

# Mechanisms and Functional Implications of Adult Neurogenesis

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The generation of new neurons is sustained throughout adulthood in the mammalian brain due to the proliferation and differentiation of adult neural stem cells. In this review, we discuss the factors that regulate proliferation and fate determination of adult neural stem cells and describe recent studies concerning the integration of newborn neurons into the existing neural circuitry. We further address the potential significance of adult neurogenesis in memory, depression, and neurodegenerative disorders such as Alzheimer's and Parkinson's disease.

Neurogenesis in the brain of adult mammals occurs throughout life, and has been clearly demonstrated at two locations under normal conditions: the subventricular zone (SVZ) of the lateral ventricles and the subgranular zone (SGZ) of the dentate gyrus in the hippocampus. Neurons born in the adult SVZ migrate over a great distance through the rostral migratory stream and become granule neurons and periglomerular neurons in the olfactory bulb. Neurons born in the adult SGZ migrate into the granule cell layer of the dentate gyrus and become dentate granule cells. Recent studies also showed that newborn neurons in the adult brain integrate into the existing circuitry and receive functional input (Figure 1). Adult neurogenesis is regulated by physiological and pathological activities at all levels, including the proliferation of adult neural stem cells (NSCs) or progenitors, differentiation and fate determination of progenitor cells, and the survival, maturation, and integration of newborn neurons. Furthermore, these cells may be required for certain forms of brain function involving the olfactory bulb and the hippocampus, which is important for some forms of learning and memory. Whether neurogenesis occurs in areas of the adult mammalian brain other than the SVZ and SGZ remains controversial (reviewed by Gould, 2007; Rakic, 2002). Adult neurogenesis also occurs in a variety of nonmammalian vertebrates and has been extensively studied in songbirds (reviewed by Chapouton et al., 2007; Nottebohm, 2004). In this review, we summarize recent findings that elucidate different aspects of regulation of adult neurogenesis in mammals and studies that address its functional significance.

# **Adult Neural Stem Cells and Adult Neural Progenitors**

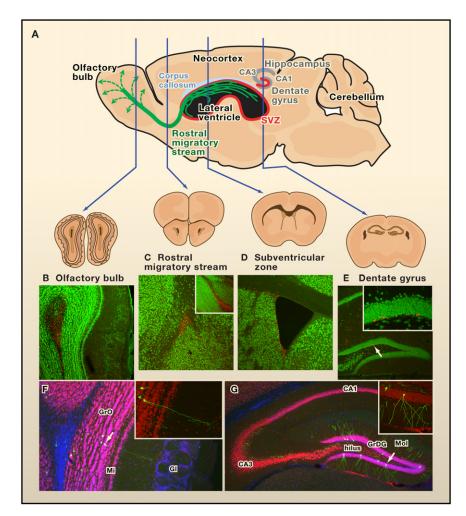
Adult NSCs are cells in the adult nervous system that can self-renew and differentiate into all types of neural cells, including neurons, astrocytes, and oligodendrocytes (Gage, 2000). Neurons are the functional components of the nervous system and are responsible for information processing and transmission; astrocytes and oligodendrocytes are collectively known as glia and play supporting roles that are essential for the proper functioning of the nervous system. The stem cell properties of adult NSCs

have been shown in vitro via neurosphere and adherent monolayer cultures but have not been demonstrated convincingly in vivo until recently (see below). Therefore, the term "neural progenitor" has been used to loosely describe all dividing cells with some capacity for differentiation.

Two types of neural progenitors can be identified in the SGZ according to their specific morphologies and expression of unique sets of molecular markers (Figure 2). Type 1 hippocampal progenitors have a radial process spanning the entire granule cell layer and ramify in the inner molecular layer. These cells express nestin, glial fibrillary acidic protein (GFAP), and the Sry-related HMG box transcription factor, Sox2 (Fukuda et al., 2003; Garcia et al., 2004; Suh et al., 2007). Although expressing the astrocyte marker GFAP, these cells are morphologically and functionally different from mature astrocytes. Type 2 hippocampal progenitors have only short processes and do not express GFAP. Type 2 cells may arise from type 1 cells, but direct evidence delineating this lineage relationship is still lacking. A recent study showed that type 2 Sox2-positive cells can self-renew and that a single Sox2positive cell can give rise to a neuron and an astrocyte, providing the first in vivo evidence of stem cell properties of hippocampal neural progenitors (Suh et al., 2007). This study also suggested that the relationship between type 1 and 2 cells could be reciprocal. The transcription factor Sox2 is important for maintaining the "stemness" not only of certain types of adult stem cells including NSCs but also of embryonic stem (ES) cells; as part of a four-factor cocktail, Sox2 contributes to inducing adult somatic cells to take on an ES cell-like fate (see Review by R. Jaenisch and R. Young, page 567 of this issue).

The SVZ is located next to the ependyma, a thin cell layer that lines the lateral ventricles of the brain (Figures 1A and 3). Ependymal cells have been suggested to be the adult NSCs responsible for neurogenesis in the SVZ (Johansson et al., 1999). Several studies have shown, however, that ependymal cells are quiescent and do not have the properties of NSCs in vitro (Capela and Temple, 2002; Doetsch et al., 1999). More importantly, cells within the SVZ (and less likely the ependyma itself) contribute to long-term neurogenesis in the olfactory bulb (Consiglio

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et al., 2004). Three types of precursor cells exist in the SVZ: type B GFAP-positive progenitors, type C transit amplifying cells and type A migrating neuroblasts (Figure 3). Type B GFAP-positive neural progenitors in the SVZ are less susceptible to antimitotic treatment and may be relatively quiescent (Doetsch et al., 1999). The identification of SVZ progenitors was mainly based on morphological analysis by electron microscopy, but type C and A cells can also be identified by bromodeoxyuridine (BrdU) and <sup>3</sup>H-thymidine labeling and by specific molecular markers, such as Dlx2, doublecortin (DCX) and the polysialylated neural adhesion molecule (PSA-NCAM) (Table S1 available online, Figure 4). Interestingly, the potential of SVZ progenitor cells appears to be limited, as the fate of their progeny is determined by the positional information established during early development of the central nervous system (CNS) (Merkle et al., 2007).

Lineage tracing studies in adult mice have demonstrated that newborn neurons, astrocytes and sometimes oligodendrocytes can be derived from cells expressing a given molecular marker, such as Nestin, GFAP, GLAST and Sox2 (reviewed by Breunig et al., 2007). However, these markers are expressed in heterogeneous populations of cells and it is not clear whether cells expressing these markers are the primary progenitors. Neither is it known whether a common progenitor exists in the adult brain

Figure 1. Neurogenesis in the Adult Rodent **Brain** 

(A) Depictions of sagittal and coronal views of mouse brain in areas where neurogenesis occurs. Red areas indicate the germinal zones in the adult mammalian brain: the subgranular zone (SGZ) of the dentate gyrus in the hippocampus and the subventricular zone (SVZ) of the lateral ventricles. Neurons generated in the SVZ migrate through the rostral migratory stream and are incorporated into the olfactory bulb.

(B-E) Neurogenesis revealed by BrdU incorporation in the olfactory bulb (B), rostral migratory stream (C), SVZ (D), and dentate gyrus (E). Inset in (C) is a sagittal view of rostral migratory stream before reaching the olfactory bulb, and inset in (E) is a high-magnification view of the area indicated by the arrow in (E). Colors indicate the following: red. BrdU: areen. NeuN.

(F and G) Newborn neurons in the olfactory bulb and dentate gyrus labeled by retrovirus-mediated expression of green fluorescent protein (GFP). Insets are high-magnification views of the cells indicated by arrows. Colors indicate the following: red, NeuN; green, GFP; blue, DAPI. Image in (F) is reproduced with permission from Cold Spring Harbor Laboratory Press (Zhao, 2007).

for all three different types of progeny or if distinct progenitors are responsible for the generation of multiple neural cell types.

#### **The Neurogenic Niche**

Although NSCs can be isolated from many areas of the adult nervous system,

adult neurogenesis has only been consistently found in the SVZ and SGZ in vivo. It is hypothesized that the microenvironments of the SGZ and SVZ, known as the neurogenic niche, may have specific factors that are permissive for the differentiation and integration of new neurons (see Review by S.J. Morrison and A.C. Spradling, page 598 of this issue).

In the SGZ, adult hippocampal progenitors are closely apposed to a dense layer of granule cells that includes both mature and newborn immature neurons (Figures 1 and 2). Within this microenvironment, there are also astrocytes, oligodendrocytes, and other types of neurons. Hippocampal astrocytes may play an important role in SGZ neurogenesis. They promote the neuronal differentiation of adult hippocampal progenitor cells and the integration of newborn neurons derived from adult hippocampal progenitors in vitro (Song et al., 2002). Blockade of the Wnt signaling pathway inhibits the neurogenic activity of astrocytes in vitro and SGZ neurogenesis in vivo, suggesting that hippocampal astrocytes may act through Wnt signaling (Lie et al., 2005).

