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Review

The role of adult neurogenesis in psychiatric and cognitive disorders

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ABSTRACT

Neurogenesis in mammals occurs throughout life in two brain regions: the ventricular–subventricular zone (V–SVZ) and the subgranular zone (SGZ) of the hippocampal dentate gyrus. Development and regulation of the V–SVZ and SGZ is unique to each brain region, but with several similar characteristics. Alterations to the production of new neurons in neurogenic regions have been linked to psychiatric and neurodegenerative disorders. Decline in neurogenesis in the SGZ correlates with affective and psychiatric disorders, and can be reversed by antidepressant and antipsychotic drugs. Likewise, neurogenesis in the V–SVZ can also be enhanced by antidepressant drugs. The regulation of neurogenesis by neurotransmitters, particularly monoamines, in both regions suggests that aberrant neurotransmitter signaling observed in psychiatric disease may play a role in the pathology of these mental health disorders. Similarly, the cognitive deficits that accompany neurodegenerative disease may also be exacerbated by decreased neurogenesis. This review explores the regulation and function of neural stem cells in rodents and humans, and the involvement of factors that contribute to psychiatric and cognitive deficits.

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1. Introduction

Neurogenesis is the process of producing new neurons from neural stem cells (NSCs). In most brain regions, this process is restricted to a limited period during development, and ends shortly after birth (Gotz and Huttner, 2005; Ming and Song, 2011; Taverna et al., 2014). However, neurogenesis is observed well into the postnatal period and throughout adulthood primarily in two discrete brain regions: the subgranular zone (SGZ) of the dentate gyrus and the ventricular–subventricular zone (V–SVZ), which lines the lateral wall of the lateral ventricles. The process of neurogenesis has been linked behaviorally and biochemically to psychiatric disorders such as major depression, schizophrenia, and

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cognitive dysfunction. The neurogenic cells of the hippocampus are commonly linked to psychiatric disorders, and neurogenesis is thought to be required for a therapeutic response to antidepressant treatment. However, neural stem cells in the V–SVZ have also displayed changes in function and number in psychiatric disease, age, and with increased stress levels, which are often a precipitating factor in the onset of psychiatric disorders. NSCs have been shown to respond to treatment with antidepressant and atypical antipsychotic drugs, which can rescue diminished neurogenesis. The functional implications of decreased neurogenesis in psychiatric disease, as well as the therapeutic implications of rescuing neurogenesis with interventions, remain unclear. The emerging links between neurogenesis and mental health disorders support the idea that neurogenic therapies may one day enhance less effective treatments for patients suffering from major depression, schizophrenia, cognitive decline, and neurodegeneration. Here, we provide an overview of neurogenesis in the SGZ and V–SVZ, and explore the current literature on the relationship between psychiatric disorders, therapeutics, and adult neurogenesis.

2. Neural stem cell developmental origins and lineage

Much of our understanding of adult NSC biology has come from studies in rodents, which have shown that NSCs in the SGZ and the V–SVZ share many similarities but are two distinct populations of cells that differ significantly in their development, organization, and function. NSCs from both the V–SVZ and SGZ are astrocyte-like cells with morphological similarity to mature glia, express molecular markers common to astrocytes, including glial fibrillary acidic protein (GFAP) and are mostly quiescent (Alvarez-Buylla et al., 2001; Laywell et al., 2000; Merkle et al., 2004; Noctor et al., 2002). In the V–SVZ, these NSCs are referred to as type B cells that, upon activation, upregulate epidermal growth factor receptor (EGFR) and the progenitor marker Nestin and divide to give rise to type C transit amplifying cells which in turn give rise to type A neuroblasts. Neuroblasts then exit the V–SVZ and undergo extensive migration through the rostral migratory stream to arrive at the olfactory bulb, where they mature into GABAeric interneurons, many of which also express dopamine (Alvarez-Buylla et al., 2001; Doetsch and Alvarez-Buylla, 1996; Doetsch et al., 1997; Ming and Song, 2011). The spatial organization of these newborn neurons in the olfactory bulb is dependent upon the location of their origin in the V–SVZ, and NSCs originating from different V–SVZ microdomains produce interneuron populations with distinct molecular markers in the olfactory bulb (Merkle et al., 2014). NSCs also give rise to oligodendrocytes and astrocytes (Doetsch et al., 2002; Lois and Alvarez-Buylla, 1993; McKay, 1997; Merkle et al., 2004) however the lineage for these cells is less clear. NSCs are tightly regulated by the niche which in the V–SVZ is bordered on one side by ciliated ependymal cells lining the lateral ventricle and on the striatal side by a vast vascular plexus. Type B NSCs span these two compartments sending an apical process through the ependymal layer into the lateral ventricle and a basal process contacting blood vessels which allows NSCs to receive molecular signals from cerebrospinal fluid (Kokovay et al., 2012; Sawamoto et al., 2006), ependymal cells (Lim et al., 2000) and the vasculature (Delgado et al., 2014; Kokovay et al., 2010; Shen et al., 2008; Tavazoie et al., 2008). In addition to type B NSCs, microglia, niche astrocytes, type C, and type A cells are closely assembled in the V–SVZ niche between the vasculature and ependymal layer.

In the hippocampus, type 1 NSCs are mostly quiescent, with their cell bodies in the SGZ and processes extending through the granular cell layer, and a tangential process extending through the border of the hilus and the granular cell layer similar to radial glia (Seri et al., 2004). Two sex determining region Y-box 2 (Sox-2)+ populations of progenitor cells are present in the hippocampus: a quiescent radial glia-like subpopulation expressing GFAP, nestin, and brain-lipid binding protein (BLBP), and a non-radial glia-like subpopulation that is more proliferative and lacks the markers associated with radial glia (Suh et al., 2007). Once activated, NSCs divide asymmetrically, giving rise to a type 2 daughter cell. type 2 cells are amplifying neural progenitor cells that lack the GFAP expression of the type 1 mother cell, but retain expression of Nestin (Encinas et al., 2006; Filippov et al., 2003; Kempermann et al., 2004). These progenitor cells proliferate in close association with astrocytes and the vasculature in the SGZ (Ashton et al., 2012; Palmer et al., 2000). Type 2 cells continue to divide on average 2.3 times before maturing into doublecortin-positive type 3 neuroblasts (Encinas et al., 2011). Neuroblasts mature into granule cells after migrating a short distance into the granular layer of the dentate gyrus. In the granule cell layer, neuroblasts fully mature into glutamatergic granule neurons and receive glutamatergic and GABAergic innervation from the entorhinal cortex while sending outputs to the CA3 pyramidal cell layer through the mossy fiber pathway (Ming and Song, 2011; van Praag et al., 2002; Zhao et al., 2006).

