. What is still largely unknown is whether endogenous neurogenesis is or can be an important contributor to any therapeutic strategies regarding mental and cognitive disorders as well as to the response of the brain to degeneration. The fact is that adult neurogenesis in mammals is restrained within specific microenvironments and furnishes new neurons only in very specific target areas and neuronal networks. It also seems that numbers of surviving NSCs are significantly reduced with ageing, resulting in depleted cell reserves at the time when they are wanted the most. Moreover, as the brain became bigger and more complicated, during evolution, comparatively less NSCs survived in adulthood. On the other hand, recent analysis revealed that the capacity of adult and even aged NSCs to generate new cells can be markedly restored experimentally (in rejuvenation experiments, or with exercise and administration of growth factors). Even more, the observation that the majority of adult-born neuronal progenitors and neurons normally die before reaching their target and before maturation indicates that with the appropriate treatments, the overall output of adult cytogenic niches can be significantly improved. In the case of cognitive and mental disorders, small level manipulations might prove to be highly efficient since it would not be necessary to exogenously divert migratory routes and to re-specify commitment. In the case of tissue degeneration, it will be necessary to recruit small numbers of progenitors in novel (for them) directions (such as towards the substantia nigra in patients with Parkinson's), or to induce both higher levels of cell generation and a redirection of cells (such as after stroke, or in Huntington's disease) (Batista et al. 2006). Again, in order to have a measure of requirements and capacity, the loss of cortical neurons in a mouse model of Alzheimer's disease has been estimated at approximately 50,000 cells (Lemmens et al. 2011), while the enlargement of the SEZ cell population in response to stroke has been documented to reach even 150,000 cells (Gotts and Chesselet 2005). Nevertheless, in the end it might be proven that in certain degenerative conditions the most important contribution of adult brain cytogenic niches is not neuronal cell replacement, but rather the creation of a neuroprotective environment (Jin et al. 2010) possibly via interactions with the immune system (Cusimano et al. 2012).

References

Ahlenius H, Visan V, Kokaia M, Lindvall O, Kokaia Z (2009) Neural stem and progenitor cells retain their potential for proliferation and differentiation into functional neurons despite lower number in aged brain. J Neurosci 29:4408–4419

Aimone JB, Wiles J, Gage FH (2009) Computational influence of adult neurogenesis on memory encoding. Neuron 61:187–202

Akita K, von Holst A, Furukawa Y, Mikami T, Sugahara K, Faissner A (2008) Expression of multiple chondroitin/dermatan sulfotransferases in the neurogenic regions of the embryonic and adult central nervous system implies that complex chondroitin sulfates have a role in neural stem cell maintenance. Stem Cells 26:798–809

Altman J (1969) Autoradiographic and histological studies of postnatal neurogenesis. IV. Cell proliferation and migration in the anterior forebrain, with special reference to persisting neurogenesis in the olfactory bulb. J Comp Neurol 137:433–457

Amrein I, Isler K, Lipp HP (2011) Comparing adult hippocampal neurogenesis in mammalian species and orders: influence of chronological age and life history stage. Eur J Neurosci 34:978–987

Arvidsson A, Collin T, Kirik D, Kokaia Z, Lindvall O (2002) Neuronal replacement from endogenous precursors in the adult brain after stroke. Nat Med 8:963–970

Barker JM, Galea LA (2008) Repeated estradiol administration alters different aspects of neurogenesis and cell death in the hippocampus of female, but not male, rats. Neuroscience 152:888–902

Barnabe-Heider F, Goritz C, Sabelstrom H, Takebayashi H, Pfrieger FW, Meletis K, Frisen J (2010) Origin of new glial cells in intact and injured adult spinal cord. Cell Stem Cell 7:470–482

Bath KG, Akins MR, Lee FS (2012) BDNF control of adult SVZ neurogenesis. Dev Psychobiol 54:578–589

Batista CM, Kippin TE, Willaime-Morawek S, Shimabukuro MK, Akamatsu W, van der Kooy D (2006) A progressive and cell non-autonomous increase in striatal neural stem cells in the Huntington's disease R6/2 mouse. J Neurosci 26:10452–10460

Bauer S, Patterson PH (2006) Leukemia inhibitory factor promotes neural stem cell self-renewal in the adult brain. J Neurosci 26:12089–12099

Becker S (2005) A computational principle for hippocampal learning and neurogenesis. Hippocampus 15:722–738

Ben Abdallah NM, Slomianka L, Vyssotski AL, Lipp HP (2010) Early age-related changes in adult hippocampal neurogenesis in C57 mice. Neurobiol Aging 31:151–161

Bizon JL, Lee HJ, Gallagher M (2004) Neurogenesis in a rat model of age-related cognitive decline. Aging Cell 3:227–234

Bjornson CR, Rietze RL, Reynolds BA, Magli MC, Vescovi AL (1999) Turning brain into blood: a hematopoietic fate adopted by adult neural stem cells in vivo. Science 283:534–537

Blackmore DG, Golmohammadi MG, Large B, Waters MJ, Rietze RL (2009) Exercise increases neural stem cell number in a growth hormone-dependent manner, augmenting the regenerative response in aged mice. Stem Cells 27:2044–2052