SVZ progenitors are adjacent to the ependymal cell layer of the lateral ventricles (Figures 1 and 3). Ependymal cells express the protein Noggin that may promote SVZ neurogenesis by antagonizing signaling of the bone morphogenetic proteins (BMPs). This is consistent with the proastrocytic role of BMPs added to

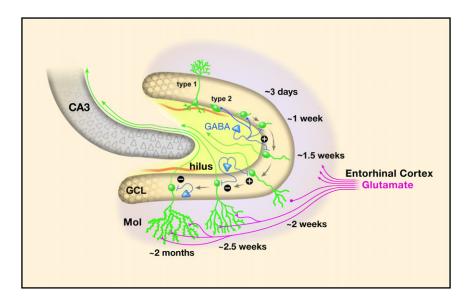


Figure 2. Neurogenesis in the Dentate **Gyrus** 

Type 1 and type 2 progenitor cells in the subgranular zone (SGZ) can be identified by their distinct morphologies and their expression of specific molecular markers. Newborn neurons in the dentate gyrus of the hippocampus go through several stages of morphological and physiological development. Specifically, a transition from GABA (blue) excitatory to GABA inhibitory and glutamate excitatory inputs to newborn neurons occurs during the third week after cell birth, concomitant with the growth of dendritic spines. Progenitor cells in the dentate gyrus are influenced by local astrocytes (not shown) and by the vasculature (red). Abbreviations are as follows: GCL, granule cell layer; Mol. molecular laver.

cultured NSCs and during embryonic development (Lim et al., 2000). Ependymal cells may also promote the self-renewal of adult NSCs in the SVZ through pigment epithelium-derived factor (Ramirez-Castillejo et al., 2006). In addition, dopaminergic fibers are found in close proximity to SVZ precursor cells. Dopaminergic signaling may promote SVZ proliferation in vivo through the D2-like dopamine receptors (Hoglinger et al., 2004).

Proliferating cells and putative neural progenitors in both SGZ and SVZ are closely associated with the vasculature, indicating that factors released from the blood vessels may have a direct impact on adult neural progenitors (Alvarez-Buylla and Lim, 2004; Palmer et al., 2000). Indeed, infusion of vascular endothelial growth factor (VEGF) promotes cell proliferation in the SVZ and SGZ, which can be blocked by a dominant-negative VEGF receptor 2 (Cao et al., 2004). In addition, VEGF is required for increased neurogenesis in adult mice exposed to an enriched environment or given the opportunity of voluntary exercise, which are both known to enhance adult neurogenesis.

The anatomical and functional components within the neurogenic niche in both SGZ and SVZ remain to be determined. Any diffusible molecules produced by local cells can influence neural progenitors. Neighboring cells can also exert their influence through direct cell-cell interactions. Furthermore, neural progenitors can be indirectly influenced by neurons outside of this microenvironment that are connected to neurons within the neurogenic niche through neural circuits. Both local and distal neurons can also exert direct influences on neural progenitors through the ambient levels of neurotransmitters in the neurogenic niche, or even through synaptic contacts with neural progenitors. Therefore, adult neurogenesis is subject to complex extrinsic regulation.

## **Regulation of Adult NSCs and Neural Progenitors**

The fundamental properties of a stem cell include the capacity to self-renew and multipotentiality enabling differentiation into a number of different cell types. Due to the lack of tools to directly identify adult NSCs and neural progenitors in vivo, the self-renewal and therefore the maintenance of adult NSCs and neural progenitors have not been clearly demonstrated. Neurogenesis declines with aging in both the SVZ and SGZ (see Review by D. Rossi et al., page 681 of this issue). Studies with neurosphere cultures suggest that the self-renewal capacity and the number of SVZ progenitors decrease significantly in aged animals (Molofsky et al., 2006). It is not known whether the number of neural progenitors in the SGZ also declines with aging, but neurogenesis in aged animals can be restored to a certain extent by voluntary exercise, suggesting that these cells still have the capability of responding to extrinsic stimuli (van Praag et al., 2005).

Our understanding of the regulation of adult neurogenesis comes mostly from studies based on cell cycle progression and imperfect markers of progenitors. Recently, new imaging tools have been developed to monitor adult neural progenitors in live subjects, although the resolution of such an approach is compromised (Table S1). Despite these limitations, studies over the past decade have identified numerous molecular pathways that participate in the regulation of adult neural progenitors.

# The Influence of Neurotransmitters

SGZ progenitor cells reside in a microenvironment of complex neuronal networks. Dentate granule cells, the principal neurons in the dentate gyrus, receive excitatory glutamatergic inputs mainly from the entorhinal cortex and GABAergic inputs mostly from the interneurons within the dentate gyrus. In addition, neurons within the dentate gyrus receive a variety of inputs from many areas of the brain through different neurotransmitters and neural peptides (Table S2). All cells within the dentate circuitry may potentially be influenced by these molecules. Therefore, the complexity of the circuitry in the neurogenic niche must be taken into account for an accurate description of the regulation of neural progenitor cells by specific neurotransmitters.

Within the dentate gyrus, the role of the NMDA receptor (one of the receptors for the excitatory neurotransmitter glutamate) in adult neurogenesis has been extensively studied. Although cell genesis in the dentate gyrus does not require a functional NMDA receptor, global NMDA receptor-dependent activity is inversely correlated with the level of hippocampal proliferation

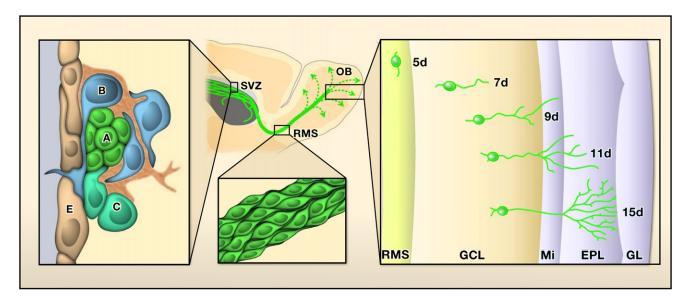


Figure 3. Neurogenesis in the Subventricular Zone

Progenitor cells (A–C) in the subventricular zone (SVZ) lie adjacent to the ependymal cell (E) layer lining the lateral ventricles and interact with basal lamina extending from the local vasculature. Newborn neurons reach the olfactory bulb (OB) through chain migrations and go through morphological and physiological development before integrating as granule neurons in the granule cell layer (GCL) and as periglomerular neurons (not shown) in the glomerular layer (GL). Abbreviations are as follows: Mi, mitral cell layer; EPL, external plexiform layer; RMS, rostral migratory stream.

(reviewed by Jang et al., 2007). It remains debatable whether adult hippocampal progenitors express functional NMDA receptors. Cultured hippocampal progenitors respond to glutamate by increased neuronal differentiation. However, the essential NR1 subunit of the NMDA receptor was not detectable in proliferating cells in vivo by immunohistochemistry (Deisseroth et al., 2004; Nacher and McEwen, 2006). In contrast to the elusive mechanism of glutamate, the neurotransmitter GABA directly depolarizes type 2 progenitors in the adult hippocampus, which results in calcium ion influx and increased expression of the neuronal differentiation factor NeuroD, suggesting that direct GABAergic input promotes the differentiation of type 2 hippocampal progenitors (Tozuka et al., 2005). Consistent with this observation, calcium ion channel antagonists and agonists decreased and increased neuronal differentiation in the adult hippocampus, respectively (Deisseroth et al., 2004).

Neural progenitors in the SVZ and SGZ are influenced by other neurotransmitters as well as by neural peptides (Table S2; reviewed by Jang et al., 2007). It is unclear whether these neurotransmitters and neural peptides exert direct effects on the neural progenitors, given that the expression of receptors for these molecules has not been extensively examined. The mechanism by which newborn neurons are regulated by signaling through certain neurotransmitters has recently been elucidated and will be discussed later.

# The Influence of Growth Factors and Other Extrinsic Signals

Growth factors such as epidermal growth factor (EGF) and fibroblast growth factor 2 (FGF2) are potent factors for the maintenance of adult NSCs in vitro. In vivo, both factors promote proliferation in the SVZ, but only FGF2 increases the number of newborn neurons in the olfactory bulb (Kuhn et al., 1997). A later

study found that EGF inhibits the differentiation of type C cells into neuroblasts (Doetsch et al., 2002). Interestingly, re-expression of ErbB2, one of the EGF receptors, can induce radial glia morphology in GFAP-positive cells in the SVZ of young adult mice, suggesting that its ligand, EGF, is indeed present in the adult SVZ (Ghashghaei et al., 2007). Although infusion of FGF2 does not affect SGZ proliferation in young mice, deletion of *fgfr1* in the CNS decreases SGZ neurogenesis (Jin et al., 2003; Zhao et al., 2007). Therefore, FGF2-mediated signaling may play a permissive role in SGZ proliferation.

Adult neural progenitors are also regulated by a variety of other extrinsic factors (Table S3). Signaling through the Sonic hedgehog pathway may regulate adult neurogenesis. The neurotrophin brain-derived neurotrophic factor (BDNF) is one of the key positive regulators of adult neurogenesis. Mice deficient in p75, one of the BDNF receptors, have a smaller olfactory bulb and decreased neurogenesis in the SVZ. The regulatory role of BDNF in hippocampal neurogenesis will be discussed in detail later. The target cells of many of the extrinsic factors are unknown. In addition to the possible direct influence on progenitor cells, these extracellular regulators could cause changes in other cell types within the neurogenic niche and exert an indirect effect on adult neural progenitors.