Lineage tracing studies have revealed that V–SVZ NSCs are derived during development from striatal radial glia. The labeled radial glia in murine neonates were observed to give rise to neurons, oligodendrocytes, and astrocytes in the V–SVZ. Lineage tracing also identified radial glia to be the origin of type B and type C cells in the adult, thus establishing striatal radial glia as the neonatal origin of V–SVZ NSCs (Merkle et al., 2004). In contrast, the origin of NSCs in the SGZ is a population of Hedgehog-responsive cells from embryonic day 15.5–17.5 in the ventral hippocampus which migrate to the ventral and dorsal DG and are established in this region by postnatal day 15 (Li et al., 2013). Descendants derived from these hedgehog-responsive cells maintain their NSC characteristics and contribute to neurogenesis in the adult. Embryonic neurogenesis and development are functionally distinct from adult hippocampal neurogenesis. Adult hippocampal neurogenesis is thought to be activity-dependent, and is established during adolescence in the rodent brain prior to sexual maturity (Nicola et al., 2015). The timing of onset for adult neurogenesis markers in the rodent hippocampus correlates with the time when activity- and experience- dependent neurogenesis becomes critical for learning, memory, and affective- related development.

3. Factors regulating neurogenesis

NSCs are highly responsive to environmental molecular cues, which help in the establishment of the niche in embryos/neonates while maintaining the neurogenic functions of the niche in the adult. The vasculature is a major regulator of NSC proliferation, migration, and differentiation. Elegant studies using an in vitro model established that secreted factors from the vasculature increase NSC self-renewal and neuron production (Shen et al., 2004). Furthermore, 3-dimensional mapping of the V–SVZ niche showed that proliferating type B and type C cells are preferentially associated with the vasculature (Shen et al., 2008; Tavazoie et al., 2008). How this association is maintained is not clear, however, disruption of integrin-α6 results in aberrant proliferation (Shen et al., 2008), suggesting that laminin–integrin interaction is required. We previously demonstrated that vascular secretion of the chemokine stromal derived factor-1 (SDF-1) is required for neurosphere-expanded NSCs to home to the vasculature. This experiment utilized transplantation of adult-derived V–SVZ NSCs transduced with shRNA against the SDF-1 chemokine receptor CXCR4 into naïve adult V–SVZ (Kokovay et al., 2010). The results of this study suggest SDF-1 may play a role as a chemoattractant to

endogenous stem cells as well. Endothelial cells have also been shown to secrete neurotrophin-3 (NT-3), which upon uptake by NSCs, induces the phosphorylation of endothelial nitric oxide synthase (eNOS) and thus increases nitric oxide (NO) production within B cells. NO reduces the cycling of B cells, therefore regulating NSC proliferation and quiescence (Delgado et al., 2014). CSF and ependymal cells have also been implicated in NSC function. Movement of CSF directs migration of neuroblasts (Sawamoto et al., 2006). Ependymal cell secretion of noggin inhibits bone morphogenic protein (BMP) signaling in type B cells, preventing glial differentiation and allowing production of type C cells (Lim et al., 2000), although others have found that noggin blocks neurogenesis while promoting oligodendrogliogenesis (Colak et al., 2008). It should be noted that these discrepant results may be due to differences in methodology, as Lim and co-workers utilized an in vitro model for noggin antagonism of BMPs while Colak et al directly tested exogenous noggin in vivo. We have shown that the close association between type B cells and ependymal cells requires the adhesion molecule vascular cell adhesion molecule 1 (VCAM1), which is expressed on the apical process of type B cells anchoring NSCs to the ependymal layer and allowing signaling between cerebrospinal fluid (CSF) and type B cell processes. Blockade of VCAM1 results in aberrant proliferation and eventual depletion of the stem cell pool (Kokovay et al., 2012). Other important environmental cues come from growth factors such as epidermal growth factor (EGF), and other EGF Receptor (EGFR) ligands (i.e. TGF (Seroogy et al., 1993; Tropepe et al., 1997)) and fibroblast growth factor (FGF) in the CSF, which stimulate proliferation of type C cells in vivo and stimulates neurosphere production in vitro (Doetsch et al., 2002; Kuhn et al., 1997; Reynolds et al., 1992). Type C cells become proliferative and migratory in the presence of EGF. Furthermore, EGF confers multipotency in type C cells, which can give rise to neurons, astrocytes and oligodendrocytes in vitro (Doetsch et al., 2002; Reynolds et al., 1992). However, EGF does not increase neurogenesis in the olfactory bulb in vivo (Kuhn et al., 1997). FGF induces proliferation in the V–SVZ and increases the number of neuroblasts and levels of neurogenesis in the olfactory bulb (Kuhn et al., 1997). Vascular endothelial growth factor (VEGF) has also been shown to promote proliferation in the V–SVZ, illustrating the necessity of vascular signals in neurogenesis (Jin et al., 2002).

The function of NSCs in the SGZ is heavily influenced by environmental molecular cues. As in the V–SVZ, the vasculature in the SGZ has strong effects on the proliferation of NSCs. Bursts of endothelial cell division are commonly observed along with clusters of increased neurogenesis (Palmer et al., 2000). The receptor for VEGF colocalizes with these clusters of increased cell division. Indeed, infusion of VEGF increases the number of doublecortin+ neuroblasts, which express VEGF Receptor 2 (Jin et al., 2002). Furthermore, treating postnatal day 16 cortical stem cell cultures with VEGF increases neurogenesis. Although EGF and FGF do not increase proliferation in the SGZ as observed in the V–SVZ, EGF does favors the generation of astrocytes and reduces the number of neuroblasts in the SGZ (Kuhn et al., 1997). Adrenal hormones have also been shown to have strong effects on neurogenesis in the SGZ. Adrenalectomized rats show an increase in the number of GFAP+ labeled astrocytes and enolase labeled neurons in the SGZ. However, replacement of corticosterone in these rats suppresses proliferation (Gould et al., 1992). These results indicate that glucocorticoids, such as corticosterone, negatively regulate neurogenesis and gliogenesis in the SGZ. The mechanism through which glucocorticoids regulate neurogenesis in the SGZ may involve N-methyl-D-aspartate receptors (NMDAR) and the excitatory effects of glutamate (Gould et al., 1997). Shh signaling has important functions in maintaining the SGZ niche after development. The loss of sonic hedgehog (Shh) or smoothened (Smo) results in severe deficiencies in the hippocampus, but without affecting the early SGZ invasion of hedgehog responsive cells from the ventral hippocampus. In turn, Shh signaling helps to retain more descendants of the hedgehog responsive cells in the adult, thereby contributing to the maintenance of the postnatal SGZ (Li et al., 2013).