Breton-Provencher V, Lemasson M, Peralta MR 3rd, Saghatelyan A (2009) Interneurons produced in adulthood are required for the normal functioning of the olfactory bulb network and for the execution of selected olfactory behaviors. J Neurosci 29:15245–15257

Buffo A, Rite I, Tripathi P, Lepier A, Colak D, Horn AP, Mori T, Gotz M (2008) Origin and progeny of reactive gliosis: a source of multipotent cells in the injured brain. Proc Natl Acad Sci U S A 105:3581–3586

Cameron HA, McKay RD (2001) Adult neurogenesis produces a large pool of new granule cells in the dentate gyrus. J Comp Neurol 435:406–417

Chmielnicki E, Benraiss A, Economides AN, Goldman SA (2004) Adenovirally expressed noggin and brain-derived neurotrophic factor cooperate to induce new medium spiny neurons from resident progenitor cells in the adult striatal ventricular zone. J Neurosci 24:2133–2142

Clark PJ, Brzezinska WJ, Puchalski EK, Krone DA, Rhodes JS (2009) Functional analysis of neurovascular adaptations to exercise in the dentate gyrus of young adult mice associated with cognitive gain. Hippocampus 19:937–950

Clarke DL, Johansson CB, Wilbertz J, Veress B, Nilsson E, Karlstrom H, Lendahl U, Frisen J (2000) Generalized potential of adult neural stem cells. Science 288:1660–1663

Colak D, Mori T, Brill MS, Pfeifer A, Falk S, Deng C, Monteiro R, Mummery C, Sommer L, Gotz M (2008) Adult neurogenesis requires Smad4-mediated bone morphogenic protein signaling in stem cells. J Neurosci 28:434–446

Curtis MA, Eriksson PS, Faull RL (2007) Progenitor cells and adult neurogenesis in neurodegenerative diseases and injuries of the basal ganglia. Clin Exp Pharmacol Physiol 34:528–532

Curtis MA, Kam M, Faull RL (2011) Neurogenesis in humans. Eur J Neurosci 33:1170–1174

Cusimano M, Biziato D, Brambilla E, Donega M, Alfaro-Cervello C, Snider S, Salani G, Pucci F, Comi G, Garcia-Verdugo JM, De Palma M, Martino G, Pluchino S (2012) Transplanted neural stem/precursor cells instruct phagocytes and reduce secondary tissue damage in the injured spinal cord. Brain 135:447–460

Deng W, Aimone JB, Gage FH (2010) New neurons and new memories: how does adult hippocampal neurogenesis affect learning and memory? Nat Rev Neurosci 11:339–350

Doetsch F, Garcia-Verdugo JM, Alvarez-Buylla A (1997) Cellular composition and three-dimensional organization of the subventricular germinal zone in the adult mammalian brain. J Neurosci 17:5046–5061

Doetsch F, Garcia-Verdugo JM, Alvarez-Buylla A (1999) Regeneration of a germinal layer in the adult mammalian brain. Proc Natl Acad Sci U S A 96:11619–11624

Doetsch F, Petreanu L, Caille I, Garcia-Verdugo JM, Alvarez-Buylla A (2002) EGF converts transit-amplifying neurogenic precursors in the adult brain into multipotent stem cells. Neuron 36:1021–1034

Drapeau E, Mayo W, Aurousseau C, Le Moal M, Piazza PV, Abrous DN (2003) Spatial memory performances of aged rats in the water maze predict levels of hippocampal neurogenesis. Proc Natl Acad Sci U S A 100:14385–14390

Elder GA, De Gasperi R, Gama Sosa MA (2006) Research update: neurogenesis in adult brain and neuropsychiatric disorders. Mt Sinai J Med 73:931–940

Enwere E, Shingo T, Gregg C, Fujikawa H, Ohta S, Weiss S (2004) Aging results in reduced epidermal growth factor receptor signaling, diminished olfactory neurogenesis, and deficits in fine olfactory discrimination. J Neurosci 24:8354–8365

Epp JR, Spritzer MD, Galea LA (2007) Hippocampus-dependent learning promotes survival of new neurons in the dentate gyrus at a specific time during cell maturation. Neuroscience 149:273–285

Eriksson PS, Perfilieva E, Bjork-Eriksson T, Alborn AM, Nordborg C, Peterson DA, Gage FH (1998) Neurogenesis in the adult human hippocampus. Nat Med 4:1313–1317

Esposito MS, Piatti VC, Laplagne DA, Morgenstern NA, Ferrari CC, Pitossi FJ, Schinder AF (2005) Neuronal differentiation in the adult hippocampus recapitulates embryonic development. J Neurosci 25:10074–10086

Estrada C, Murillo-Carretero M (2005) Nitric oxide and adult neurogenesis in health and disease. Neuroscientist 11:294–307

Etxeberria A, Mangin JM, Aguirre A, Gallo V (2010) Adult-born SVZ progenitors receive transient synapses during remyelination in corpus callosum. Nat Neurosci 13:287–289

Fancy SP, Baranzini SE, Zhao C, Yuk DI, Irvine KA, Kaing S, Sanai N, Franklin RJ, Rowitch DH (2009) Dysregulation of the Wnt pathway inhibits timely myelination and remyelination in the mammalian CNS. Genes Dev 23:1571–1585