# Intracellular Mechanisms

In addition to the canonical intracellular signaling pathways downstream of the growth factors, neurotrophins, and morphogens, a variety of other intracellular mechanisms have been implicated in the regulation of adult neurogenesis (Table S3). Among these, several transcription factors have been shown to play critical roles in postnatal neurogenesis. TLX, an orphan nuclear receptor, and Bmi-1 are required for the maintenance of adult forebrain NSCs. Pax6 promotes neuronal differentiation

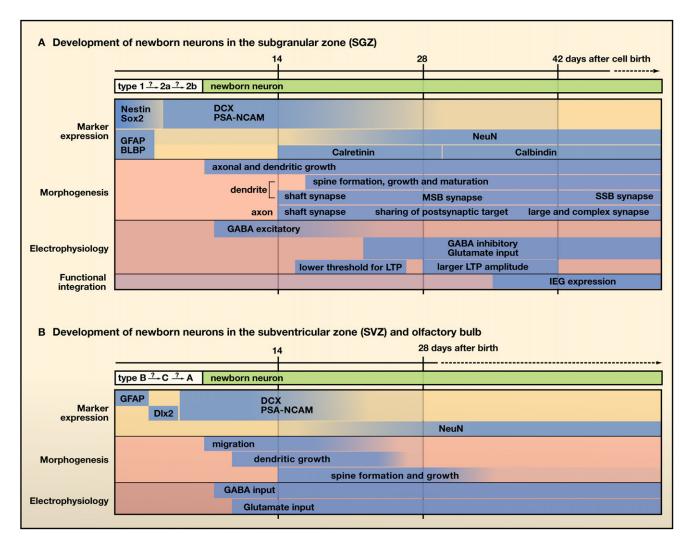


Figure 4. Development of Newborn Neurons in the SGZ and SVZ

Development of newborn neurons in the SGZ (A) and in the SVZ-olfactory bulb (B), as characterized by expression of specific markers, morphogenesis, synapse formation, electrophysiological properties, and functional integration. Abbreviations are as follows: MSB, multiple-synapse boutons; SSB, single-synapse boutons; LTP, long-term potentiation; IEG, immediate early gene.

of SVZ progenitors, whereas Olig2 has an opposite effect. Adult neurogenesis is also subject to epigenetic regulation (Table S3). For example, adult NSCs lacking the methyl-CpG binding protein 1 (MBD1) exhibit increased genomic instability and reduced neuronal differentiation. In addition, genes involved in cell cycle regulation, DNA repair and chromosome stability are required for the proper function of adult neural progenitors. The early processes of adult neurogenesis might also be influenced by somatic gene insertions, as the retrotransposon long interspersed nuclear element-1 (LINE-1) is expressed in adult hippocampal neural progenitors in vitro (see Table S3 for references).

In summary, numerous extrinsic factors and intracellular pathways have been implicated in regulating adult NSCs and neural progenitors. Many of these studies rely on systemic administration of factors, or genetic deletion of specific genes. Therefore, one cannot rule out the possibility of indirect mechanisms or of secondary effects from defects during early development. Targeting approaches that have greater specificity are needed in the future for an accurate description of molecular mechanisms of adult neural progenitor regulation.

#### **The Migration of Newborn Neurons**

Neuroblasts originating from SVZ progenitors migrate tangentially up to a distance of 5 mm in the rodent. They migrate through a path known as the rostral migratory stream (Figures 1A and 3) to the olfactory bulb, and then turn radially toward the granule cell layer and to the periglomerular cell layer after they reach the olfactory bulb (reviewed by Lledo and Saghatelyan, 2005). This migration is not guided by radial glia or existing axon fibers but through "chain migration," by forming elongated cell aggregates that are ensheathed by astrocytes. Although astrocytes do not appear to play an essential role in this chain migration, they may be involved in modulating the level of GABA, which has a negative effect on the speed of neuroblast migration. The

olfactory bulb and septum might provide chemoattractant and repellent signals, respectively, and the repellent signals from the septum might contain the axon guidance molecules Slit 1 and Slit 2. Interestingly, newborn cells reach the olfactory bulb more quickly in adult than in postnatal mice, although the distance they need to travel is much longer.

Migration along the rostral migratory stream and in the olfactory bulb is regulated by cell-cell and cell-extracellular matrix interactions (reviewed by Lledo and Saghatelyan, 2005). Disruption of EphB2/ephrin-B2 or neuregulin/ErbB4 pathways leads to severe defects in the chain migration of SVZ neuroblasts. The NCAM protein is required for the proper organization of the rostral migratory stream. Radial migration in the olfactory bulb is partially dependent on the extracellular matrix protein tenascin-R and the glycoprotein Reelin. The role of Reelin is likely to be cell nonautonomous as grafted wild-type cells were not able to migrate into the granule cell layer of the olfactory bulb in reeler mice, which have a mutant form of Reelin.

Newborn neurons in the SGZ only migrate a short distance into the granule cell layer. A recent study suggested that the protein Disrupted-in-schizophrenia (DISC1) may be involved in newborn neuron migration in the SGZ, as cells with less DISC1 migrate further into the granule cell layer and even into the molecular layer of the dentate gyrus (Figures 1G and 2) (Duan et al., 2007). The migration of newborn neurons in the dentate gyrus may also be controlled by guidance cues, as these cells only migrate to the hilus or the molecular layer under pathological conditions, such as in animal models of temporal lobe epilepsy. Signaling through the Reelin pathway may be involved in such regulation (Gong et al., 2007).

## Survival, Maturation, and Integration of Newborn Neurons

Newborn neurons in the dentate gyrus go through several developmental stages with distinctive physiological and morphological properties (Figures 2 and 4) (Esposito et al., 2005; Ge et al., 2006; Overstreet Wadiche et al., 2005; Zhao et al., 2006). Similar to immature neurons in the developing brain, newborn granule cells initially become depolarized in response to GABA because of their higher intracellular concentration of chloride ions. The response to GABA switches from depolarization to hyperpolarization at 2-4 weeks after neuronal birth, which coincides with the growth of dendritic spines and the onset of glutamatergic responses. Within this time window, new neurons have lower thresholds for long-term potentiation (Ge et al., 2007; Schmidt-Hieber et al., 2004). Interestingly, new neurons already form synapses with hilar and CA3 targets at 2 weeks after birth, although the complexity of these efferent synapses increases as neurons mature (F.H. Gage, unpublished data; H.J. Cheng and H. Song, personal communication).

Newborn neurons in the dentate gyrus display typical features of mature granule cells at 4 weeks of age, but they continue to change both physiologically and morphologically (Ge et al., 2007; Toni et al., 2007; Zhao et al., 2006). The amplitude of long-term potentiation is larger in new neurons 4-6 weeks after birth, which may be mediated by the NR2B subunit of the NMDA receptor. The density of mushroom spines continues to increase after 8 weeks. In addition, spines from 4-week-old neurons are more likely to be associated with multiple-synapse boutons than older neurons. Once they mature, newborn granule cells receive similar glutamatergic and GABAergic inputs as existing neurons in the dentate gyrus (Laplagne et al., 2006, 2007). Although 1- to 3-week-old neurons have lower thresholds for induction of long-term potentiation, they do not display activity-dependent expression of immediate early genes at this stage (Jessberger and Kempermann, 2003). However, the animals' experience during this time window can affect the expression of activity-dependent immediate early genes in newborn neurons when they are 6 weeks old or older (Kee et al., 2007; Tashiro et al., 2007).

The initial depolarization by GABA plays a critical role in the maturation of newborn granule cells, as knockdown of the chloride ion channel NKCC1 leads to a significant defect in neuronal maturation (Ge et al., 2006). The DISC1 protein controls dendritic growth and physiological maturation in newborn dentate granule cells (Duan et al., 2007). Physiological and pathological conditions also affect neuronal maturation. For example, voluntary exercise accelerates the formation of mushroom spines. Seizure activity promotes spine formation on immature neurons. The molecular pathways mediating these effects remain to be determined.

Newborn neurons in the olfactory bulb also go through distinct stages of development (Figures 3 and 4) (Lledo et al., 2006; Petreanu and Alvarez-Buylla, 2002). These neurons develop functional GABA receptors before glutamate receptors and the formation of dendritic spines (reviewed by Lledo and Saghatelyan, 2005). Odor deprivation reduces the complexity of dendritic arborization of newborn cells, but these new neurons display enhanced excitability and action potential-dependent GABA release (Saghatelyan et al., 2005).

Many newborn neurons die within 4 weeks after birth, and their survival is subject to regulation by diverse mechanisms. In the SGZ, the survival of 1- to 3-week-old newborn neurons is influenced by the animals' experience, such as spatial learning and exposure to an enriched environment (Kee et al., 2007; Tashiro et al., 2007). Signaling through the NMDA receptor plays a cell autonomous role in neuronal survival during the third week after birth, which coincides with the formation of dendritic spines and functional glutamatergic inputs. Furthermore, the survival of NR1-deficient newborn neurons can be rescued to a certain extent by global inhibition of neuronal activity (Tashiro et al., 2006). Similar to neurogenesis in the SGZ, the survival of newborn granule neurons in the olfactory bulb depends on sensory input (Petreanu and Alvarez-Buylla, 2002). Hence, the modulation of neuronal activity in both newborn and mature neurons in the circuit likely plays an essential role in the survival of newborn neurons. In addition, cell survival may be regulated by other mechanisms; for example, BDNF enhances the survival of newborn cells in the hippocampus.

In summary, newborn neurons in both SGZ and SVZ are functionally integrated into the existing circuitry. The survival and the integration of newborn neurons in SGZ are largely determined during a critical time window (1-3 weeks) when these neurons are immature and display unique physiological properties, a finding that has led to the hypothesis that immature neurons may contribute to distinct forms of learning and memory, which has been examined by both computational and experimental approaches.

#### The Regulation and Function of SVZ Neurogenesis

SVZ neurogenesis is regulated by the olfactory experience of animals (reviewed by Lledo et al., 2006; Lledo and Saghatelyan, 2005). Deprivation of olfactory sensory inputs hinders maturation and survival of newborn neurons in the olfactory bulb, although its effects on cell proliferation in the SVZ are unclear. More specifically, sensory experience and the activity of young neurons are critical for the survival of 14- to 28-day-old neurons. In contrast, enriched odor exposure increases the survival of newborn neurons and transiently improves odor memory, suggesting a role for SVZ neurogenesis in this memory process.

Further studies revealed that it was olfactory learning, not simple exposure to odors, that enhanced SVZ neurogenesis. More 21-day-old newborn neurons survived in the olfactory bulb of mice that learned an odor discrimination task (Alonso et al., 2006). Moreover, negative information might have a dominant role in this enhanced survival, which coincided with the highest activated loci driven by the nonreinforced odorant (Alonso et al., 2006). However, odor discrimination learning had no or even an opposite effect on the survival of 30-day-old newborn neurons, which did not correlate with odor-induced activity (Mandairon et al., 2006). Given the difference in the age of young neurons studied, olfactory learning may distinctively modulate newborn neurons depending on their maturation status. Nonetheless, olfactory learning is a key regulator of SVZ neurogenesis.