4. Neurotransmitter regulation of neurogenesis

NSCs are highly influenced by monoaminergic neurotransmitters. Two neurotransmitter in particular are common targets for psychiatric pharmacological therapies: dopamine (DA) and serotonin (5-HT). These monoamines have been shown to influence proliferation and neurogenesis within the adult brain and these classical neuromodulators can have a profound effect on neurogenesis as levels of monoaminergic neurotransmitters change in the brain under conditions of psychiatric disease, age, or neurodegeneration.

4.1. Neurotransmitter regulation of stem cells in the SGZ

SGZ NSCs are highly dependent upon serotonergic innervation by projections from the raphe nuclei (Mongeau et al., 1997). Lesioned 5-HT projections from the raphe to the dentate gyrus decreases proliferation of progenitor cells (Brezun and Daszuta, 1999). Adult neurogenesis has been shown to be enhanced in mice lacking the 5-HT transporter, a genetic manipulation that leads to increased extracellular levels of 5-HT in the brain (Schmitt et al., 2007). The 5-HT_{1A} receptor is thought to mediate a bulk of the neurogenic activity in the dentate gyrus. Depletion of 5-HT and simultaneous activation of 5-HT_{1A} receptors by 8-OH-DPAT results in increased proliferation in the SGZ (Huang and Herbert, 2005). Further, activation of 5-HT_{1A} receptors alone has been reported to increase proliferation (Santarelli et al., 2003) and blockade of 5-HT_{1A} receptors in the dentate gyrus reduces proliferation of progenitors (Radley and Jacobs, 2002). In schizophrenia, 5-HT_{1A} activation has been shown to improve cognitive symptoms and promote neurogenesis (Schreiber and Newman-Tancredi, 2014; Sumiyoshi et al., 2001). This 5-HT_{1A} – mediated neurogenesis may be due, in part, to the activation of this receptor on SGZ astrocytes, which can regulate neurotrophic factor secretion (Aberg et al., 2000; Manev et al., 2001; Whitaker-Azmitia et al., 1993). Agonism of 5-HT_{2C} receptors in the SGZ also produces an increase in neurogenesis (Banasr et al., 2004). Other 5-HT receptor subtypes have been identified in the SGZ, but their influence on neurogenesis in this region is still under debate (Alenina and Klempin, 2015; Lucas et al., 2007). The specific effects of 5-HT receptor activation is not currently well characterized. Future studies will likely focus on understanding which 5-HT receptor subtypes influence type 1, type 2, and type 3 stem and progenitor cells, and on determining if 5-HT receptor activation produces a direct or indirect effect on neurogenesis.

Inhibitory signaling from GABA has been shown to be a critical regulator of neurogenesis in the dentate gyrus (Song et al., 2012). Type 2 amplifying progenitor cells are activated by GABA, which promotes activity-dependent differentiation of NSCs, likely through a $GABA_A$-dependent mechanism (Tozuka et al., 2005). This GABA-mediated depolarization of progenitors in the subgranular zone has been linked to the incorporation of AMPA receptors into immature granule cells, a process necessary for learning and memory formation (Chancey et al., 2013). Type 1 cells were found to be sensitive to signaling via the $GABA_B$ receptor, where chronic $GABA_BR$ blockade increased neurogenesis in the subgranular zone (Felice et al., 2012). Migration of progenitors in the dentate gyrus is also GABA-dependent. Transgenic animals lacking the GABA α4

Table 1
Neurotransmitter regulation of neurogenesis in the SGZ.

5-HT	↑neurogenesis
5-HT_{1A}	↑neurogenesis and proliferation
5-HT_{2C}	↑neurogenesis
Other 5-HT receptors	Disputed effects
$GABA_AR$	↑differentiation
$GABA_BR$	↓neurogenesis
GABA α4	↑migration into granular cell layer
GABA α2	↓migration into granular cell layer

receptor subunit had a significantly shorter migration distance into the granular cell layer, while animals lacking the α2 subunit displayed an increase in the number of neuroblasts that migrated into the granular cell layer (Duveau et al., 2011). The role of GABA in the dentate gyrus is heavily dependent upon receptor type and subunit expression, conferring the capacity for differential modulation of hippocampal NSCs by GABA. It is well established that stress and anxiety can modulate GABA receptor expression, and these also alter neurogenesis (Earnheart et al., 2007). The specific mechanisms by which different GABA receptor and subunit arrangements alter SGZ neurogenesis are complicated and a complete picture of GABA involvement in this process is currently unavailable. However, GABA signaling plays an obvious role in modulating readouts of neurogenesis, and given the pharmacological tools immediately available for augmenting GABA function, a greater understanding of the specifics of GABA signaling will likely advance our ability to directly influence SGZ neurogenesis in the adult brain. See Table 1 for a summary of the most prominent neurotransmitter actions in the regulation of SGZ neurogenesis.