Fawcett JW, Asher RA (1999) The glial scar and central nervous system repair. Brain Res Bull 49:377–391

Ferretti P (2011) Is there a relationship between adult neurogenesis and neuron generation following injury across evolution? Eur J Neurosci 34:951–962

Ferron SR, Charalambous M, Radford E, McEwen K, Wildner H, Hind E, Morante-Redolat JM, Laborda J, Guillemot F, Bauer SR, Farinas I, Ferguson-Smith AC (2011) Postnatal loss of Dlk1 imprinting in stem cells and niche astrocytes regulates neurogenesis. Nature 475:381–385

Fietz SA, Kelava I, Vogt J, Wilsch-Brauninger M, Stenzel D, Fish JL, Corbeil D, Riehn A, Distler W, Nitsch R, Huttner WB (2010) OSVZ progenitors of human and ferret neocortex are epithelial-like and expand by integrin signaling. Nat Neurosci 13:690–699
Franklin RJ, ffrench-Constant C (2008) Remyelination in the CNS: from biology to therapy. Nat Rev Neurosci 9:839–855
Fushiki S, Perez Velazquez JL, Zhang L, Bechberger JF, Carlen PL, Naus CC (2003) Changes in neuronal migration in neocortex of connexin43 null mutant mice. J Neuropathol Exp Neurol 62:304–314
Gajera CR, Emich H, Lioubinski O, Christ A, Beckervordersandforth-Bonk R, Yoshikawa K, Bachmann S, Christensen EI, Gotz M, Kempermann G, Peterson AS, Willnow TE, Hammes A (2010) LRP2 in ependymal cells regulates BMP signaling in the adult neurogenic niche. J Cell Sci 123:1922–1930
Galea LA, McEwen BS (1999) Sex and seasonal differences in the rate of cell proliferation in the dentate gyrus of adult wild meadow voles. Neuroscience 89:955–964
Galli R, Borello U, Gritti A, Minasi MG, Bjornson C, Coletta M, Mora M, De Angelis MG, Fiocco R, Cossu G, Vescovi AL (2000) Skeletal myogenic potential of human and mouse neural stem cells. Nat Neurosci 3:986–991
Ge S, Goh EL, Sailor KA, Kitabatake Y, Ming GL, Song H (2006) GABA regulates synaptic integration of newly generated neurons in the adult brain. Nature 439:589–593
Ge S, Yang CH, Hsu KS, Ming GL, Song H (2007) A critical period for enhanced synaptic plasticity in newly generated neurons of the adult brain. Neuron 54:559–566
Gil-Mohapel J, Simpson JM, Titterness AK, Christie BR (2010) Characterization of the neurogenesis quiescent zone in the rodent brain: effects of age and exercise. Eur J Neurosci 31:797–807
Golmohammadi MG, Blackmore DG, Large B, Azari H, Esfandiary E, Paxinos G, Franklin KB, Reynolds BA, Rietze RL (2008) Comparative analysis of the frequency and distribution of stem and progenitor cells in the adult mouse brain. Stem Cells 26:979–987
Gotts JE, Chesselet MF (2005) Mechanisms of subventricular zone expansion after focal cortical ischemic injury. J Comp Neurol 488:201–214
Grote HE, Hannan AJ (2007) Regulators of adult neurogenesis in the healthy and diseased brain. Clin Exp Pharmacol Physiol 34:533–545
Guo F, Maeda Y, Ma J, Xu J, Horiuchi M, Miers L, Vaccarino F, Pleasure D (2010) Pyramidal neurons are generated from oligodendroglial progenitor cells in adult piriform cortex. J Neurosci 30:12036–12049
Hack MA, Saghatelyan A, de Chevigny A, Pfeifer A, Ashery-Padan R, Lledo PM, Gotz M (2005) Neuronal fate determinants of adult olfactory bulb neurogenesis. Nat Neurosci 8:865–872
Han YG, Spassky N, Romaguera-Ros M, Garcia-Verdugo JM, Aguilar A, Schneider-Maunoury S, Alvarez-Buylla A (2008) Hedgehog signaling and primary cilia are required for the formation of adult neural stem cells. Nat Neurosci 11:277–284
Hauser T, Klaus F, Lipp HP, Amrein I (2009) No effect of running and laboratory housing on adult hippocampal neurogenesis in wild caught long-tailed wood mouse. BMC Neurosci 10:43
Havrda MC, Harris BT, Mantani A, Ward NM, Paolella BR, Cuzon VC, Yeh HH, Israel MA (2008) Id2 is required for specification of dopaminergic neurons during adult olfactory neurogenesis. J Neurosci 28:14074–14086
Heine VM, Maslam S, Joels M, Lucassen PJ (2004) Prominent decline of newborn cell proliferation, differentiation, and apoptosis in the aging dentate gyrus, in absence of an age-related hypothalamus-pituitary-adrenal axis activation. Neurobiol Aging 25:361–375
Heldmann U, Mine Y, Kokaia Z, Ekdahl CT, Lindvall O (2011) Selective depletion of Mac-1-expressing microglia in rat subventricular zone does not alter neurogenic response early after stroke. Exp Neurol 229:391–398
Herculano-Houzel S (2009) The human brain in numbers: a linearly scaled-up primate brain. Front Hum Neurosci 3:31