The regulation of SVZ neurogenesis by olfactory experience and learning leads to the hypothesis that adult SVZ neurogenesis plays a role in olfactory learning (Lledo et al., 2006). This hypothesis is supported by some correlative evidence. NCAM knockout mice, in which both postnatal and adult SVZ neurogenesis are reduced, have deficits in spontaneous odor discrimination and short-term odor memory. In addition, fine olfactory discrimination was impaired in aging mice, mice heterozygous for leukemia inhibitory factor receptor (Lifr+/-), and waved-1 mutant mice (a hypermorph of  $Tgf\alpha$ ), in which SVZ neurogenesis were greatly reduced. However, it is not clear whether these defects in odor discrimination were directly caused by decreased neurogenesis in the adult olfactory bulb. Therefore, specific ablation approaches are needed to elucidate the functional significance of SVZ neurogenesis.

# **Implications of Hippocampal Neurogenesis** in Learning and Memory

Because of the differential connectivity of the hippocampus along the dorsal-ventral (septo-temporal) axis, the dorsal hippocampus may have a preferential role in learning and memory, whereas the ventral hippocampus is involved in affective behaviors (Bannerman et al., 2004). In this section, we discuss the putative function of SGZ neurogenesis in learning and memory, which is supported by correlative evidence, ablation studies and computational modeling.

# **Correlations between Hippocampal Neurogenesis** and Cognition

Many genetic and environmental factors that affect hippocampal neurogenesis cause corresponding changes in cognitive performance. Adult hippocampal neurogenesis can be influenced by the genetic background of mice at the levels of cell proliferation, differentiation, and survival (Kempermann and Gage, 2002, and references therein). A correlation between hippocampal neurogenesis and learning in a spatial memory task (the Morris water maze) was observed in mice of different strains. In addition, some mutant mice with decreased SGZ neurogenesis have impaired performance on hippocampus-dependent learning tasks, although such a correlation is not detected in every case (Table 1).

In addition to genetic determinants, environment has a major impact on SGZ neurogenesis (reviewed by Olson et al., 2006). For example, voluntary running increases SGZ cell proliferation, whereas exposure to an enriched environment promotes the survival of 1- to 3-week-old immature neurons, which are the likely substrates for experience-specific modulation (Kee et al., 2007; Tashiro et al., 2007). Both voluntary exercise and environmental enrichment improve the performance of young and aged mice in the Morris water maze (Table 1). Environmental enrichment also leads to better recognition memory (Bruel-Jungerman et al., 2005). Studies of mice deficient in presenilin-1, in which hippocampal neurogenesis induced by environmental enrichement was attenuated, suggested a function of neurogenesis in the clearance of memory traces in the hippocampus (Table 1). Running-induced neurogenesis, which is correlated with an induction of long-term potentiation in the dentate gyrus, can be modulated by the social status of animals and is likely to be mediated by molecules such as BDNF and VEGF (Olson et al., 2006).

In contrast to physical exercise and enriched environment, aging and stress are two major negative regulators of SGZ neurogenesis (reviewed by Klempin and Kempermann, 2007; Mirescu and Gould, 2006). Although the correlation between stress and cognition is controversial (Shors, 2004), aged animals display impaired learning and memory in the Morris water maze and several other tasks. Furthermore, a correlation between SGZ neurogenesis and performance in the Morris water maze was observed in individual aged animals in some but not in other studies.

Although these studies demonstrate a correlation between the level of hippocampal neurogenesis and cognition, it is possible that other factors, such as structural plasticity and neurotrophin and hormone levels, also contribute to environmentally-induced changes in hippocampus-dependent learning and memory (Olson et al., 2006). In fact, hippocampal neurogenesis was reported to be dispensable for the beneficial effects of enriched environment on performance in the Morris water maze (Meshi et al., 2006). Hence, whether hippocampal neurogenesis is a major causal factor for the changes in cognition under these conditions is yet to be determined.

#### Modulation of SGZ Neurogenesis by Learning

The regulation of neurogenesis by neural activity suggests that learning might induce the activation of newborn neurons and subsequently enhance their survival and incorporation into circuits. However, numerous investigations have revealed that the regulation of SGZ neurogenesis by learning is complex.

SGZ neurogenesis is only enhanced by learning tasks that depend on the hippocampus. The survival of 7-day-old neurons in rat SGZ is increased by trace eyeblink conditioning and by learning the Morris water maze but not by hippocampus-independent tasks, such as delay eyeblink conditioning and active shock avoidance (reviewed by Leuner et al., 2006). In addition, the survival of newborn neurons is increased by a long-delay

Table 1. Genetic and Environmental Regulation of Subgranular Zone Neurogenesis and Their Correlation with Cognition					
System Regulators	Effects on Neurogenesis	Effects on Cognition	References <sup>a</sup>		
Genetic Regulation					
Genetic background	Varied proliferation	Correlated performance with proliferation	Kempermann and Gage, 2002		
mbd1 <sup>-/-</sup>	Decreased proliferation	Impaired learning and memory	Zhao et al., 2003		
fgfr1 <sup>flox/-</sup> , nes-cre	Decreased proliferation	Defective memory consolidation	Zhao et al., 2007		
NT-3 <sup>flox/-</sup> ; nes-cre	Decreased neuron differentiation/survival	Defective learning	Shimazu et al., 2006		
neurokinin1 <sup>-/-</sup>	Increased proliferation	No improvement in learning and memory	Morcuende et al., 2003		
Physical Activity					
Voluntary running	Increased proliferation	Improved learning and memory	van Praag et al., 1999		
Hindlimb suspension	Decreased proliferation	Not available	Yasuhara et al., 2007		
Enriched Environment (EE)					
Exposure to EE	Increased survival	Improved learning and memory	Kempermann and Gage, 1997		
presenilin-1 <sup>-/-</sup>	Attenuation of the induction of neurogenesis by EE	Reduced memory clearance induced by postlearning EE	Feng et al., 2001		
Stress <sup>b</sup>					
Psychosocial stress	Decreased proliferation	Impaired spatial memory	Ohl et al., 1999		
Unexpected chronic mild stress	Decreased neurogenesis	No simple correlation	Minuer et al., 2007		
Aging					
Aged rats	Decreased proliferation and neurogenesis	Correlated impairment in learning or memory	Drapeau et al., 2003; Driscoll et al., 2006		
Aged rats	Decreased proliferation and neurogenesis	Not correlated to cognition	Merrill et al., 2003; Bizon et al., 2004		
Aged animals in EE	Increased neurogenesis <sup>c</sup>	Improved learning and memory	Kempermann et al., 1998		
Aged animals with running	Increased neurogenesis <sup>c</sup>	Improved learning and memory	van Praag et al., 2005		

<sup>&</sup>lt;sup>a</sup> See Supplemental References for complete listings.

conditioning task, which requires the hippocampus. Conversely, pretraining in delayed conditioning, which makes the subsequent trace conditioning independent of the hippocampus, renders trace conditioning ineffective in promoting the survival of newborn neurons (Leuner et al., 2006).

Moreover, it is learning and not simple training that elicits the survival effects. A correlation has been found between the survival of 7-day-old neurons and learning and memory performance of the individual rats despite the variable space effect during training (Sisti et al., 2007). Similarly, learning appears to promote the survival of newborn neurons only in cognitively unimpaired aged rats (Drapeau et al., 2007).

Furthermore, learning elicits different influences on neural precursors at different developmental stages. For instance, in contrast to the 7-day-old cells, the survival of 3-day-old newborn cells is inhibited by training in the Morris water maze through increased apoptosis. Interestingly, blocking apoptosis during the late phase of Morris water maze training led to impaired performance in rats, implicating a requirement for selective integration

of newborn neurons in spatial learning and memory. (Dupret et al., 2007).

Finally, different phases of learning have different impacts on SGZ neurogenesis. The early phase of training in the Morris water maze, during which rapid improvement of performance is achieved, has no effect on cell proliferation, whereas the late asymptotic phase increases cell proliferation and decreases the survival of new cells produced in the early phase (Dobrossy et al., 2003). This type of intricate regulation of SGZ neurogenesis by learning was also observed in the social transmission of the food preference paradigm, a natural form of associative learning dependent on the hippocampus (Olariu et al., 2005).

Thus the regulation of SGZ neurogenesis by hippocampusdependent learning is complicated and can be affected by factors such as the age of the newborn neurons, the stage of learning and specific learning protocols.

#### What Is the Role of SGZ Neurogenesis in Learning?

To investigate the function of adult hippocampal neurogenesis in learning and memory, several experimental methods have been

<sup>&</sup>lt;sup>b</sup> The relationship between stress and learning is complicated and is subjected to regulations by factors such as gender and task difficulty, etc. (Shors et al., 2004).

<sup>&</sup>lt;sup>c</sup> Hippocampal neurogenesis in aged rodents that are subjected to environmental enrichment or voluntary running is increased compared to sedentary aged controls.

developed to decrease or even ablate SGZ neurogenesis in adult animals. These include (1) low-dose irradiation of either whole brain or restricted brain regions (Santarelli et al., 2003; Snyder et al., 2005); (2) systemic treatment with antimitotic drugs, such as methylazoxymethanol acetate (MAM) (Shors et al., 2001); (3) using aging as a natural process to reduce neurogenesis (see above) and (4) using genetically engineered mice to specifically eliminate neural progenitors, such as the *GFAP-tk* mice in which the proliferating GFAP+ progenitors are susceptible to ganciclovir treatment (Saxe et al., 2006). Although none of these methods specifically targets adult progenitors, they begin to reveal a causal link between SGZ neurogenesis and cognition and suggest several potential roles for SGZ neurogenesis.