4.2. Neurotransmitter regulation of stem cells in the V–SVZ

The adult V–SVZ also receives serotonergic input from the raphe nuclei (Brezun and Daszuta, 1999). Lesion studies in which the serotonergic raphe nuclei inputs to the V–SVZ are ablated reveal a decrease in neurogenesis (Banasr et al., 2004; Brezun and Daszuta, 1999). The serotonin (5-HT) receptor family contains a myriad of 5-HT receptors. Functionally, the 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2C} and 5-HT_{5A} receptors have been demonstrated in the V–SVZ (Banasr et al., 2004; Soumier et al., 2010; Tong et al., 2014). In these studies, agonism of the 5-HT_{1A} and 5-HT_{2C} receptors increase proliferation of neural stem cells in the V–SVZ, while agonism of the 5-HT_{1B} receptor resulted in a decline in proliferative activity (Banasr et al., 2004; Soumier et al., 2010). Supraependymal axons that enervate the V–SVZ originate from the median and dorsal raphe. These axons line the apical surface of the V–SVZ and make contact directly on type B cells and ependymal cells. Lesion studies in which the raphe nuclei inputs to the V–SVZ are ablated reveal a decrease in neurogenesis. Infusion of 5-HT_{2C} agonizts into the lateral ventricles induces proliferation of type B cells, while the antagonist induces the opposite effect reducing proliferation. Although modulation of 5-HT_{2C} significantly affects type B cell proliferation, type C and A cells remain unaffected (Tong et al., 2014). The effects of serotonergic innervation on ependymal cells remain to be studied, but 5-HT signaling might affect ependymal cell cilia, as serotonin has been shown to increase cilia beating frequency on ependymal cells in the brainstem of rats (Nguyen et al., 2001). Serotonin is one of the primary neurotransmitters involved in mood regulation and mood disorders. It is possible, therefore, that changes in serotonin regulation seen with mood disorders may also result in a decline in neurogenesis in the V–SVZ, although the functional and behavioral implications of this in adults are not yet clear.

The V–SVZ receives dopaminergic innervation from the substantia nigra (SNc) and ventral tegmental area (VTA) (Baker et al., 2004; Freundlieb et al., 2006; Hoglinger et al., 2004). Axonal projections from the posterior SNc innervate the posterodorsal V–SVZ while the anterior SNc projects axons to the anterior V–SVZ and the rostral migratory stream (Hoglinger et al., 2014). The VTA preferentially projects axons to the ventral V–SVZ (Hoglinger et al., 2014). These dopaminergic projections contact type C progenitor cells that express cognate D1-like and D2-like dopamine receptors (Coronas et al., 2004; Hoglinger et al., 2004; Winner et al., 2009). These G protein-coupled receptors are classically divided into two groups based on their activity: D1-like (D1 and D5 receptors), which activate adenylyl cyclase, and D2-like (D2, D3, and D4), which inhibit adenylyl cyclase. In the developing brain, activation of the D1 receptor on proliferating cells decreases proliferation of progenitors by retarding the progression from G_1 to S phase of the cell cycle. However, activation of D2-like receptors enhanced proliferation of progenitors by promoting the transition from G_1 to S phase (Ohtani et al., 2003). It is likely that a similar response remains in the adult neural stem cell population of the V–SVZ.

In the adult brain, loss of dopaminergic signaling in the V–SVZ has detrimental effects on neural stem cell proliferative capacity. Lesion of dopaminergic inputs using 6-hydroxydopamine (6-OHDA) or 1-methyl-4-pheynyl-1,2,3,6-tetrahydropyridine (MPTP) produced a loss of tyrosine hydroxylase (TH)-positive dopaminergic projections to the V–SVZ, and a decline in neural stem cell proliferation (Baker et al., 2004; Freundlieb et al., 2006; Hoglinger et al., 2004; Winner et al., 2009). O'Keeffe and coworkers (O'Keeffe et al., 2009) reveal a concomitant decline in EGF production in the V–SVZ following dopaminergic lesion, and have demonstrated a reversal of this deficit through levodopa administration. This study implies a critical role for dopamine in the V–SVZ as it appears to be linked to expression of EGF, a major contributor to V–SVZ proliferation (Craig et al., 1996; Reynolds et al., 1992). The sensitivity of the V–SVZ neural stem cell population to treatment with levodopa indicates a potential role for this region in psychiatric disease. See Table 2 for a summary of the most prominent neurotransmitter actions in the regulation of V–SVZ neurogenesis.

4.3. Antidepressant drug actions in neurogenic regions

Given the influence of neurotransmitters on NSC function, perhaps it is not surprising that antidepressant drugs can preferentially enhance neurogenesis in both the hippocampus and V–SVZ. In hippocampus, selective serotonin reuptake inhibitors (SSRIs), atypical antidepressants, selective norepinephrine reuptake inhibitors, monoamine oxidase inhibitors (MAOIs), and tricyclic antidepressants all have been shown to increase neurogenesis in chronically treated animals (Malberg, 2004). For example, the commonly used SSRI fluoxetine is effective at producing an increase in hippocampal neurogenesis if treatment is continuous for at least 14 days (Malberg, 2004). Interestingly, electroconvulsive shock therapy (ECT), often used as a last line of treatment against depressive disorders resistant to pharmacological treatment, is also a potent inducer of neural stem cell proliferation (Madsen et al., 2000).

It has been established that neurogenesis in the hippocampus

Table 2
Neurotransmitter regulation of neurogenesis in the V–SVZ.

5HT	↑neurogenesis
5-HT_{1A}	↑proliferation
5-HT_{2C}	↑proliferation
5-HT_{1B}	↓proliferation
DA	↑proliferation
D1-like receptors	↓proliferation
D2-like receptors	↑proliferation

is, in fact, necessary for the production of behavioral effects of antidepressant drugs, and that ablation of neurogenesis also prevents behavioral improvements in animals being treated with antidepressants (Santarelli et al., 2003). Reports on the necessity of neurogenesis in effective treatment of mood disorders are not surprising given the changes that take place in the hippocampus of patients with depression or other affective disorders. Cognitive deficits, mood dysregulation, and declines in hippocampal volume have all been correlated with mental disorders that display decreased neurogenesis, such as major depression, post-traumatic stress disorder, schizophrenia, and Alzheimer's disease (Bremner et al., 1995; Bremner, 2001; DeCarolis and Eisch, 2010). Interestingly, in Huntington's disease, in which patients exhibit early signs of cognitive distress, neurogenesis appears to decline preferentially in the striatum of humans (Ernst et al., 2014). Given the underlying structural and cognitive deficits in these mental disorders, targeting neurogenesis directly as a therapeutic intervention may lead to improved patient outcomes in future mental health treatment paradigms.

The effects of antidepressant treatments are somewhat different in the V–SVZ, where it has been reported that chronic fluoxetine alone decreases neurogenesis (Ohira and Miyakawa, 2011). However, if the antidepressant treatment is given in conjunction with corticosterone or chronic stress, which both decrease neurogenesis and are major contributors to the development of mood disorders, then antidepressant drugs actually reverse this decline in neurogenesis (Hitoshi et al., 2007; Lau et al., 2007). Further, antidepressant treatment following stroke, which increases neurogenesis, can enhance proliferation of neural stem cells and improve their migration toward sites of brain damage, but does not enhance survival, differentiation, or behavioral outcomes in either hippocampus or V–SVZ (Sun et al., 2015).

