Cell and Tissue Research (2018) 373:693–709
https://doi.org/10.1007/s00441-017-2735-4

REVIEW

Review: adult neurogenesis contributes to hippocampal plasticity

Tomohisa Toda[1] · Fred H. Gage[1]

Received: 25 July 2017 / Accepted: 27 October 2017 / Published online: 29 November 2017

Abstract Adult hippocampal neurogenesis is the process by which new functional neurons are added to the adult dentate gyrus of the hippocampus. Animal studies have shown that the degree of adult hippocampal neurogenesis is regulated by local environmental cues as well as neural network activities. Furthermore, accumulating evidence has suggested that adult hippocampal neurogenesis plays prominent roles in hippocampus-dependent brain functions. In this review, we summarize the mechanisms underlying the regulation of adult hippocampal neurogenesis at various developmental stages and propose how adult-born neurons contribute to structural and functional hippocampal plasticity.

Keywords Adult hippocampal neurogenesis · Learning · Memory · Hippocampal plasticity · Pattern separation

Introduction

Despite earlier evidence pointing to the existence of dividing cells in the adult brain, it is only recently that a consensus has been reached that new neurons are added to the adult mammalian brain. In the 1960s, a series of studies by Joseph Altman using [3-H]-thymidine autoradiography reported evidence of newborn neurons in adult rat and cat brains (Altman 1962, 1963; Altman and Das 1965, 1966). However, these findings were ignored for three decades due to technical concerns and lack of acceptance of this concept by the field.

After three decades of debate (Eckenhoff and Rakic 1988; Kaplan 1985; Rakic 1985), several new technologies, including the use of synthetic thymidine analogue 5-bromo-2′-deoxyuridine as well as multi-color immunolabeling for cell type-specific markers and confocal microscopy with stereological calculation of immunolabeled cells, were developed that helped to confirm the existence of adult neurogenesis. These technological developments allowed researchers to determine the existence of adult-born neurons; eventually, adult neurogenesis was confirmed in the dentate gyrus (DG) of the hippocampus of rodents by our group and others (Kempermann et al. 1997b; Kuhn et al. 1996; Seki and Arai 1999). Subsequently, two important findings were reported. First, using several different in vivo and ex vivo techniques, researchers found adult neurogenesis not only in the DG of mammalian model animals but also in the DG of the human hippocampus (Eriksson et al. 1998; Knoth et al. 2010; Roy et al. 2000; Spalding et al. 2013). Because the hippocampus is strongly associated with learning and memory, these findings prompted researchers to hypothesize that adult neurogenesis could play functional roles in human cognition. Second, several studies revealed that the process (proliferation, migration, differentiation, maturation, etc.) of adult hippocampal neurogenesis is highly regulated by experience as well as by environmental and biological factors (i.e., aging) (Cameron and McKay 1999; Gould et al. 1999; Kempermann et al. 1997b, 1998, 2002; Mirescu et al. 2004, Tanapat et al. 1999; van Praag et al. 1999). Although the proportion of adult-born neurons is a minor population compared with the total number of DG neurons, the continuous addition of new neurons over a lifetime (approximately 700 cells per day in human) implies that adult neurogenesis could add substantial structural and functional plasticity into the tri-synaptic circuits of the hippocampus (Spalding et al. 2013). Since the rate of adult neurogenesis is regulated, the degree of hippocampal plasticity (meta-plasticity) could be regulated through the modulated of adult neurogenesis. These studies have prompted the field to hypothesize and investigate the roles of hippocampal adult neurogenesis in cognitive function and brain plasticity.

In this review, we focus on the contribution of adult neurogenesis to structural and functional plasticity in the DG of the hippocampus in the rodent model.