The function of neurogenesis in learning was first examined by Shors and colleagues (Shors et al., 2001) in MAM-treated rats that failed to form conditioned responses in trace eyeblink conditioning or trace fear conditioning but not contextual fear conditioning, which are all hippocampus-dependent tasks. Similarly, no defect in contextural fear conditioning was detected in tlx conditional knockout mice, in which hippocampal neurogenesis was greatly reduced (Zhang et al., 2008). In contrast, irradiated rats or mice and ganciclovir-treated GFAP-tk mice are defective in learning contextual fear conditioning tasks (Saxe et al., 2006; Winocur et al., 2006). Besides the different cell ablation methods and conditioning protocols used in these studies, only very young cells were targeted by the MAM treatment, whereas both young cells and mature newborn neurons were affected in the irradiated animals and GFAP-tk mice. Therefore, it is possible that immature and mature newborn neurons play different roles in learning, given their distinct electrophysiological properties.

The role of hippocampal neurogenesis in spatial learning and memory is rather elusive (reviewed by Leuner et al., 2006). X-ray irradiation of 2-month-old mice leads to impaired spatial learning and memory in the Barnes maze but not in the Morris water maze (Raber et al., 2004). In contrast, X-ray irradiation of 3-week-old mice leads to opposite observations: impaired spatial learning and memory in the Morris water maze but not in the Barnes maze (Rola et al., 2004). Furthermore, many other studies were not able to detect any defects in spatial learning in animals with reduced or abolished neurogenesis (Madsen et al., 2003; Meshi et al., 2006; Saxe et al., 2006; Shors et al., 2002; Snyder et al., 2005), despite the fact that impaired long-term retention of memories was observed in irradiated rats and in tlx mutant mice (Snyder et al., 2005; Zhang et al., 2008). Inducible deletion of tlx in adult mice also led to defective learning in the Morris water maze. Intriguingly, ablation of hippocampal neurogenesis even caused an improvement in hippocampus-dependent working memory in the eight-armed radial maze (Saxe et al., 2007), suggesting that adult-born neurons may have distinct roles in the formation of different types of memories.

Place and object recognition memories have also been examined in animals with ablated neurogenesis. Conducting the test in an enriched context, Winocur et al. (2006) reported that irradiated rats had defects in the delayed nonmatching-to-sample test when there was a long time interval between sample trials and test trials. However, defective object recognition memory was not detected in irradiated or MAM-treated rats in a simpler

context (Bruel-Jungerman et al., 2005; Madsen et al., 2003). Nevertheless, Madsen et al. (2003) observed a defect in place recognition shortly after irradiation. In addition, MAM treatment prevented the enhancement of object recognition memory by an enriched environment (Bruel-Jungerman et al., 2005).

Although these functional studies suggest some potential roles for SGZ neurogenesis in cognition, it is difficult to reach any definitive conclusions due to the controversial results. These discrepancies are probably due to differences in animal species and strains, the detailed behavioral procedures and the different knockdown strategies. More importantly, all the available strategies rely on global treatment of animals and may cause a variety of undesired side effects. Furthermore, all current studies have employed behavioral tasks based on lesion models where the whole hippocampus is affected. Given that new neurons in the SGZ constitute only a small part of the anatomical structure of the hippocampus, impaired behavior caused by a lack of neurogenesis will be easier to detect if the behavioral tests are aimed at challenging these new neurons. Therefore, to definitively demonstrate the functions of SGZ neurogenesis, selective ablation approaches with few side effects and specific behavioral tests need to be developed in the future.

# Functional Study of SGZ Neurogenesis by Computational Modeling

The role of hippocampal neurogenesis is also addressed by computational simulation, based on the computational modeling of hippocampal function. Most computational studies that model hippocampal function are based on its simplified trisynaptic excitatory circuit (dentate gyrus  $\rightarrow$  CA3  $\rightarrow$  CA1). It is proposed that the dentate gyrus performs pattern separation on inputs from the entorhinal cortex by sending orthogonal and sparse signals to the pyramidal neurons in hippocampal region CA3 via the mossy fiber projection. CA3 serves as a temporary storage site via its recurrent collaterals; CA1 recodes Schaffer collateral inputs from CA3 by competitive learning and plays a role in consolidation by setting up associatively learned backprojections to neocortex to facilitate recall. The pattern separation role of dentate gyrus has been recently demonstrated experimentally by either dentate gyrus-specific lesions or specific deletion of NMDA receptors in dentate gyrus (Gilbert et al., 2001; McHugh et al., 2007).

Several computational studies assumed that there was constant turnover of mature neurons in the dentate gyrus as a result of a balance between neurogenesis and apoptosis. Using a simple three-layered network, Deisseroth et al. (2004) and Chambers et al. (2004) found that neurogenesis elicited a more rapid clearance of old memory and enhanced the recall fidelity of new memories. Becker (2005) modeled neurogenesis in the dentate gyrus in a more complicated network system simulating the entire hippocampus and found that the constant neuron turnover through neurogenesis helps to create distinct memory traces for highly similar patterns. However, the turnover of mature neurons has not been convincingly demonstrated experimentally in the dentate gyrus. In addition, all of the above models do not distinguish the characteristics of immature neurons from that of mature ones. Wiskott et al. (2006) took the enhanced plasticity of immature neurons into consideration in their theory and proposed that neurogenesis helps the dentate gyrus to avoid catastrophic interference of old memories when adapting to new environments. However, the applicability of this model to the hippocampal system is unclear, as it did not take the sparse coding role of the dentate gyrus into consideration and used a small hidden layer to represent it. Alternatively, Aimone et al. (2006) suggested that adding plastic immature neurons into the dentate gyrus would hinder its function in pattern separation. They proposed that young neurons may facilitate the formation of temporal association in memory. Together, these computational studies suggest several potential functions of hippocampal neurogenesis and provide some theoretical guidance for future experimental work.

#### Implication of SGZ Neurogenesis in Mood Regulation

The potential role of SGZ neurogenesis in mood regulation was first suggested by Gould and colleagues (Gould et al., 1992), who showed that SGZ cell division is suppressed by corticosteroids, which is often elevated in human patients suffering major depression and in stressed animals (Table 1). Given that stress is thought to precipitate and exacerbate depression, the regulation of SGZ neurogenesis by stress has been extensively studied in a variety of species.

#### Stress Decreases SGZ Cell Proliferation

With only a few exceptions, numerous studies have demonstrated that a variety of chronic stressors cause reduction in cell proliferation in SGZ (Table S4; reviewed by Mirescu and Gould, 2006). In contrast, the effect of acute stress on SGZ cell proliferation depends on the specific type of stress as well as the sex of the animal. For example, acute foot shock but not acute restraint stress leads to the reduction of cell proliferation, and this change is only seen in male rats (references in Mirescu and Gould, 2006; Shors et al., 2007). "Controllability" is one of the factors that may influence the negative impact of stress on individuals. Using learned helplessness, a widely used rodent model for depression, Shors et al. (2007) reported that controllable stress causes less reduction in SGZ cell proliferation than uncontrollable stress in male rats. Although the effect of stress in adult animals is transient, stress in prenatal and postnatal animals exerts long-lasting effects (references in Mirescu and Gould, 2006). In contrast to cell proliferation, the regulation of cell survival by stress is less clear. In some cases, the total number of new neurons is not affected by stress, probably due to a compensatory effect on cell survival.

Elevation of corticosterone (glucocorticoid) levels by the activated hypothalamic-pituitary-adrenal axis is a main mechanism for stress-mediated suppression of SGZ cell proliferation. This finding is supported by two lines of evidence: first, corticosterone decreases cell proliferation whereas adrenalectomy increases SGZ neurogenesis, despite the fact that the level of corticosterone is not always inversely correlated with the level of SGZ proliferation; and second, the glucocorticoid level is increased by a variety of stress paradigms and adrenalectomy prevents the stress-induced suppression of SGZ cell proliferation (reviewed by Mirescu and Gould, 2006).

# **Antidepressants Increase SGZ Neurogenesis**

In contrast to stress, both physical and chronic chemical antidepressant treatments increase cell proliferation in SGZ (Table S4; reviewed by Warner-Schmidt and Duman, 2006). For example, chronic fluoxetine administration increases the proliferation of the type 2 hippocampal progenitors in mice (Encinas et al., 2006). In addition, chronic administration of fluoxetine or rolipram enhances the survival of newborn neurons. Acute treatment with 5-HT4 (serotonin) receptor agonists, which are putative antidepressants, also increases neurogenesis (Table 1). Furthermore, antidepressants are able to prevent or reverse the stress-induced decrease in neurogenesis (reviewed by Warner-Schmidt and Duman, 2006).

The effect of most chemical antidepressants is mediated through changes in serotonin and norepinephrine levels in the brain, consistent with the critical role of monoamines in affective disorders. With some exceptions, the level of serotonin in the brain is positively correlated with the level of SGZ neurogenesis, as observed by lesion/grafting of serotonergic neurons in raphe nuclei or by pharmacological manipulation of serotonin receptors (Table S4). In addition, a deficit in the 5-HT1A receptor prevents both neurogenic and behavioral effects of fluoxetine (Santarelli et al., 2003). Similarly, depletion of norepinephrine by a selective noradrenergic neurotoxin decreases SGZ cell proliferation. On the other hand, stimulating norepinephrine release in the hippocampus promotes SGZ neurogenesis by enhancing the survival of newborn neurons (Table S4).

BDNF is a key factor in mood regulation. The expression levels of BDNF and SGZ neurogenesis are coregulated by both stress and antidepressants (Duman and Monteggia, 2006). Infusion of BDNF into the dentate gyrus mimics the effect of antidepressants in several behavioral tests and increased neurogenesis. Moreover, antidepressant treatments failed to increase SGZ neurogenesis in mouse strains with compromised BDNF-TrkB signaling, suggesting that this pathway is required for neurogenesis induced by antidepressants.