Hodge RD, Kowalczyk TD, Wolf SA, Encinas JM, Rippey C, Enikolopov G, Kempermann G, Hevner RF (2008) Intermediate progenitors in adult hippocampal neurogenesis: Tbr2 expression and coordinate regulation of neuronal output. J Neurosci 28:3707–3717

Hoehn BD, Palmer TD, Steinberg GK (2005) Neurogenesis in rats after focal cerebral ischemia is enhanced by indomethacin. Stroke 36:2718–2724

Hoglinger GU, Rizk P, Muriel MP, Duyckaerts C, Oertel WH, Caille I, Hirsch EC (2004) Dopamine depletion impairs precursor cell proliferation in Parkinson disease. Nat Neurosci 7:726–735

Jabes A, Lavenex PB, Amaral DG, Lavenex P (2010) Quantitative analysis of postnatal neurogenesis and neuron number in the macaque monkey dentate gyrus. Eur J Neurosci 31:273–285

Jablonska B, Aguirre A, Raymond M, Szabo G, Kitabatake Y, Sailor KA, Ming GL, Song H, Gallo V (2010) Chordin-induced lineage plasticity of adult SVZ neuroblasts after demyelination. Nat Neurosci 13:541–550

Jackson EL, Garcia-Verdugo JM, Gil-Perotin S, Roy M, Quinones-Hinojosa A, VandenBerg S, Alvarez-Buylla A (2006) PDGFR alpha-positive B cells are neural stem cells in the adult SVZ that form glioma-like growths in response to increased PDGF signaling. Neuron 51:187–199

Jessberger S, Toni N, Clemenson GD Jr, Ray J, Gage FH (2008) Directed differentiation of hippocampal stem/progenitor cells in the adult brain. Nat Neurosci 11:888–893

Jin K, Wang X, Xie L, Mao XO, Greenberg DA (2010) Transgenic ablation of doublecortin-expressing cells suppresses adult neurogenesis and worsens stroke outcome in mice. Proc Natl Acad Sci U S A 107:7993–7998

Jin K, Zhu Y, Sun Y, Mao XO, Xie L, Greenberg DA (2002) Vascular endothelial growth factor (VEGF) stimulates neurogenesis in vitro and in vivo. Proc Natl Acad Sci U S A 99:11946–11950

Kazanis I, Belhadi A, Faissner A, ffrench-Constant C (2007) The adult mouse subependymal zone regenerates efficiently in the absence of tenascin-C. J Neurosci 27:13991–13996

Kazanis I, ffrench-Constant C (2012) The number of stem cells in the subependymal zone of the adult rodent brain is correlated with the number of ependymal cells and not with the volume of the niche. Stem Cells Dev 21:1090–1096

Kazanis I, Lathia J, Moss L, ffrench-Constant C (2008) The neural stem cell microenvironment. In: StemBook eTSCRC (ed) StemBook, vol stembook.1.15.1

Kazanis I, Lathia JD, Vadakkan TJ, Raborn E, Wan R, Mughal MR, Eckley DM, Sasaki T, Patton B, Mattson MP, Hirschi KK, Dickinson ME, ffrench-Constant C (2010) Quiescence and activation of stem and precursor cell populations in the subependymal zone of the mammalian brain are associated with distinct cellular and extracellular matrix signals. J Neurosci 30: 9771–9781

Kempermann G, Wiskott L, Gage FH (2004) Functional significance of adult neurogenesis. Curr Opin Neurobiol 14:186–191

Kerever A, Schnack J, Vellinga D, Ichikawa N, Moon C, Arikawa-Hirasawa E, Efird JT, Mercier F (2007) Novel extracellular matrix structures in the neural stem cell niche capture the neurogenic factor fibroblast growth factor 2 from the extracellular milieu. Stem Cells 25:2146–2157

Kippin TE, Martens DJ, van der Kooy D (2005) p21 loss compromises the relative quiescence of forebrain stem cell proliferation leading to exhaustion of their proliferation capacity. Genes Dev 19:756–767

Klaus F, Amrein I (2012) Running in laboratory and wild rodents: differences in context sensitivity and plasticity of hippocampal neurogenesis. Behav Brain Res 227:363–370

Klaus F, Hauser T, Lindholm AK, Cameron HA, Slomianka L, Lipp HP, Amrein I (2012) Different regulation of adult hippocampal neurogenesis in Western house mice (Mus musculus domesticus) and C57BL/6 mice. Behav Brain Res 227:340–347

Knoth R, Singec I, Ditter M, Pantazis G, Capetian P, Meyer RP, Horvat V, Volk B, Kempermann G (2010) Murine features of neurogenesis in the human hippocampus across the lifespan from 0 to 100 years. PLoS One 5:e8809

Komitova M, Mattsson B, Johansson BB, Eriksson PS (2005a) Enriched environment increases neural stem/progenitor cell proliferation and neurogenesis in the subventricular zone of stroke-lesioned adult rats. Stroke 36:1278–1282

Komitova M, Zhao LR, Gido G, Johansson BB, Eriksson P (2005b) Postischemic exercise attenuates whereas enriched environment has certain enhancing effects on lesion-induced subventricular zone activation in the adult rat. Eur J Neurosci 21:2397–2405