✉ Fred H. Gage
gage@salk.edu

[1] Laboratory of Genetics – LOG-G, The Salk Institute for Biological Studies, 10010 North Torrey Pines Road, La Jolla, CA 92037, USA

Cell biological features of adult neurogenesis

Soon after the discovery of adult-born neurons in the DG of rodent and human brains, the morphological and molecular features of cells related to adult neurogenesis were extensively investigated (Fig. 1). Adult neural stem cells (type 1 radial glia-like cells; RGLs) are found in the narrow area between the granule cell layer and the hilus, the so-called sub-granular zone (SGZ). The SGZ provides an essential environmental niche for RGLs, and the microenvironment in the SGZ allows RGLs to proliferate and maintain the neural stem cell pool. One prominent feature of adult hippocampal neurogenesis is that the rate of neurogenesis is regulated by an individual's experience (described below). Since the tri-synaptic circuit in the hippocampus is strongly associated with learning and memory, the addition of adult newborn neurons in the DG could provide another layer of structural and functional plasticity in those processes in addition to the plasticity of existing circuits.

Two essential characteristics of neural stem cells are self-renewal and multipotency to generate specific neural cell types. Clonal analysis showed that RGLs in the DG have these two features (Bonaguidi et al. 2011, 2012). However, an alternative "disposable stem cell" model was proposed following the observation of serial labeling of dividing cells, in which activated RGLs differentiated into astrocytes after several rounds of cell division (Encinas et al. 2011). These two models are not mutually exclusive, and recent evidence suggests that RGLs are a heterogeneous population, differentially responding to the stimuli depending on their subtype (Jhaveri et al. 2015). Further investigation of RGLs using single-cell RNA sequencing methods currently under development should help to reveal the nature of the heterogeneity of RGLs (Lacar et al. 2016; Shin et al. 2015). RGLs generate transient amplifying progenitors (type 2a and 2b cells), type 2 cells give rise to neuroblasts (type 3) that are still able to proliferate, and neuroblasts differentiate into DG neurons (Fig. 1) (Bonaguidi et al.; Lugert et al. 2010; Suh et al. 2007). In addition to DG neurons, adult neural stem cells in the SGZ give rise to a small population of glial cells, such as astrocytes (Encinas et al. 2011; van Praag et al. 1999).

Adult neurogenesis in the forebrain is evolutionarily conserved across mammals, birds, reptiles, amphibians and fish. However, compared to other species, neurogenic regions in the mammalian adult brain are restricted to specialized brain areas such as the SGZ of DG and the subventricular zone (SVZ) of the lateral ventricle. The DG of the mammalian hippocampus is highly convoluted and much larger than a homologous structure in other species, and adult hippocampal neurogenesis in the SGZ niche of the DG is highly conserved in most mammals (Patzke et al. 2015). Interestingly, however, in cetaceans, adult neurogenesis in the DG is less evident (Patzke et al. 2015). It is not quite clear yet whether cetaceans lost the ability to maintain adult neural stem cells in the SGZ niche of the adult brain during evolution. It is possible that adult hippocampal neurogenesis is an evolutionarily novel system that developed to increase the structural and functional plasticity in the hippocampus. It may also be possible that, due to the higher metabolic requirement to maintain neural stem cells in the brain of cetaceans, which live mostly underwater, adult neural stem cells are depleted during ontogeny. Of note, the existence of postnatal neurogenesis in the human olfactory bulb, which had previously been postulated, has been questioned despite the fact that high proliferative activity in the SVZ and migrating cells in the rostral migratory stream were observed (Bergmann et al. 2012; Curtis et al. 2007; Sanai et al. 2011). This apparent loss of neurogenesis the adult olfactory bulb in humans may be because humans rely more on the visual systems than rodents, and, in parallel, humans have lost a number of olfactory receptor genes. In this light, the retention of neurogenesis in the adult hippocampal neurogenesis in humans implies that it plays some significant role in behavior. Intriguingly, the neuroblasts and/or newborn neurons that are most likely derived from the SVZ in humans migrate into several other brain regions, including the frontal cortex and the cingulate cortex in the infant brain and the striatum in the adult brain (Ernst et al. 2014; Paredes et al. 2016; Sanai et al. 2011). Because birth is one of the largest environment changes that occurs during our life, and because birth regulates brain development (Toda et al. 2013), neurogenesis and migration into the human frontal cortex occurring during perinatal periods may provide additional plasticity to adapt to environmental changes after birth. These observations also imply that the processes of adult hippocampal neurogenesis in the human brain could also differ from those in other mammalian brains, although the differences have not yet been extensively characterized. It would be intriguing to figure out how adult hippocampal neurogenesis and perinatal neurogenesis in the human brain have evolved to functionally contribute to cognition through comparing the neurogenesis-dependent functions and genetic/environmental factors involved in adult/perinatal neurogenesis. Recent technical progresses in generating human hippocampal and cerebral organoids may enable us to eventually address some of these evolutionary questions (Bredenoord et al. 2017; Sakaguchi et al. 2015).