5. Neurogenesis in humans

The discovery of neurogenesis in the human adult and the regenerative capacity of neural stem cells has spurred interest in designing novel therapies for conditions such as stroke, traumatic brain injury, and neurodegenerative diseases. However, many studies on NSCs employ rodent models and little is known about adult neurogenesis in humans. Neurogenesis in the adult human SGZ was first demonstrated in the late 1990s by Eriksson and coworkers (Eriksson et al., 1998). In this study, terminally ill cancer patients were injected with the nucleotide analog bromodeoxyuridine (BrdU) for diagnostic purposes during their cancer treatment. Immunohistochemical analysis of postmortem brain samples revealed BrdU incorporation within the DNA of dividing cells of the hippocampus, which appear morphologically indistinguishable from adult-born hippocampal neurons observed in rodent models. Ethical concerns prohibit further studies such as this one in terminally ill human subjects, but the strong evidence of adult hippocampal neurogenesis gained from this patient population was an invaluable contribution to the scientific community.

A later study provided additional direct evidence of adult hippocampal neurogenesis in humans. Nuclear bomb testing during the Cold War produced elevated levels of ^{14}C in the atmosphere, which are mirrored in the ^{14}C incorporation into the human body (Harkness, 1972). Levels of ^{14}C have been declining since testing in the 1950s, but are still detectable and correlate with levels in human tissue. Spalding and colleagues found that postmortem brain samples probed for ^{14}C levels in the hippocampus revealed that adult neurogenesis does occur, at least into the fifth decade of life, in this brain region (Spalding et al., 2013). Further, neurogenesis is restricted to a subpopulation of cells in the hippocampus that is subjected to turnover throughout life. Specifically, the dentate gyrus of the hippocampus is the location of high cell turnover, according to ^{14}C measurements taken in aged tissue. However, there is still a net loss in neurons in the dentate gyrus throughout life, indicating that continued neurogenesis throughout adulthood delays, but does not arrest, neuronal volume loss with age.

Investigations in human V–SVZ and olfactory bulb revealed a cytoarchitecturally distinct V–SVZ niche organization and neuroblast migration compared to rodents (Bergmann et al., 2012; Ernst et al., 2014; Sanai et al., 2011). In humans, the V–SVZ displays a dense ribbon of astrocytes after a subependymal gap (Sanai et al., 2004). These astrocytes show multipotency in vitro and can generate neurons, astrocytes and oligodendrocytes (Sanai et al., 2011). Although these putative neural stem cells display strong germinal capacity in vitro, their migratory route differs between rodents and humans. Early work by Sanai and colleagues revealed that neurogenesis in the olfactory bulb is virtually absent in human adult tissue (Sanai et al., 2004). More recent work has revealed that olfactory neurogenesis does occur in humans, but only in infants up to 18 months of age. The level of olfactory neurogenesis declines dramatically by 24 months of age and is virtually absent in adult tissue (Sanai et al., 2011). In support of these studies, recent studies estimated cell turnover predicted to be only 1% of human olfactory bulb cells across a 100 year lifespan using ^{14}C dating (Bergmann et al., 2012). ^{14}C dating, along with other histological evidence, shows that instead of giving rise to new neurons in the olfactory bulb, neuroblasts from the V–SVZ migrate to the striatum in humans (Ernst et al., 2014). This difference in NSC migration between rodents and humans suggests the presence of a functionally divergent mechanism for V–SVZ neurogenesis across species. The striatum is commonly associated with motor function, but recently it has been identified as necessary for cognitive flexibility, as evolutionary expansion of this region correlates with an increase in cognitive function and ability in modern humans (Ernst and Frisen, 2015). Carbon dating of two different neuronal populations in the striatum of humans identified postnatal turnover of interneurons but not of medium spiny neurons, suggesting progenitors from human V–SVZs contribute to the population of interneurons in the striatum. However, recent work has demonstrated that subpopulations of astrocytes in the striatal tissue can give rise to new neurons in this region, suggesting that the striatum may have an inherent capacity to regenerate neurons independent of the neighboring neurogenic cells in the V–SVZ (Magnusson et al., 2014). Regardless of the NSC source, discovery of striatum-specific neuronal turnover is of particular interest in the study of neurodegenerative diseases with prominent striatal involvement, such as Huntington's disease. Some studies suggest cell death in the striatum (as in the case of Huntington's disease) induces proliferation and thickening of the human V–SVZ, instigating migration to the striatum through the caudate nucleus (Curtis et al., 2007). Interestingly, carbon dating indicates a decrease in new neurons in the striatum of Huntington's disease patients when compared to age-matched healthy subjects (Ernst et al., 2014), suggesting that this increase in proliferation does not compensate for neuronal loss.

In humans, neurogenic regions receive similar innervation by monoaminergic projections as observed in rodents, however there are no reports on how NSCs in the SGZ and SVZ respond to neurotransmitter signaling in the human brain. It is well established that SGZ neurogenesis increases in response to antidepressant treatment in animal models (Santarelli et al., 2003). Given the highly conserved nature of neurotransmitter signaling in higher mammals, it is reasonable to presume that similar effects on NSC proliferation and migration may eventually be observed in human neurogenic regions. Neurotransmitters can also influence growth

factors, neurotrophic receptors, and other factors involved in neurogenesis (Hagg, 2009). Future advances in our ability to study neurotransmission and neurogenesis in vivo may eventually broaden our understanding of neurogenesis regulation by neurotransmitters in the human brain. For now, animal models are providing the first answers to these questions on neurotransmitter regulation of NSCs.

6. Adult human neurogenesis and psychiatric disorders

The functional implications of adult human hippocampal neurogenesis remain unclear. It is thought that neurogenesis in hippocampus is particularly important in memory formation and consolidation, and dysfunctional neurogenic patterns are likely involved in mood and psychiatric disorders. For example, in a postmortem examination of hippocampal tissue from schizophrenic patients, it was found that there is a dramatic decrease in the number of proliferating cells in the SGZ (Allen et al., 2015). Stress and depression contribute to decreased neurogenesis, and antidepressant treatment has been shown to reverse this loss of hippocampal neurogenesis (Mahar et al., 2014). Future work will clarify the connections between neurogenesis and psychiatric disorders, and may lead to the development of targeted neurogenesis therapies for mental illnesses.