Kuhn HG, Winkler J, Kempermann G, Thal LJ, Gage FH (1997) Epidermal growth factor and fibroblast growth factor-2 have different effects on neural progenitors in the adult rat brain. J Neurosci 17:5820–5829

Lemasson M, Saghatelyan A, Olivo-Marin JC, Lledo PM (2005) Neonatal and adult neurogenesis provide two distinct populations of newborn neurons to the mouse olfactory bulb. J Neurosci 25:6816–6825

Lemmens MA, Sierksma AS, Rutten BP, Dennissen F, Steinbusch HW, Lucassen PJ, Schmitz C (2011) Age-related changes of neuron numbers in the frontal cortex of a transgenic mouse model of Alzheimer's disease. Brain Struct Funct 216:227–237

Leuner B, Mendolia-Loffredo S, Kozorovitskiy Y, Samburg D, Gould E, Shors TJ (2004) Learning enhances the survival of new neurons beyond the time when the hippocampus is required for memory. J Neurosci 24:7477–7481

Li BS, Ma W, Zhang L, Barker JL, Stenger DA, Pant HC (2001) Activation of phosphatidylinositol-3 kinase (PI-3 K) and extracellular regulated kinases (Erk1/2) is involved in muscarinic receptor-mediated DNA synthesis in neural progenitor cells. J Neurosci 21:1569–1579

Li L, Harms KM, Ventura PB, Lagace DC, Eisch AJ, Cunningham LA (2010) Focal cerebral ischemia induces a multilineage cytogenic response from adult subventricular zone that is predominantly gliogenic. Glia 58:1610–1619

Lie DC, Colamarino SA, Song HJ, Desire L, Mira H, Consiglio A, Lein ES, Jessberger S, Lansford H, Dearie AR, Gage FH (2005) Wnt signalling regulates adult hippocampal neurogenesis. Nature 437:1370–1375

Liu C, Teng ZQ, Santistevan NJ, Szulwach KE, Guo W, Jin P, Zhao X (2010) Epigenetic regulation of miR-184 by MBD1 governs neural stem cell proliferation and differentiation. Cell Stem Cell 6:433–444

Lois C, Alvarez-Buylla A (1994) Long-distance neuronal migration in the adult mammalian brain. Science 264:1145–1148

Lu Z, Elliott MR, Chen Y, Walsh JT, Klibanov AL, Ravichandran KS, Kipnis J (2011) Phagocytic activity of neuronal progenitors regulates adult neurogenesis. Nat Cell Biol 13:1076–1083

Lucassen PJ, Stumpel MW, Wang Q, Aronica E (2010) Decreased numbers of progenitor cells but no response to antidepressant drugs in the hippocampus of elderly depressed patients. Neuropharmacology 58:940–949

Luo J, Daniels SB, Lennington JB, Notti RQ, Conover JC (2006) The aging neurogenic subventricular zone. Aging Cell 5:139–152

Luo J, Shook BA, Daniels SB, Conover JC (2008) Subventricular zone-mediated ependyma repair in the adult mammalian brain. J Neurosci 28:3804–3813

Ma DK, Jang MH, Guo JU, Kitabatake Y, Chang ML, Pow-Anpongkul N, Flavell RA, Lu B, Ming GL, Song H (2009) Neuronal activity-induced Gadd45b promotes epigenetic DNA demethylation and adult neurogenesis. Science 323:1074–1077

Marshall GP 2nd, Demir M, Steindler DA, Laywell ED (2008) Subventricular zone microglia possess a unique capacity for massive in vitro expansion. Glia 56:1799–1808

Menn B, Garcia-Verdugo JM, Yaschine C, Gonzalez-Perez O, Rowitch D, Alvarez-Buylla A (2006) Origin of oligodendrocytes in the subventricular zone of the adult brain. J Neurosci 26:7907–7918

Mercier F, Kitasako JT, Hatton GI (2002) Anatomy of the brain neurogenic zones revisited: fractones and the fibroblast/macrophage network. J Comp Neurol 451:170–188

Merkle FT, Mirzadeh Z, Alvarez-Buylla A (2007) Mosaic organization of neural stem cells in the adult brain. Science 317:381–384

Mirzadeh Z, Merkle FT, Soriano-Navarro M, Garcia-Verdugo JM, Alvarez-Buylla A (2008) Neural stem cells confer unique pinwheel architecture to the ventricular surface in neurogenic regions of the adult brain. Cell Stem Cell 3:265–278

Molofsky AV, Slutsky SG, Joseph NM, He S, Pardal R, Krishnamurthy J, Sharpless NE, Morrison SJ (2006) Increasing p16INK4a expression decreases forebrain progenitors and neurogenesis during ageing. Nature 443:448–452

Morshead CM, Craig CG, van der Kooy D (1998) In vivo clonal analyses reveal the properties of endogenous neural stem cell proliferation in the adult mammalian forebrain. Development 125:2251–2261

Morshead CM, van der Kooy D (1992) Postmitotic death is the fate of constitutively proliferating cells in the subependymal layer of the adult mouse brain. J Neurosci 12:249–256

Mouret A, Lepousez G, Gras J, Gabellec MM, Lledo PM (2009) Turnover of newborn olfactory bulb neurons optimizes olfaction. J Neurosci 29:12302–12314