Extrinsic factors regulating adult neurogenesis

Morphogens, cytokines and growth factors

A number of extrinsic and intrinsic factors have been found to regulate adult neurogenesis at various developmental stages, including morphogens/growth factors and their receptors,

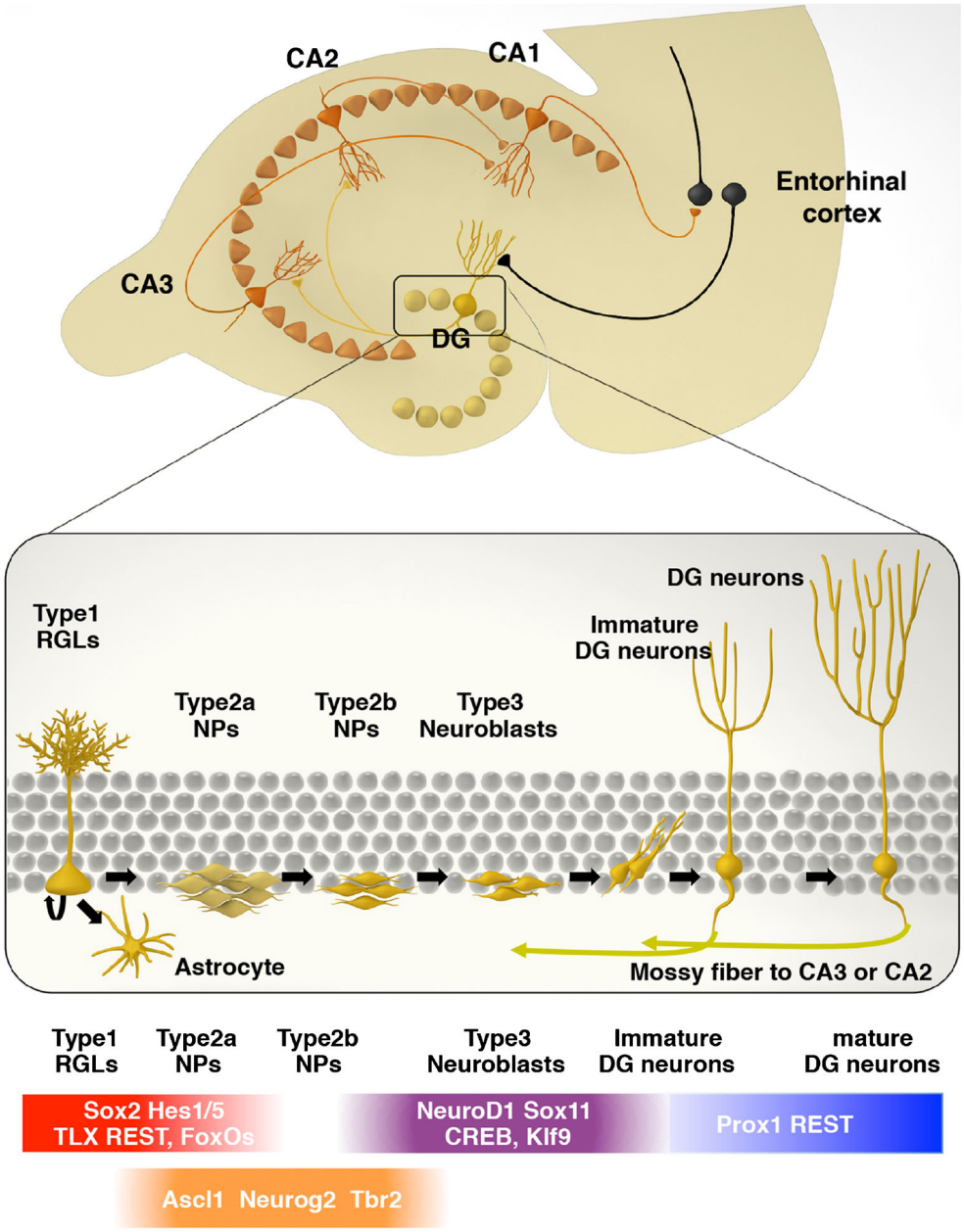

Fig. 1 Neural circuits in the hippocampus (*upper panel*). Adult neural stem cells in the hippocampus (radial glia-like cells, type 1 cells) and their differentiation in the SGZ of the DG (*lower panel*) with cell type-specific transcription factors

hormones, neurotransmitters, cell adhesion molecules, cytoplasmic factors, transcriptional factors, and epigenetic modifiers. Most molecular factors are common to both embryonic and adult neurogenesis, but some have only been reported during the processes of adult neurogenesis. It is likely, and becoming apparent in some cases, that these unique molecular factors may help explain how adult neural stem cells react to complex environmental changes in different contexts that underlie the increase in the degree of plasticity observed in adult neurogenesis.

To identify the molecular factors regulating adult neurogenesis, a useful and robust in vitro system has been developed to isolate and culture adult neural stem cells. Our group has established protocols to isolate and propagate FGF-2-responsive neural progenitor cells from several areas of rat brains (Gage et al. 1995; Palmer et al. 1995) and mouse brains (Ray and Gage 2006). Furthermore, these neural progenitors possess multipotency, the ability to differentiate into several neural cell types (Palmer et al. 1997, 1999). Isolation of hippocampal adult