Adult neurogenesis in the human V–SVZ is increasingly recognized as a potential player in the development of psychiatric and cognitive disorders. Recent attention has been given to the role of the striatum in schizophrenia, where dopamine hyperactivity is thought to contribute to the pathology of schizophrenia (Simpson et al., 2010). Several reports have suggested that increased adult neurogenesis in the V–SVZ may alleviate symptoms of schizophrenia by targeting dopamine signaling at NSCs (Inta et al., 2012). Given the evidence indicating that progenitors from the V–SVZ migrate to the striatum in humans, it is plausible to speculate that alterations in V–SVZ neurogenic activity may contribute to the pathology of schizophrenia in humans. A more thorough understanding of V–SVZ neurogenesis and the migratory capacity of progenitors to the striatum in humans may be helpful in harnessing the regenerative capacity of NSCs to treat neurodegenerative and psychiatric diseases in humans.

7. Conclusions and future perspectives

The discovery of the remarkable process of adult neurogenesis has revolutionized our understanding of the brain's response to disease and damage. The changes that occur in neurogenic cell populations in response to stress, psychiatric disorders, and in the early stages of neurodegenerative disease indicate that neural stem cells may hold therapeutic potential for treatment of these pathologies. Evidence of neural stem cell responsiveness to drugs used in treating psychiatric disorders further supports this idea. Neurogenesis in the SGZ has been shown to be necessary for effective treatment of mood and psychiatric disorders, while the V–SVZ is not typically linked to psychiatric dysfunction. However, the recent evidence of V–SVZ neural stem cell control, in part by monoamines involved in mood, cognitive, and neurodegenerative disorders, indicates that neurogenesis in this region may also play a role in maintenance of normal mood and cognitive regulation. In humans, it is likely that the ultimate fate of V–SVZ neural stem cells is integration into the striatal tissue rather than the olfactory bulb, as seen in rodents. The involvement of the human V–SVZ and striatum in adult neurogenesis has revised our understanding of neurodegenerative diseases that have an early cognitive or mood component. Our knowledge of adult neurogenesis and neural stem cell regulation has grown exponentially over the last two decades, however we still lack a complete understanding of the neurogenic process in the human brain. Further work on understanding human adult neurogenesis may reveal a critical role of the V–SVZ and striatum in mood, cognition, and neurodegeneration.

Author information

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References

Aberg, M.A., et al., 2000. Peripheral infusion of IGF-I selectively induces neurogenesis in the adult rat hippocampus. J. Neurosci. 20, 2896–2903.
Alenina, N., Klempin, F., 2015. The role of serotonin in adult hippocampal neurogenesis. Behav. Brain Res. 277, 49–57.
Allen, K.M., Fung, S.J., Shannon Weickert, C., 2015. Cell proliferation is reduced in the hippocampus in schizophrenia. Aust. N. Zeal. J. Psychiatry.
Alvarez-Buylla, A., Garcia-Verdugo, J.M., Tramontin, A.D., 2001. A unified hypothesis on the lineage of neural stem cells. Nat. Rev. Neurosci. 2, 287–293.
Ashton, R.S., et al., 2012. Astrocytes regulate adult hippocampal neurogenesis through ephrin-B signaling. Nat. Neurosci. 15, 1399–1406.
Baker, S.A., Baker, K.A., Hagg, T., 2004. Dopaminergic nigrostriatal projections regulate neural precursor proliferation in the adult mouse subventricular zone. Eur. J. Neurosci. 20, 575–579.
Banasr, M., et al., 2004. Serotonin-induced increases in adult cell proliferation and neurogenesis are mediated through different and common 5-HT receptor subtypes in the dentate gyrus and the subventricular zone. Neuropsychopharmacology 29, 450–460.
Bergmann, O., et al., 2012. The age of olfactory bulb neurons in humans. Neuron 74, 634–639.
Bremner, J.D., et al., 1995. MRI-based measurement of hippocampal volume in patients with combat-related posttraumatic stress disorder. Am. J. Psychiatry 152, 973–981.
Bremner, J.D., 2001. Hypotheses and controversies related to effects of stress on the hippocampus: an argument for stress-induced damage to the hippocampus in patients with posttraumatic stress disorder. Hippocampus 11, 75–81, discussion 82-84.
Brezun, J.M., Daszuta, A., 1999. Depletion in serotonin decreases neurogenesis in the dentate gyrus and the subventricular zone of adult rats. Neuroscience 89, 999–1002.
Chancey, J.H., et al., 2013. GABA depolarization is required for experience-dependent synapse unsilencing in adult-born neurons. J. Neurosci. 33, 6614–6622.
Colak, D., et al., 2008. Adult neurogenesis requires Smad4-mediated bone morphogenic protein signaling in stem cells. J. Neurosci. 28, 434–446.
Coronas, V., et al., 2004. Dopamine D3 receptor stimulation promotes the proliferation of cells derived from the post-natal subventricular zone. J. Neurochem. 91, 1292–1301.
Craig, C.G., et al., 1996. In vivo growth factor expansion of endogenous subependymal neural precursor cell populations in the adult mouse brain. J. Neurosci. 16, 2649–2658.
Curtis, M.A., Eriksson, P.S., Faull, R.L., 2007. Progenitor cells and adult neurogenesis in neurodegenerative diseases and injuries of the basal ganglia. Clin. Exp. Pharmacol. Physiol. 34, 528–532.
DeCarolis, N.A., Eisch, A.J., 2010. Hippocampal neurogenesis as a target for the treatment of mental illness: a critical evaluation. Neuropharmacology 58, 884–893.
Delgado, A.C., et al., 2014. Endothelial NT-3 delivered by vasculature and CSF promotes quiescence of subependymal neural stem cells through nitric oxide induction. Neuron 83, 572–585.
Doetsch, F., Alvarez-Buylla, A., 1996. Network of tangential pathways for neuronal migration in adult mammalian brain. Proc. Natl. Acad. Sci. USA 93, 14895–14900.
Doetsch, F., García-Verdugo, J.M., 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., et al., 2002. EGF converts transit-amplifying neurogenic precursors in the adult brain into multipotent stem cells. Neuron 36, 1021–1034.