Nait-Oumesmar B, Picard-Riera N, Kerninon C, Decker L, Seilhean D, Hoglinger GU, Hirsch EC, Reynolds R, Baron-Van Evercooren A (2007) Activation of the subventricular zone in multiple sclerosis: evidence for early glial progenitors. Proc Natl Acad Sci U S A 104:4694–4699

Neumeister B, Grabosch A, Basak O, Kemler R, Taylor V (2009) Neural progenitors of the postnatal and adult mouse forebrain retain the ability to self-replicate, form neurospheres, and undergo multipotent differentiation in vivo. Stem Cells 27:714–723

Ninkovic J, Mori T, Gotz M (2007) Distinct modes of neuron addition in adult mouse neurogenesis. J Neurosci 27:10906–10911

Nissant A, Bardy C, Katagiri H, Murray K, Lledo PM (2009) Adult neurogenesis promotes synaptic plasticity in the olfactory bulb. Nat Neurosci 12:728–730

Palmer TD, Willhoite AR, Gage FH (2000) Vascular niche for adult hippocampal neurogenesis. J Comp Neurol 425:479–494

Parent JM, Jessberger S, Gage FH, Gong C (2007) Is neurogenesis reparative after status epilepticus? Epilepsia 48(Suppl 8):69–71

Parras CM, Galli R, Britz O, Soares S, Galichet C, Battiste J, Johnson JE, Nakafuku M, Vescovi A, Guillemot F (2004) Mash1 specifies neurons and oligodendrocytes in the postnatal brain. EMBO J 23:4495–4505

Peretto P, Dati C, De Marchis S, Kim HH, Ukhanova M, Fasolo A, Margolis FL (2004) Expression of the secreted factors noggin and bone morphogenetic proteins in the subependymal layer and olfactory bulb of the adult mouse brain. Neuroscience 128:685–696

Peretto P, Giachino C, Aimar P, Fasolo A, Bonfanti L (2005) Chain formation and glial tube assembly in the shift from neonatal to adult subventricular zone of the rodent forebrain. J Comp Neurol 487:407–427

Perry VH, Nicoll JA, Holmes C (2010) Microglia in neurodegenerative disease. Nat Rev Neurol 6:193–201

Phillips W, Morton AJ, Barker RA (2005) Abnormalities of neurogenesis in the R6/2 mouse model of Huntington's disease are attributable to the in vivo microenvironment. J Neurosci 25:11564–11576

Picard-Riera N, Decker L, Delarasse C, Goude K, Nait-Oumesmar B, Liblau R, Pham-Dinh D, Evercooren AB (2002) Experimental autoimmune encephalomyelitis mobilizes neural progenitors from the subventricular zone to undergo oligodendrogenesis in adult mice. Proc Natl Acad Sci U S A 99:13211–13216

Pinnock SB, Balendra R, Chan M, Hunt LT, Turner-Stokes T, Herbert J (2007) Interactions between nitric oxide and corticosterone in the regulation of progenitor cell proliferation in the dentate gyrus of the adult rat. Neuropsychopharmacology 32:493–504

Pinnock SB, Herbert J (2008) Brain-derived neurotropic factor and neurogenesis in the adult rat dentate gyrus: interactions with corticosterone. Eur J Neurosci 27:2493–2500

Pluchino S, Muzio L, Imitola J, Deleidi M, Alfaro-Cervello C, Salani G, Porcheri C, Brambilla E, Cavasinni F, Bergamaschi A, Garcia-Verdugo JM, Comi G, Khoury SJ, Martino G (2008) Persistent inflammation alters the function of the endogenous brain stem cell compartment. Brain 131:2564–2578

Quinones-Hinojosa A, Sanai N, Soriano-Navarro M, Gonzalez-Perez O, Mirzadeh Z, Gil-Perotin S, Romero-Rodriguez R, Berger MS, Garcia-Verdugo JM, Alvarez-Buylla A (2006) Cellular composition and cytoarchitecture of the adult human subventricular zone: a niche of neural stem cells. J Comp Neurol 494:415–434

Ramaswamy S, Goings GE, Soderstrom KE, Szele FG, Kozlowski DA (2005) Cellular proliferation and migration following a controlled cortical impact in the mouse. Brain Res 1053:38–53

Ramirez-Castillejo C, Sanchez–Sanchez F, Andreu-Agullo C, Ferron SR, Aroca-Aguilar JD, Sanchez P, Mira H, Escribano J, Farinas I (2006) Pigment epithelium-derived factor is a niche signal for neural stem cell renewal. Nat Neurosci 9:331–339

Rao MS, Shetty AK (2004) Efficacy of doublecortin as a marker to analyse the absolute number and dendritic growth of newly generated neurons in the adult dentate gyrus. Eur J Neurosci 19:234–246

Rietze RL, Valcanis H, Brooker GF, Thomas T, Voss AK, Bartlett PF (2001) Purification of a pluripotent neural stem cell from the adult mouse brain. Nature 412:736–739

Roth TC 2nd, LaDage LD, Freas CA, Pravosudov VV (2012) Variation in memory and the hippocampus across populations from different climates: a common garden approach. Proc Biol Sci 279:402–410