neural progenitors allowed us to test their cellular plasticity, and the transplantation of adult rat hippocampal neural progenitors into several brain areas revealed that they could proliferate and mature in the neurogenic brain regions but not in non-neurogenic regions (Gage et al. 1995;

Suhonen et al. 1996). In addition, transplanted neural progenitors can differentiate into non-hippocampal neurons (Suhonen et al. 1996), indicating that environmental cues play crucial roles in specifying the cell fate of adult-born neurons. In vitro neural stem cell culture technology has allowed researchers to prepare relatively pure material for biochemical and cell biological assays and has facilitated the identification of a number of essential factors, both cell-intrinsic and cell-extrinsic environmental, in addition to in vivo transgenic approaches.

Morphogens and cytokines have been found to be essential for the formation and maintenance of RGLs in the SGZ. For example, sonic hedgehog (Shh) signaling through the primary cilia is essential for the formation and maintenance of RGLs (Ahn and Joyner 2005; Breunig et al. 2008; Han et al. 2008; Li et al. 2013). A recent report showed that some hippocampal RGLs derive from the ventral hippocampus and that distinct sources of Shh signaling contribute to the formation and maintenance of RGLs, depending on developmental timing (Li et al. 2013). It is not yet clear whether all RGLs in the SGZ of the adult brain derive from the ventral hippocampus, since RGLs could be generated locally (Li and Pleasure 2005), but it will be intriguing to determine whether the heterogeneity of RGLs is derived from their developmental origins.