Duveau, V., et al., 2011. Spatiotemporal specificity of GABAA receptor-mediated regulation of adult hippocampal neurogenesis. Eur. J. Neurosci. 34, 362–373.
Earnheart, J.C., et al., 2007. GABAergic control of adult hippocampal neurogenesis in relation to behavior indicative of trait anxiety and depression states. J. Neurosci. 27, 3845–3854.
Encinas, J.M., Vaahtokari, A., Enikolopov, G., 2006. Fluoxetine targets early progenitor cells in the adult brain. Proc. Natl. Acad. Sci. USA 103, 8233–8238.
Encinas, J.M., et al., 2011. Division-coupled astrocytic differentiation and age-related depletion of neural stem cells in the adult hippocampus. Cell Stem Cell 8, 566–579.
Eriksson, P.S., et al., 1998. Neurogenesis in the adult human hippocampus. Nat. Med. 4, 1313–1317.
Ernst, A., et al., 2014. Neurogenesis in the striatum of the adult human brain. Cell 156, 1072–1083.
Ernst, A., Frisen, J., 2015. Adult neurogenesis in humans- common and unique traits in mammals. PLoS Biol. 13, e1002045.
Felice, D., et al., 2012. Blockade of the GABA(B) receptor increases neurogenesis in the ventral but not dorsal adult hippocampus: relevance to antidepressant action. Neuropharmacology 63, 1380–1388.
Filippov, V., et al., 2003. Subpopulation of nestin-expressing progenitor cells in the adult murine hippocampus shows electrophysiological and morphological characteristics of astrocytes. Mol. Cell. Neurosci. 23, 373–382.
Freundlieb, N., et al., 2006. Dopaminergic substantia nigra neurons project topographically organized to the subventricular zone and stimulate precursor cell proliferation in aged primates. J. Neurosci. 26, 2321–2325.
Gotz, M., Huttner, W.B., 2005. The cell biology of neurogenesis. Nat. Rev. Mol. Cell. Biol. 6, 777–788.
Gould, E., et al., 1992. Adrenal hormones suppress cell division in the adult rat dentate gyrus. J. Neurosci. 12, 3642–3650.
Gould, E., Tanapat, P., Cameron, H.A., 1997. Adrenal steroids suppress granule cell death in the developing dentate gyrus through an NMDA receptor-dependent mechanism. Brain 103, 91–93.
Hagg, T., 2009. From neurotransmitters to neurotrophic factors to neurogenesis. Neuroscientist 15, 20–27.
Harkness, D.D., 1972. Further investigations of the transfer of bomb ^{14}C to man. Nature 240, 302–303.
Hitoshi, S., et al., 2007. Antidepressant drugs reverse the loss of adult neural stem cells following chronic stress. J. Neurosci. Res. 85, 3574–3585.
Hoglinger, G.U., et al., 2004. Dopamine depletion impairs precursor cell proliferation in Parkinson disease. Nat. Neurosci. 7, 726–735.
Hoglinger, G.U., et al., 2014. Origin of the dopaminergic innervation of adult neurogenic areas. J. Comp. Neurol. 522, 2336–2348.
Huang, G.J., Herbert, J., 2005. Serotonin modulates the suppressive effects of corticosterone on proliferating progenitor cells in the dentate gyrus of the hippocampus in the adult rat. Neuropsychopharmacology 30, 231–241.
Inta, D., et al., 2012. Postnatal neurogenesis and dopamine alterations in early psychosis. Recent Pat. CNS Drug Discov. 7, 236–242.
Jin, K., et al., 2002. Vascular endothelial growth factor (VEGF) stimulates neurogenesis in vitro and in vivo. Proc. Natl. Acad. Sci USA 99, 11946–11950.
Kempermann, G., et al., 2004. Milestones of neuronal development in the adult hippocampus. Trends Neurosci. 27, 447–452.
Kokovay, E., et al., 2010. Adult SVZ lineage cells home to and leave the vascular niche via differential responses to SDF1/CXCR4 signaling. Cell Stem Cell 7, 163–173.
Kokovay, E., et al., 2012. VCAM1 is essential to maintain the structure of the SVZ niche and acts as an environmental sensor to regulate SVZ lineage progression. Cell Stem Cell 11, 220–230.
Kuhn, H.G., et al., 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.
Lau, W.M., et al., 2007. Corticosteroid decreases subventricular zone cell proliferation, which could be reversed by paroxetine. Restor. Neurol. Neurosci. 25, 17–23.
Laywell, E.D., et al., 2000. Identification of a multipotent astrocytic stem cell in the immature and adult mouse brain. Proc. Natl. Acad. Sci. USA 97, 13883–13888.
Li, G., et al., 2013. The ventral hippocampus is the embryonic origin for adult neural stem cells in the dentate gyrus. Neuron 78, 658–672.
Lim, D.A., et al., 2000. Noggin antagonizes BMP signaling to create a niche for adult neurogenesis. Neuron 28, 713–726.
Lois, C., Alvarez-Buylla, A., 1993. Proliferating subventricular zone cells in the adult mammalian forebrain can differentiate into neurons and glia. Proc. Natl. Acad. Sci. USA 90, 2074–2077.
Lucas, G., et al., 2007. Serotonin(4) (5-HT(4)) receptor agonists are putative antidepressants with a rapid onset of action. Neuron 55, 712–725.
Madsen, T.M., et al., 2000. Increased neurogenesis in a model of electroconvulsive therapy. Biol. Psychiatry 47, 1043–1049.
Magnusson, J.P., et al., 2014. A latent neurogenic program in astrocytes regulated by Notch signaling in the mouse. Science 346, 237–241.
Mahar, I., et al., 2014. Stress, serotonin, and hippocampal neurogenesis in relation to depression and antidepressant effects. Neurosci. Biobehav. Rev. 38, 173–192.
Malberg, J.E., 2004. Implications of adult hippocampal neurogenesis in antidepressant action. J. Psychiatry Neurosci. 29, 196–205.
Manev, R., Uz, T., Manev, H., 2001. Fluoxetine increases the content of neurotrophic protein S100beta in the rat hippocampus. Eur. J. Pharmacol. 420, R1–R2.
McKay, R., 1997. Stem cells in the central nervous system. Science 276, 66–71.
Merkle, F.T., et al., 2004. Radial glia give rise to adult neural stem cells in the subventricular zone. Proc. Natl. Acad. Sci. USA 101, 17528–17532.