Ruckh JM, Zhao JW, Shadrach JL, van Wijngaarden P, Rao TN, Wagers AJ, Franklin RJ (2012) Rejuvenation of regeneration in the aging central nervous system. Cell Stem Cell 10:96–103

Sanai N, Nguyen T, Ihrie RA, Mirzadeh Z, Tsai HH, Wong M, Gupta N, Berger MS, Huang E, Garcia-Verdugo JM, Rowitch DH, Alvarez-Buylla A (2011) Corridors of migrating neurons in the human brain and their decline during infancy. Nature 478:382–386

Sanai N, Tramontin AD, Quinones-Hinojosa A, Barbaro NM, Gupta N, Kunwar S, Lawton MT, McDermott MW, Parsa AT, Manuel-Garcia Verdugo J, Berger MS, Alvarez-Buylla A (2004) Unique astrocyte ribbon in adult human brain contains neural stem cells but lacks chain migration. Nature 427:740–744

Santarelli L, Saxe M, Gross C, Surget A, Battaglia F, Dulawa S, Weisstaub N, Lee J, Duman R, Arancio O, Belzung C, Hen R (2003) Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. Science 301:805–809

Sawamoto K, Wichterle H, Gonzalez-Perez O, Cholfin JA, Yamada M, Spassky N, Murcia NS, Garcia-Verdugo JM, Marin O, Rubenstein JL, Tessier-Lavigne M, Okano H, Alvarez-Buylla A (2006) New neurons follow the flow of cerebrospinal fluid in the adult brain. Science 311:629–632

Scott CE, Wynn SL, Sesay A, Cruz C, Cheung M, Gomez Gaviro MV, Booth S, Gao B, Cheah KS, Lovell-Badge R, Briscoe J (2010) SOX9 induces and maintains neural stem cells. Nat Neurosci 13:1181–1189

Seri B, Garcia-Verdugo JM, Collado-Morente L, McEwen BS, Alvarez-Buylla A (2004) Cell types, lineage, and architecture of the germinal zone in the adult dentate gyrus. J Comp Neurol 478:359–378

Shen Q, Wang Y, Kokovay E, Lin G, Chuang SM, Goderie SK, Roysam B, Temple S (2008) Adult SVZ stem cells lie in a vascular niche: a quantitative analysis of niche cell–cell interactions. Cell Stem Cell 3:289–300

Sierra A, Encinas JM, Deudero JJ, Chancey JH, Enikolopov G, Overstreet-Wadiche LS, Tsirka SE, Maletic-Savatic M (2010) Microglia shape adult hippocampal neurogenesis through apoptosis-coupled phagocytosis. Cell Stem Cell 7:483–495

Sirko S, von Holst A, Wizenmann A, Gotz M, Faissner A (2007) Chondroitin sulfate glycosaminoglycans control proliferation, radial glia cell differentiation and neurogenesis in neural stem/progenitor cells. Development 134:2727–2738

Small SA, Tsai WY, DeLaPaz R, Mayeux R, Stern Y (2002) Imaging hippocampal function across the human life span: is memory decline normal or not? Ann Neurol 51:290–295

Snyder JS, Choe JS, Clifford MA, Jeurling SI, Hurley P, Brown A, Kamhi JF, Cameron HA (2009) Adult-born hippocampal neurons are more numerous, faster maturing, and more involved in behavior in rats than in mice. J Neurosci 29:14484–14495

Snyder JS, Soumier A, Brewer M, Pickel J, Cameron HA (2011) Adult hippocampal neurogenesis buffers stress responses and depressive behaviour. Nature 476:458–461

Stancik EK, Navarro-Quiroga I, Sellke R, Haydar TF (2010) Heterogeneity in ventricular zone neural precursors contributes to neuronal fate diversity in the postnatal neocortex. J Neurosci 30:7028–7036

Sturrock RR (1980) Myelination of the mouse corpus callosum. Neuropathol Appl Neurobiol 6:415–420

Suh H, Consiglio A, Ray J, Sawai T, D'Amour KA, Gage FH (2007) In vivo fate analysis reveals the multipotent and self-renewal capacities of Sox2 + neural stem cells in the adult hippocampus. Cell Stem Cell 1:515–528

Suhonen JO, Peterson DA, Ray J, Gage FH (1996) Differentiation of adult hippocampus-derived progenitors into olfactory neurons in vivo. Nature 383:624–627

Szulwach KE, Li X, Smrt RD, Li Y, Luo Y, Lin L, Santistevan NJ, Li W, Zhao X, Jin P (2010) Cross talk between microRNA and epigenetic regulation in adult neurogenesis. J Cell Biol 189:127–141

Tavazoie M, Van der Veken L, Silva-Vargas V, Louissaint M, Colonna L, Zaidi B, Garcia-Verdugo JM, Doetsch F (2008) A specialized vascular niche for adult neural stem cells. Cell Stem Cell 3:279–288

Thored P, Heldmann U, Gomes-Leal W, Gisler R, Darsalia V, Taneera J, Nygren JM, Jacobsen SE, Ekdahl CT, Kokaia Z, Lindvall O (2009) Long-term accumulation of microglia with proneurogenic phenotype concomitant with persistent neurogenesis in adult subventricular zone after stroke. Glia 57:835–849