BDNF also plays a role in regulating SGZ neurogenesis in the absence of antidepressants (see references in Duman and Monteggia, 2006). Conditions that induce BDNF expression, such as physical exercise, dietary restriction, and enriched environment, also increase SGZ neurogenesis. The survival of newborn cells is decreased in BDNF heterozygous mice (*BDNF*<sup>+/-</sup>) and transgenic mice that express a dominant negative form of the TrkB receptor to which BDNF binds. Moreover, an enriched environment fails to enhance the survival of newborn cells in *BDNF*<sup>+/-</sup> mice (Rossi et al., 2006). These findings suggest a role for BDNF signaling in enhancing the survival of newborn neurons. In contrast, the role of BDNF in SGZ cell proliferation is unclear.

The expression of VEGF and insulin-like growth factor 1 (IGF1) are also coregulated with SGZ neurogenesis by antidepressants (Warner-Schmidt and Duman, 2006, 2007). Infusion of VEGF stimulates SGZ cell proliferation and mimics the action of antidepressants in behavior paradigms such as novelty suppressed feeding, the forced swimming test, and learned helplessness, whereas inhibiting VEGF signaling blocks both neurogenic and behavioral effects of antidepressants. Similarly, infusion of IGF1 elicits anxiolytic and antidepressant-like effects in behavioral tests (Malberg et al., 2007), and systematic administration of IGF1 increases SGZ neurogenesis (see references in Duman and Monteggia, 2006). Therefore, VEGF and IGF1 are also molecular candidates for mediating both neurogenic and behavioral effects of antidepressants.

Table 2. The Influence of Hippocampal Neurogenesis on Antidepressant Effects						
Species	Strain	Antidepressant	Behavioral Tests	Effect	Reference <sup>a</sup>	
Mouse	129/SvEvTac	Fluoxetine	NSF	Prevent antidepressant effect	Santarelli et al., 2003	
Mouse	129/SvEvTac	Imipramine	NSF	Prevent antidepressant effect	Santarelli et al., 2003	
Mouse	129/SvEvTac	MCH1 antagonist	NSF	No effect	David et al., 2007	
Mouse	129/SvEvTac	Enriched environment	NSF	No effect	Meshi et al., 2006	
Mouse	BALB/c	Fluoxetine	CUS	Prevent antidepressant effect	Santarelli et al., 2003	
Mouse	BALB/cJ	Fluoxetine	FST	No effect	Hollick et al., 2007	
Mouse	BALB/cJ	Fluoxetine	NIH	No effect	Hollick et al., 2007	
Rat	Fisher 344	Fluoxetine	FST	Prevent antidepressant effect	Airan et al., 2007	
Rat	Long Evans	Cannabinoid agonist	NSF	Prevent antidepressant effect	Jiang et al., 2005	
Rat	Long Evans	Cannabinoid agonist	FST	Prevent antidepressant effect	Jiang et al., 2005	

In all studies, hippocampal neurogenesis was ablated by X-ray irradiation.

Abbreviations are as follows: NSF, novelty-suppressed feeding; CUS, chronic unpredictable stress; FST, forced swimming test; NIH, novelty-induced hypophagia.

The transcription factor cAMP-response element-binding protein (CREB) is an intracellular effector of monoamine, BDNF, and VEGF signaling pathways (reviewed in Warner-Schmidt and Duman, 2006). SGZ cell proliferation and survival are both subjected to regulation by cAMP. CREB is also implicated in regulating hippocampal neurogenesis, despite its elusive mechanism. Signaling through the GABAA receptors might be another link between mood and neurogenesis. Reducing the level of  $\gamma 2$  subunit of GABAA receptors in immature but not mature neurons leads to a reduction in SGZ neurogenesis and heightened anxiety in a series of behavior paradigms (Earnheart et al., 2007).

# Is SGZ Neurogenesis Necessary for Antidepressant Function?

The requirement of SGZ neurogenesis for the behavioral effects of antidepressants has been investigated using X-ray irradiation to abolish SGZ neurogenesis in rodent brains (Table 2). The importance of SGZ neurogenesis for the effectiveness of antidepressants was first demonstrated by Santarelli and colleagues, who showed that X-ray irradiation prevents the behavioral effects of fluoxetine and imipramine in behavior paradigms such as novelty-suppressed feeding and chronic unpredictable stress (Santarelli et al., 2003). Similarly, the antidepressant effect of cannabinoids is blocked by irradiation. The dependence of behavioral effects of antidepressants on neurogenesis is influenced by factors such as species, the genetic background of animals, the nature of antidepressants, and the type of behavioral paradigms (Table 2). For instance, the essential role of SGZ neurogenesis for fluoxetine function was found in Fisher 344 rats and 129/SvEvTac mice but not in BALB/cJ mice. In fact, using several inbred mouse strains, a recent report has demonstrated that the behavioral effects and increased SGZ cell proliferation in response to fluoxetine are dependent on the genetic composition of the mice (Miller et al., 2007). Unlike fluoxetine, the antidepressant-like effects of a melanin-concentrating hormone receptor antagonist are independent of SGZ neurogenesis. In BALB/cJ mice, the behavioral effect of fluoxetine is dependent on SGZ neurogenesis in chronic unpredictable stress but not in the forced swimming test or in novelty-induced hypophagia. In addition, the antidepressant-like effect of the enriched environment in one study was found to be independent of SGZ neurogenesis. Thus, different antidepressants may act through different mechanisms and SGZ neurogenesis may be one of the many substrates of certain antidepressants. The apparently conflicting observations may also result from the choice of behavioral tests.

Despite all the progress in the field, it remains unclear whether impaired SGZ neurogenesis is an etiological factor for depression. In fact, SGZ neurogenesis and depressed-like behavior are not well correlated in at least two rodent models of depression, learned helplessness and chronic mild stress (references in Warner-Schmidt and Duman, 2006) (Table S4). Moreover, ablating neurogenesis does not affect the anxiety-related or depressed-like behavior in a battery of tests of anxiety and depression (Santarelli et al., 2003; Saxe et al., 2006). Thus, it is unclear whether SGZ neurogenesis plays a role in baseline anxiety in rodents. Finally, despite the fact that hippocampus atrophy is often detected in depressed patients, whether and to what extent the reduction in SGZ neurogenesis contributes to this atrophy has not been directly investigated. Therefore, further studies are needed to test whether impaired SGZ neurogenesis is a pivotal component for the pathophysiology of depression.

#### **Adult Neurogenesis and CNS Disorders**

Neurogenesis also occurs in human brains in the SGZ and possibly the SVZ (Curtis et al., 2007; Eriksson et al., 1998; Sanai et al., 2004). Unlike rodents and nonhuman primates, in which neurogenesis in adult cortex is under debate, studies in humans did not reveal any evidence for the occurrence of neurogenesis in adult human cortex. This finding is supported by several independent approaches, including the BrdU method and a cell birth-dating method based on the level of <sup>14</sup>C in the genomic DNA of individual cortical neurons (Eriksson et al., 1998;

<sup>&</sup>lt;sup>a</sup> See Supplemental References for complete listings.

Spalding et al., 2005). In addition, a magnetic resonance spectroscopy-based strategy has been developed to monitor the number of neural progenitors in live animals and humans, confirming the presence of cell proliferation in the hippocampus and its absence in the cortex (Manganas et al., 2007). Together with other in vivo imaging methods aimed at adult neurogenesis (Pereira et al., 2007), this finding facilitates the examination of adult neurogenesis in humans under various physiological and pathological conditions. These technical advances will no doubt contribute to the further understanding of the basic biology and therapeutic potential of adult neurogenesis in human CNS diseases. Next, we discuss the effects of pathological conditions on adult neurogenesis in both rodent models and human patients.

#### **Epilepsy**

Seizure activity increases proliferation in both SVZ and SGZ, but most studies focus on examining the SGZ because epilepsy causes cognitive defects (reviewed by Jessberger and Parent, 2007). Neurogenesis in the SGZ can be elevated for up to 5 weeks after seizure but eventually declines to the basal or even a lower level. Seizure induces the proliferation of both progenitors and neuroblasts, which is unlikely to be a compensatory effect in response to neuronal death. Seizure causes abnormal morphogenesis in newborn neurons, such as hilar basal dendrite formation and ectopic hilar migration of newborn neurons. Seizure activity also leads to mossy fiber sprouting of neurons born prior to seizure activity (Jessberger et al., 2007; Walter et al., 2007).

Seizure-induced new neurons functionally integrate into the hippocampal circuitry despite their abnormal connectivity. Interestingly, the antiepileptic drug VPA can inhibit seizure-induced neurogenesis and also protect rats from seizure-associated deficiency in a hippocampus-dependent learning task. However, the level of SGZ neurogenesis does not always correlate with susceptibility to developing epilepsy. The role of seizure-associated aberrant neurogenesis in epilepsy is yet to be determined.

#### Stroke

Neurogenesis in both the hippocampus and SVZ is enhanced in models of focal and global ischemia in rodents (reviewed by Lindvall and Kokaia, 2007). After ischemic stroke, newborn cells in the SVZ are able to migrate to the site of injury, which is guided by blood vessels. These cells express markers of the resident neurons. The recruitment of newborn neurons to the infarct site may also happen in human stroke patients. It is not clear whether or for how long these new neurons survive or the extent to which they integrate into the existing circuitry.

#### **Neurodegenerative Diseases**

Conflicting observations have been reported regarding the level of neurogenesis in models of Alzheimer's disease (Verret et al., 2007 and the references therein). Although most mouse models based on mutations in the amyloid precursor protein (APP) exhibit decreased neurogenesis, transgenic mice with different presenilin mutations have either increased or decreased neurogenesis. The wild-type presenilin and the soluble form of APP have both been implicated in the function of adult neurogenesis (Table S3 and Table 1), but the deregulated signaling of APP and presenilin may only contribute partially to the changes in adult neurogenesis in Alzheimer's disease.