Bone morphogenetic protein (BMP) signaling is also implicated in the regulation of adult neurogenesis. BMPs are a subgroup of the transforming growth factor-beta of cytokines, and BMPs are supplied by the local microenvironment. BMP signaling regulates the balance between proliferation and quiescence of RGLs through BMPR-IA and Smad4, as well as the amplification and maturation of intermediate neural progenitor pools through BMPRII (Bonaguidi et al. 2008; Bond et al. 2014; Mira et al. 2010). Thus, BMP signaling modulates several aspects of the process of adult neurogenesis using different receptors, suggesting that the specific receptor-signaling cascades may contribute to organizing the strength of downstream BMP signaling in the context of adult neurogenesis. Recently, it was reported that the levels of Bmp4 and Bmp6 are increased in endothelial cells and microglia of the hippocampus, and the attenuation of BMP signaling could increase the proliferation of neural progenitors in the aged hippocampus (Yousef et al. 2015). These findings suggest that the increase in BMP secretion as a result of aging of the environmental niche could be one reason that adult neurogenesis is reduced during aging, implying that the reduction in adult neurogenesis during aging could be the consequence of systemic changes in the brain. Additionally, it appears that an increase in Noggin, which is a BMP signaling antagonist, mediates the effect of antidepressant treatment through an increase in adult neurogenesis (Brooker et al. 2017). Thus, the modulation of BMP signaling could be a therapeutic target for treating adult neurogenesis-related diseases. Interestingly, certain levels of BMP4 in combination with FGF-2 reversibly induce the quiescent state of neural stem cells in vitro. Epigenetic profiling of these cells has identified nuclear factor one X as a mediator to induce the quiescent state (Martynoga et al. 2013). Since BMP signaling also promotes astrogenesis (Bonaguidi et al. 2005), the tight control of BMP signaling seems to be critical in the balance between the maintenance and differentiation of adult neural stem cells. Although it is still not clear how much BMP4/FGF-2-induced quiescent neural stem cells in vitro resemble RGLs in vivo, further intensive characterization, such as transcriptional and epigenetic comparisons, may be able to establish a powerful in vitro model to investigate bona fide quiescent neural stem cells.

Canonical Wnt/β-catenin signaling and non-canonical Wnt signaling also play fundamental roles in the regulation of adult neurogenesis (also reviewed in Goncalves et al. 2016b; Inestrosa and Arenas 2010). Wnt3, presumably secreted from astrocytes, induces the nuclear translocation of β-catenin and subsequently activates the expression of *NeuroD1* and *Prox1,* which facilitates proliferation and neuronal cell fate specification (Karalay et al. 2011; Kuwabara et al. 2009; Lie et al. 2005; Song et al. 2002). Ephrin-B signaling also regulates the proliferation and cell fate specification by activating the Wnt signaling pathway (Ashton et al. 2012). Recently, our group also found that non-canonical Wnt/Planer cell polarity signaling regulates the neurogenesis as well as morphogenesis of DG neurons (Schafer et al. 2015). Thus, similar to the BMP signaling pathway, the same morphogens could work in the different stages of adult neurogenesis through distinct pathways.

In addition to locally secreted factors, recent studies have shown that systemic milieux play prominent roles in the regulation of adult neurogenesis. Using homo- or heterochronic parabiosis between young and old animals, one study has shown that several chemokines, such as CCL11, increase with age, and the increase in these chemokines reduces adult neurogenesis and impairs hippocampus-dependent learning and memory (Villeda et al. 2011). Subsequent studies showed that β2-microglobulin, a component of the major histocompatibility complex class 1 molecule that is known to be involved in synaptic plasticity (Corriveau et al. 1998; Huh et al. 2000), inhibits adult neurogenesis. β2-microglobulin is somehow secreted, circulates in the blood, and, interestingly, the levels of β2-microglobulin increase with age (Smith et al. 2015). A recent report also found a positive systemic factor for cognitive functions from human umbilical cord plasma (Castellano et al. 2017). Therefore, although the source of systemic changes due to aging and the underlying molecular mechanisms through which those changes regulate adult neurogenesis remain elusive, identifying the positive and negative systemic factors for adult neurogenesis/plasticity should enable researchers to develop therapeutic tools for age-dependent cognitive decline.