Merkle, F.T., et al., 2014. Adult neural stem cells in distinct microdomains generate previously unknown interneuron types. Nat. Neurosci. 17, 207–214.
Ming, G.L., Song, H., 2011. Adult neurogenesis in the mammalian brain: significant answers and significant questions. Neuron 70, 687–702.
Mongeau, R., Blier, P., de Montigny, C., 1997. The serotonergic and noradrenergic systems of the hippocampus: their interactions and the effects of antidepressant treatments. Brain Res. Brain Res. Rev. 23, 145–195.
Nguyen, T., et al., 2001. Intracellular pathways regulating ciliary beating of rat brain ependymal cells. J. Physiol. 531, 131–140.
Nicola, Z., Fabel, K., Kempermann, G., 2015. Development of the adult neurogenic niche in the hippocampus of mice. Front. Neuroanat. 9, 53.
Noctor, S.C., et al., 2002. Dividing precursor cells of the embryonic cortical ventricular zone have morphological and molecular characteristics of radial glia. J. Neurosci. 22, 3161–3173.
O'Keeffe, G.C., et al., 2009. Dopamine-induced proliferation of adult neural precursor cells in the mammalian subventricular zone is mediated through EGF. Proc. Natl. Acad. Sci. USA 106, 8754–8759.
Ohira, K., Miyakawa, T., 2011. Chronic treatment with fluoxetine for more than 6 weeks decreases neurogenesis in the subventricular zone of adult mice. Mol. Brain 4, 10.
Ohtani, N., et al., 2003. Dopamine modulates cell cycle in the lateral ganglionic eminence. J. Neurosci. 23, 2840–2850.
Palmer, T.D., Willhoite, A.R., Gage, F.H., 2000. Vascular niche for adult hippocampal neurogenesis. J. Comp. Neurol. 425, 479–494.
Radley, J.J., Jacobs, B.L., 2002. 5-HT1A receptor antagonist administration decreases cell proliferation in the dentate gyrus. Brain Res. 955, 264–267.
Reynolds, B.A., Tetzlaff, W., Weiss, S., 1992. A multipotent EGF-responsive striatal embryonic progenitor cell produces neurons and astrocytes. J. Neurosci. 12, 4565–4574.
Sanai, N., et al., 2004. Unique astrocyte ribbon in adult human brain contains neural stem cells but lacks chain migration. Nature 427, 740–744.
Sanai, N., et al., 2011. Corridors of migrating neurons in the human brain and their decline during infancy. Nature 478, 382–386.
Santarelli, L., et al., 2003. Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. Science 301, 805–809.
Sawamoto, K., et al., 2006. New neurons follow the flow of cerebrospinal fluid in the adult brain. Science 311, 629–632.
Schmitt, A., et al., 2007. Adult neurogenesis in serotonin transporter deficient mice. J. Neural Transm. 114, 1107–1119.
Schreiber, R., Newman-Tancredi, A., 2014. Improving cognition in schizophrenia with antipsychotics that elicit neurogenesis through 5-HT(1A) receptor activation. Neurobiol. Learn Mem. 110, 72–80.
Seri, B., et al., 2004. Cell types, lineage, and architecture of the germinal zone in the adult dentate gyrus. J. Comp. Neurol. 478, 359–378.
Seroogy, K.B., et al., 1993. Cellular localization of transforming growth factor-alpha mRNA in rat forebrain. J. Neurochem. 60, 1777–1782.
Shen, Q., et al., 2004. Endothelial cells stimulate self-renewal and expand neurogenesis of neural stem cells. Science 304, 1338–1340.
Shen, Q., et al., 2008. Adult SVZ stem cells lie in a vascular niche: a quantitative analysis of niche cell–cell interactions. Cell Stem Cell 3, 289–300.
Simpson, E.H., Kellendonk, C., Kandel, E., 2010. A possible role for the striatum in the pathogenesis of the cognitive symptoms of schizophrenia. Neuron 65, 585–596.
Song, J., et al., 2012. Modification of hippocampal circuitry by adult neurogenesis. Dev. Neurobiol. 72, 1032–1043.
Soumier, A., et al., 2010. Region- and phase-dependent effects of 5-HT(1A) and 5-HT(2C) receptor activation on adult neurogenesis. Eur. Neuropsychopharmacol. 20, 336–345.
Spalding, K.L., et al., 2013. Dynamics of hippocampal neurogenesis in adult humans. Cell 153, 1219–1227.
Suh, H., et al., 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.
Sumiyoshi, T., et al., 2001. The effect of tandospirone, a serotonin(1A) agonist, on memory function in schizophrenia. Biol. Psychiatry 49, 861–868.
Sun, X., et al., 2015. Fluoxetine enhanced neurogenesis is not translated to functional outcome in stroke rats. Neurosci. Lett. 603, 31–36.
Tavazoie, M., et al., 2008. A specialized vascular niche for adult neural stem cells. Cell Stem Cell 3, 279–288.
Taverna, E., Gotz, M., Huttner, W.B., 2014. The cell biology of neurogenesis: toward an understanding of the development and evolution of the neocortex. Annu. Rev. Cell Dev. Biol. 30, 465–502.
Tong, C.K., et al., 2014. Axonal control of the adult neural stem cell niche. Cell Stem Cell 14, 500–511.
Tozuka, Y., et al., 2005. GABAergic excitation promotes neuronal differentiation in adult hippocampal progenitor cells. Neuron 47, 803–815.
Tropepe, V., et al., 1997. Transforming growth factor-alpha null and senescent mice show decreased neural progenitor cell proliferation in the forebrain subependyma. J. Neurosci. 17, 7850–7859.
van Praag, H., et al., 2002. Functional neurogenesis in the adult hippocampus. Nature 415, 1030–1034.
Whitaker-Azmitia, P.M., Clarke, C., Azmitia, E.C., 1993. Localization of 5-HT1A receptors to astroglial cells in adult rats: implications for neuronal-glial interactions and psychoactive drug mechanism of action. Synapse 14, 201–205.
Winner, B., et al., 2009. Dopamine receptor activation promotes adult neurogenesis in an acute Parkinson model. Exp. Neurol. 219, 543–552.
Zhao, C., et al., 2006. Distinct morphological stages of dentate granule neuron maturation in the adult mouse hippocampus. J. Neurosci. 26, 3–11.