Mouse models of Parkinson's disease have been generated by overexpressing the wild-type or mutant forms of human  $\alpha$ -synuclein, which accumulates in neurodegenerative diseases including Parkinson's disease, dementia with Lewy bodies and multiple system atrophy. Overexpression of wild-type human  $\alpha$ -synuclein significantly decreases the survival of newborn neurons in both SGZ and SVZ, without affecting cell proliferation, whereas expression of mutant  $\alpha$ -synuclein primarily inhibited cell proliferation in the SVZ (Winner et al., 2007).

Cell proliferation is increased in the SGZ of postmortem Alzheimer's patients, decreased in the SGZ and SVZ of Parkinson's patients, and increased in the SVZ of Huntington's patients. The change in adult neurogenesis resulting from neurodegenerative diseases is likely to be caused by selective death of certain neurons and inflammation in diseased brains. Therefore, the proposed contribution of neurogenesis to the pathology of these diseases needs further clarification.

#### **Inflammation and Other Immune Responses**

Although inflammation is not strictly a CNS disorder; it is frequently associated with brain injury, neurodegenerative diseases, and radiation treatment for brain tumors, which often causes deficits in cognition. Adult neurogenesis is also downregulated by endotoxin-induced inflammation and can be restored by anti-inflammatory treatments (Ekdahl et al., 2003; Monje et al., 2003). In addition, blocking inflammation partially rescues adult neurogenesis in irradiated animals. The cytokine interleukin-6 may mediate the inhibitory effect of endotoxin-activated microglia (Table S3). Interestingly, microglia exposed to certain cytokines enhance neurogenesis of adult neural progenitor cells, suggesting that inflammatory responses under different pathological conditions may have distinct effects on adult neurogenesis (Butovsky et al., 2006). Reactive astrogliosis is another injuryinduced reaction in the brain that has a negative impact on adult neurogenesis.

Several recent studies have used genetic tools to examine the regulation of adult neurogenesis by the immune system, including cytokine signaling, the complement system, and Toll-like receptor-mediated innate immunity (Table S3). These studies provide the first molecular mechanisms that might link immune responses with neurogenesis and suggest that adult neurogenesis may be differentially regulated by different mechanisms of the immune response.

Adult neurogenesis is also influenced by many other pathological conditions, including HIV infection and drug addiction. It is becoming increasingly clear that adult neurogenesis readily responds to and is correlated with brain pathology, implicating endogenous neural progenitors in the repair of damaged brain tissue. In addition to the therapeutic potential of neural progenitors in CNS disorders, NSCs provide the opportunity to learn more about brain tumor formation as brain tumor cells share certain key characteristics with NSCs. An emerging concept in cancer biology is that tumors contain a small population of cancer stem cells that may be relatively quiescent and hence are able to escape the antimitotic effects of cancer therapies. NSCs (type B cells) in the adult SVZ are able to survive antimitotic treatments (Doetsch et al., 1999), and certain types of brain tumors may arise from NSCs (reviewed by Oliver and Wechsler-Reya, 2004). Understanding the biology of NSCs thus may help to develop more efficient therapeutics for treating brain tumors.

#### **Concluding Remarks**

The past decade has witnessed remarkable progress in research on adult neurogenesis. Several principles have emerged from these studies. (1) Neurogenesis appears to be conserved across all mammalian species. (2) The process of neurogenesis from cell birth to functional integration is readily influenced by external factors. (3) Despite occurring in different macro- and microenvironments, adult neurogenesis shares similar mechanisms with embryonic or postnatal neurogenesis. For example, many trophic factors play similar roles in the regulation of embryonic and adult neurogenesis. (4) Distinct developmental origins lead to the production of different types of adult-born neurons through SVZ and SGZ neurogenesis. As a result, the detailed mechanisms of SVZ and SGZ neurogenesis are quite different, even though they share some common regulators. Moreover, adult-born neurons from the SVZ and SGZ integrate into disparate functional circuits in the brain, which are subjected to differential regulation by the experiences of the animal. (5) Despite the differences between SVZ and SGZ neurogenesis, the activities of immature newborn neurons from both origins are critical for their survival, maturation, and subsequent integration into the existing neural circuits. (6) Although the exact nature of their contribution to adult brain function remains unknown, these newborn neurons are certainly playing some role in behavior.

Nevertheless, key issues remain to be addressed. Currently, the term "neural stem cells" is mainly used to refer to the properties of self-renewal and multipotentiality in tissue culture: whether these cells exist in vivo and how to identify them and to prospectively isolate them are challenges for future investigations. Regarding the niche hypothesis, it remains unknown what the cellular and molecular components of the niche are and how they interact with the putative NSCs. Moreover, our understanding is still limited in terms of the molecular mechanisms underlying cell proliferation, differentiation, survival, maturation and integration during adult neurogenesis. Despite efforts to analyze the function of hippocampal neurogenesis, the precise role it plays in cognitive or emotional behaviors is still unclear. Less research has been published on the functional significance of olfactory neurogenesis, though consistent changes in olfactory behavior have been reported following reduction of neurogenesis. Decoding the functional role of neurogenesis will not only provide us with fundamental knowledge about the olfactory and hippocampal systems but will also help us to develop new treatments for neurological diseases in humans.

#### SUPPLEMENTAL DATA

Supplemental Data include four tables and Supplemental References and can be found with this article online at http://www.cell.com/cgi/content/full/132/4/ 645/DC1/.

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**Supplemental Data** 

**Mechanisms and Functional Implications** 

of Adult Neurogenesis

Chunmei Zhao, Wei Deng, and Fred H Gage

Table S1. Methods in adult neurogenesis research

Method	Examples	Target cells	Applications	Advantages	Disadvantages
nucleic acid analogues	BrdU, 3H-Thymidine	dividing cells and their progeny	proliferation and survival	systemic, quantification,	do not reveal cell morphology, difficult to
				phenotyping of newborn cells	phenotype newborn cells (3H-thymidine),
				(BrdU), sensitive (3H-Thymidine)	dilution effect (BrdU)
retrovirus		dividing cells and their progeny	morphology and physiology	visualization, fixed or live	invasive, not ideal for cell number
				specimen, target individual cells,	quantification
				functional study of single cells	
cell proliferation markers	Ki67, MCM2, PCNA, pH3	dividing cells	proliferation	no side effects	snapshot at the time of sample processing
markers for progenitors	nestin, Sox2, GFAP, LeX	putative progenitors	properties of progenitors	specific for progenitors	target heterogeneous populations of cells,
		· · · · ·			snapshot
markers for immature neurons	PSA-NCAM, DCX,	immature neurons	overall neurogenesis	no side effects	target heterogeneous populations of cells
	Calretinin				(PSA-NCAM, DCX), snapshot
transgenic mouse	nestin-GFP, Sox2-GFP,	progenitor cells or immature neurons	property of specific cell types	no side effects	target heterogeneous populations of cells,
	GFAP-GFP, POMC-GFP				snapshot
in vivo imaging	Two-photon imaging,	neurons in the OB	turnover of neurons in the OB		do not reveal cellular property
	Magnetic Resonance	progenitor cells	number of progenitor cells	no side effects	
	Spectroscopy				

See Manganas et al., 2007, Mizrahi et al., 2006 and Pereira et al., 2007 for in vivo imaging, and Gage et al., 2007 for other methods . See supplementary material for the complete list of references.

Table S2. Extrinsic afferents to the dentate gyrus

Neurotransmitters or neural peptides	anatomical source	target area in DG
Acetylcholine	Septum	hilus and mol
Cholesystokinin	Entorhinal cortex	mol
Enkephalin	Entorhinal cortex	mol
Dopamine	Ventral tegmental area	hilus, GCL and mol
Gamma aminobutyric acid (GABA)	Septum	hilus
Glutamate	Entorhinal cortex	hilus, GCL and mol
Norepinephrine	Locus coeruleus	hilus
Serotonin	Median raphe nucleus	hilus
Substance P	Supreamammillary region	inner third of mol

The information in this table is mainly based on the review article by Freund and Buzsaki, 1996. mol: molecular layer; GCL, granule cell layer.