Thored P, Wood J, Arvidsson A, Cammenga J, Kokaia Z, Lindvall O (2007) Long-term neuroblast migration along blood vessels in an area with transient angiogenesis and increased vascularization after stroke. Stroke 38:3032–3039

Tureyen K, Vemuganti R, Sailor KA, Bowen KK, Dempsey RJ (2004) Transient focal cerebral ischemia-induced neurogenesis in the dentate gyrus of the adult mouse. J Neurosurg 101:799–805

Urbach A, Redecker C, Witte OW (2008) Induction of neurogenesis in the adult dentate gyrus by cortical spreading depression. Stroke 39:3064–3072

van Praag H, Shubert T, Zhao C, Gage FH (2005) Exercise enhances learning and hippocampal neurogenesis in aged mice. J Neurosci 25:8680–8685

Villeda SA, Luo J, Mosher KI, Zou B, Britschgi M, Bieri G, Stan TM, Fainberg N, Ding Z, Eggel A, Lucin KM, Czirr E, Park JS, Couillard-Despres S, Aigner L, Li G, Peskind ER, Kaye JA, Quinn JF, Galasko DR, Xie XS, Rando TA, Wyss-Coray T (2011) The ageing systemic milieu negatively regulates neurogenesis and cognitive function. Nature 477:90–94

von Holst A, Sirko S, Faissner A (2006) The unique 473HD-Chondroitinsulfate epitope is expressed by radial glia and involved in neural precursor cell proliferation. J Neurosci 26:4082–4094

Walton NM, Sutter BM, Laywell ED, Levkoff LH, Kearns SM, Marshall GP 2nd, Scheffler B, Steindler DA (2006) Microglia instruct subventricular zone neurogenesis. Glia 54:815–825

Wang C, Liu F, Liu YY, Zhao CH, You Y, Wang L, Zhang J, Wei B, Ma T, Zhang Q, Zhang Y, Chen R, Song H, Yang Z (2011) Identification and characterization of neuroblasts in the subventricular zone and rostral migratory stream of the adult human brain. Cell Res 21:1534–1550

Weisz VI, Argibay PF (2009) A putative role for neurogenesis in neuro-computational terms: inferences from a hippocampal model. Cognition 112:229–240

Westenbroek C, Den Boer JA, Veenhuis M, Ter Horst GJ (2004) Chronic stress and social housing differentially affect neurogenesis in male and female rats. Brain Res Bull 64:303–308

Winner B, Cooper-Kuhn CM, Aigner R, Winkler J, Kuhn HG (2002) Long-term survival and cell death of newly generated neurons in the adult rat olfactory bulb. Eur J Neurosci 16:1681–1689

Yamashita T, Ninomiya M, Hernandez Acosta P, Garcia-Verdugo JM, Sunabori T, Sakaguchi M, Adachi K, Kojima T, Hirota Y, Kawase T, Araki N, Abe K, Okano H, Sawamoto K (2006) Subventricular zone-derived neuroblasts migrate and differentiate into mature neurons in the post-stroke adult striatum. J Neurosci 26:6627–6636

Yang Z (2008) Postnatal subventricular zone progenitors give rise not only to granular and periglomerular interneurons but also to interneurons in the external plexiform layer of the rat olfactory bulb. J Comp Neurol 506:347–358

Yoshihara H, Arai F, Hosokawa K, Hagiwara T, Takubo K, Nakamura Y, Gomei Y, Iwasaki H, Matsuoka S, Miyamoto K, Miyazaki H, Takahashi T, Suda T (2007) Thrombopoietin/MPL signaling regulates hematopoietic stem cell quiescence and interaction with the osteoblastic niche. Cell Stem Cell 1:685–697

Zawadzka M, Rivers LE, Fancy SP, Zhao C, Tripathi R, Jamen F, Young K, Goncharevich A, Pohl H, Rizzi M, Rowitch DH, Kessaris N, Suter U, Richardson WD, Franklin RJ (2010) CNS-resident glial progenitor/stem cells produce Schwann cells as well as oligodendrocytes during repair of CNS demyelination. Cell Stem Cell 6:578–590

Zhang R, Zhang Z, Wang L, Wang Y, Gousev A, Zhang L, Ho KL, Morshead C, Chopp M (2004) Activated neural stem cells contribute to stroke-induced neurogenesis and neuroblast migration toward the infarct boundary in adult rats. J Cereb Blood Flow Metab 24:441–448

Zhao S, Chai X, Frotscher M (2007) Balance between neurogenesis and gliogenesis in the adult hippocampus: role for reelin. Dev Neurosci 29:84–90

Zhao X, Ueba T, Christie BR, Barkho B, McConnell MJ, Nakashima K, Lein ES, Eadie BD, Willhoite AR, Muotri AR, Summers RG, Chun J, Lee KF, Gage FH (2003) Mice lacking methyl-CpG binding protein 1 have deficits in adult neurogenesis and hippocampal function. Proc Natl Acad Sci U S A 100:6777–6782

Ziabreva I, Perry E, Perry R, Minger SL, Ekonomou A, Przyborski S, Ballard C (2006) Altered neurogenesis in Alzheimer's disease. J Psychosom Res 61:311–316