Table S3: The regulation of adult	NSCs/neural pr	ogenitors				
Factors and pathways	Proliferation	Differentiation	Survival	Neurogenesis	Other functions	References
Extrinsic factors						
Growth factors & neurotrophins	S					
Amphiregulin	+		. (007)			Falk and Frisen, 2002
BDNF	+ (SVZ)		+ (SGZ)	+		Henry et al., 2007; Sairanen et al., 2005; Scharfman et al., 2005; Young et al., 2007
EGF	+				maintenance of NSCs	Doetsch et al., 2002; Ghashghaei et al., 2007; Kuhn et
						al., 1997; Raynolds and Weiss, 1992
FGF2	+				maintenance of NSCs	Jin et al., 2003; Palmer et al., 1995; Zhao et al., 2007
NGF	. (aging brain)	+ (oligodendrocyte)	+	+		Frielingsdorf et al., 2007 Hsieh et al., 2004a; Lichtenwalner et al., 2001
IGF-1 PDGF	+ (aging brain)	+ (oligodendrocyte) + (astrocyte)				Jackson et al., 2006
PEDF	+	· (doi:00)10)				Ramirez-Castillejo et al., 2006
$TGF\alpha$	+					Cameron et al. 1998
TGFβ				+		Battista et al., 2006
VEGF	+	+ (neuron)		+		Cao et al., 2004; Fabel et al., 2003; Jin et al., 2002
Morphogens BMP		+ (astrocyte)				Nakashima et al., 1999; Yanagisawa et al., 2001
Neurogenesin-1		+ (neuron)				Ueki et al., 2003
Noggin		+ (neuron)		+		Lim et al., 2000
Shh	+					Ahn and Joyner 2005; Banerjee et al., 2005; Lai et al.,
M/mt2						2003; Machold et al., 2003; Palma et al., 2005
Wnt3 Cytokines	+			+		Lie et al., 2005
CNTF				+	self-renewal of adult NSCs	Chojnacki et al., 2003; Emsley and Hagg 2003;
						Shimazaki et al., 2001
G-CSF		+ (neuron)				Schneider et al., 2005
IFN <sub>γ</sub>				+		Wong et al., 2004
IL-6 LIF	-	. (aatraauta)		-		Vallieres et al., 2002 Nakashima et al., 1999
TNFα		+ (astrocyte)			+ (cell death)	Wong et al., 2004
Neurotransmitters					(con death)	Trong of all, 2004
Acetylchoine			+			Kotani et al., 2006; Harist et al., 2004; Mechawar et al.,
						2004; Mohapel et al., 2005
Dopamine	+ or -					Coronas et al., 2004; Hoglinger et al., 2004; Kippin et al.,
GABA					differentiation of type 2 cells in SGZ	2005a; van Kampen et al., 2004 Tozuka et al., 2005
Glutamate	+ or -				uneremation of type 2 cens in 332	Cameron et al., 1995; Deisseroth et al., 2004; Gould et
- Cratamate						al., 1997; Nacher et al., 2001
Nitric oxide	+ or -					Cheng et al., 2003; Moreno-Lopez et al., 2004; Packer et
						al., 2003; Reif et al., 2004; Zhang et al., 2001; Zhu et al.,
Noroninophrino						2003; etc
Norepinephrine Serotonin						see table 5 see table 5
Hormones						ood table o
Corticosterone	-			-		Cameron et al., 1994
Estrogen				+ or no effect		Lagace et al., 2007; Tanapat et al., 1999
Male pheromone				+		Mak et al., 2007
Nandrolone <i>Drug</i> s	-					Brannvall et al., 2005
Nicotine	-			_		Abrous et al., 2002
Opiate	-			-		Eisch et al., 2000; kahn et al., 2005
Other extrinsic factors						
Ccg	+			+		Taupin et al., 2000
Complement factor C3a				(+)		Rahpeymai et al., 2006
Docosahexaenoic acid (DHA Galectin	,			+		Kawakita et al., 2006 Ishibashi et al., 2007
PACAP	+					Mercer et al., 2007
sAPP	+					Caille et al., 2004
Intracellular pathways						
Receptors						
Smoothened	(+)			(+)		Balordi and Fishell, 2007
TNF-R1	(-)			(-)		losif et al., 2006
Toll-like receptor 2				(+)		Rolls et al., 2007
Toll-like receptor 4  Transcription factors	(-)	(-) (neuron)				Rolls et al., 2007
Bmi-1					maintenance of adult NSCs	Molofsky et al., 2005
NeuroD					formation of DG	Liu et al., 2000
Olig2		+ (oligodendrocyte)				Hack et al., 2005
Pax6		+ (neuron)				Hack et al., 2005
TLX					maintenance of adult NSCs	Shi et al., 2004; Sun et al., 2007
Epigenetic regulations MBD1		(+) (neuron)			genome stability	Zhao et al., 2003
Histone deacetylase	+ (with TLX)	- (neuron)			genome stability	Hsieh et al., 2004b; Sun et al., 2007
Cell cycle regulation	(	()				
P16INK4a	(-)					Molofsky et al., 2006
p21	(-)					Kippin et al., 2005b
p53	(-)					Gil-Perotin et al., 2006
Other intracellular pathways NRSE dsRNA		+ (neuron)				Kuwabara et al., 2004
Retrotransposition		· (ilculoii)				Muotri et al., 2005
Tolomoro	(.)					Former et al. 2004

This table is a partial list of the factors that have been reported to regulate adult NSCs. The precise roles of these factors need to be further investigated. Because of the heterogeneous nature of the current culturing methods to maintain NSCs in vitro and the lack of definitive markers to identify NSCs in vivo, the target cells of these factors are mostly unclear. (-): enhanced by loss of the gene; (+): decreased or inhibited by loss of the gene. See supplementary material for the complete list of references.

Table S4. Regulation of SGZ neurogenesis by stress and antidepressants

Treatment	Effect	Species	References
Stress			
psychosocial/subordination	Decreased proliferation	Rat, Tree Shrews	Gould et al., 1997; Van der Hart et al., 2002; Czeh et al., 2001; 2002; Yap et al., 2006
psychosocial/resident-intruder	Decreased proliferation	Mouse, Marmoset monkey	Gould et al., 1998
predator odor	Decreased proliferation	Rat	Tanapat et al., 2001
isolation	Decreased proliferation	Mouse	Dong et al., 2004
sleep deprivation	Decreased proliferation	Rat	Mirescu et al., 2006
sleep deprivation	Decreased proliferation	Rat	Roman et al., 2005
sleep deprivation	No effect on survival	Rat	Roman et al., 2005
restraint	Decreased proliferation	Rat	Pham et al., 2003
restraint	Increased proliferaion	Mouse	Bain et al., 2004
foot shock	Decreased proliferation	Rat	Malberg and Duman, 2003;
			Vollmayr et al., 2003
cold immobulization	Decreased proliferation	Rat	Heine et al., 2004
chronicle mild stress (CMS)	Decreased proliferation	Mouse	Alonso et al., 2004
chronicle mild stress (CMS)	Decreased survival	Rat	Lee et al., 2006
chronicle mild stress (CMS)	No effect on proliferation	Rat	Airan et al., 2007
chronicle mild stress (CMS)	No effect on survival	Rat	Airan et al., 2007
prenatal stress	Decreased proliferation	Rat, Rhesus	Lemaire et al., 2000; Coe et al., 2003
postnatal stress	Decreased proliferation	Rat	Tanapat et al., 1998
corticosterone (CORT)	Decreased proliferation	Rat	Gould et al., 1992; Cameron et al., 1998
corticosterone (CORT)	Decreased survival	Rat	Wong and Herbert, 2004
adrenalectomy	Increased proliferaion	Rat	Cameron and McKay, 1999
adrenalectomy	Increased survival	Rat	Wong and Herbert, 2004
acrematectomy	ilicieaseu suivivai	Nai	World and Heibert, 2004
Anti-depressants	Increased preliferation	Pat Mouse	Malberg et al., 2000; Manev et al., 2001
Fluoxetine (SSRI)	Increased proliferation	Rat, Mouse	0 , , ,
Fluoxetine (SSRI)	Increased survival	Rat	Nakagawa et al., 2002a
Imipramine (TCA)	Increased proliferation	Rat	Santarelli et al., 2003
Tranylcypromine (MAOI)	Increased proliferation	Rat	Malberg et al., 2000
Reboxetine (NRI)	Increased proliferation	Rat	Malberg et al., 2000
Rolipram	Increased proliferation and survival	Rat	Nakagawa et al., 2002a; 2002b
Electroconvulsive therapy	Increased proliferation	Rat	Malberg et al., 2000; Madsen et al., 2000
Voluntary exercise	Increased proliferation	Mouse	van Praag et al., 1999
Enriched environment	Increased proliferation	Rat	Leal-Galicia et al., 2007
Estrogen	Increased proliferation	Rat	Tanapat et al., 1999
Estrogen	No effect	Mouse	Legace et al., 2007
VGF	Increased proliferation	Rat	Thakker-Varia et al., 2007
DHEA	Increased proliferation	Rat	Karishma and Herbert, 2002
Monoamines			
Serotonin:			
Raphie nuclei lesion	Decreased proliferation	Rat	Brezun and Daszuta, 1999
Fetal raphie nuclei graphing	Increased proliferation	Rat	Brezun and Daszuta, 2000
Fetal raphie nuclei graphing	Reversed effect of lesion	Rat	Brezun and Daszuta, 2000
PCPA (inhibitors for serotonin synthesis)	Decreased proliferation	Rat	Brezun and Daszuta, 1999
PCPA (inhibitors for serotonin synthesis)	No effect on proliferation	Mouse	Gur et al., 2007
5-HT1A receptor agonist	Increased proliferation	Rat, Mouse	Santarelli et al., 2003; Banasr et al., 2004
5-HT1A receptor agonist	Reversed effect of PCPA	Rat	Banasr et al., 2004
5-HT1A receptor antagonist	Decreased proliferation	Rat	Radley and Jacobs, 2002
5-HT1A receptor antagonist	No effect	Rat	Huang and Herbert, 2006
5-HT1B receptor agonist	Reversed effect of PCPA	Rat	Banasr et al., 2004
5-HT1B/1D receptor antagonist	No effect	Rat	Banasr et al., 2004
5-HT2A/2C receptor agonist	No effect	Rat	Banasr et al., 2004
5-HT2A/2C receptor antagonist	Decreased proliferation	Rat	Banasr et al., 2004
5-HT2C receptor agonist	No effect	Rat	Banasr et al., 2004
5-HT2C receptor antagonist	No effect	Rat	Banasr et al., 2004
5HT4 receptor agonist	Increased neurogenesis	Mouse	Lucas et al., 2007
Norepinepherin:	· ·		
selective noradrenogic neurotoxin	Decreased proliferation	Rat	Kulkarni et al., 2002
α2-adrenoceptor antagonist	Increased survival	Rat	Rizk et al., 2006
Anti-depressants blockade of stress effects			
Clorimipramine (TCA)	Blocked subordination	Tree shrews	Van der Hart et al., 2002
Tianeptine	Blocked subordination	Tree shrews	Czeh et al., 2001
NK1R antagonist	Blocked subordination	Tree shrews	Van der Hart et al., 2002
AVP1b antagonist	Blocked CMS	Mouse	Alonso et al., 2004
CRF-R1 antagonist	Blocked CMS	Mouse	Alonso et al., 2004
Fluoxetine	Blocked CMS	Mouse	Alonso et al., 2004
Fluoxetine	Blocked inescapable shock	Rat	Malberg and Duman, 2003
Fluoxetine	Blocked maternal separation	Rat	Lee et al., 2001
Curcumin	Blocked CMS	Rat	Xu et al., 2007
ECS	Blocked CORT treatment	Rat	Hellsten et al., 2002
L00	DIOUNEU OON I HEALIIEIK	nui	riolistati et al., 2002

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