Cell–cell contact-mediated signaling such as Notch signaling is also essential to maintain RGLs. Notch signaling regulates proliferation and cell fate specification of RGLs and intermediate progenitor cells, and it plays fundamental roles in many aspects of developmental processes as well as in the maintenance of adult brains (Ables et al. 2011; Imayoshi and Kageyama 2014; Lui et al. 2011). Depletion of the downstream mediator of the Notch pathway, RBPj, induced the transient increase in adult neurogenesis, which subsequently caused the depletion of adult neural progenitors and reduced the adult neural pools (Ehm et al. 2010). Similarly, conditional knockout of Notch1 in RGLs resulted in a reduction in the numbers of adult-born neurons as well as RGLs and intermediate neural progenitors (Ables et al. 2010). Interestingly, physical activity rescued the total number of newborn neurons in the conditional Notch-1 KO mice without resulting in an increase in RGLs and intermediate progenitors, in contrast to the normal condition (Suh et al. 2007). Thus, Notch signaling is critical for the proliferation and activation of RGLs and intermediate progenitors but is not necessary for the proliferation of neuroblasts. Physical voluntary activity or the modulation of downstream signaling of physical activity may provide a therapy for neurogenesis-related disorders without increasing the RGL and intermediate progenitor pools.

Synaptic and non-synaptic regulation of newborn neurons

One of the unique features of adult neurogenesis is that a number of neurotransmitters are already in place to regulate the process. Compared to the embryonic brain, the adult brain has built up highly organized neural circuits and the DG receives intensive glutamatergic innervations from the entorhinal cortex (the perforant pathway) as well as local inputs from several types of GABA (γ-aminobutyric acid)-ergic interneurons (Fig. 2) (Amaral et al. 2007). In addition, the DG receives a variety of modulatory inputs, including cholinergic and GABAergic inputs from the septal nuclei, glutamatergic inputs from the supramammillary area, serotonergic inputs from the raphe nuclei, noradrenergic inputs from the nucleus locus coeruleus and dopaminergic inputs from the ventral tagmental area (Fig. 2) (Amaral et al. 2007). Thus, the anatomical features of the neural circuits innervating the DG imply that experience-dependent neural activity, as well as the emotional state of animals, has the potential to directly and/or indirectly regulate adult neurogenesis on demand. In fact, glutamatergic inputs through NMDA receptors were found to be critical for the survival of immature neurons in a time-dependent manner (Tashiro et al. 2006). There are several sources of glutamatergic input onto adult-born neurons. Combining electron microscopy and retrovirus-based newborn neuron tracing, our group found that some of the inputs likely originated from the entorhinal cortex, and newborn neurons preferentially contacted preexisting axonal boutons (Toni et al. 2007). Two- to four-week-old adult-born neurons compete with existing mature DG neurons to receive glutamatergic synaptic inputs from the entorhinal cortex to be integrated into the circuit (Toni et al. 2007). Interestingly, decreasing the spine density of mature DG neurons by a genetically inducible system increased the integration and survival of adult-born neurons, and the increased integration of adult-born neurons in aged animals improved contextual memory (McAvoy et al. 2016), suggesting that increasing adult hippocampal neurogenesis may be implemented to improve memory precision in aged humans.

More recently, it has been shown that vesicular release from astrocytes is also critical for the NMDA receptor-dependent integration of newborn DG neurons (Sultan et al. 2015). Furthermore, by taking advantage of a rabies virus-based monosypantic retrograde tracing technique (Wickersham et al. 2007), synaptic inputs onto adult-born neurons were traced and a variety of afferents have been located, including mossy cells, interneurons, CA3 neurons, and mature DG neurons, in addition to cholinergic septal cells in the lateral entorhinal and perirhinal cortex (Deshpande et al. 2013; Vivar et al. 2012). With neuronal maturation, the fraction of inputs from hilar cells and the entorhinal cortex increased, whereas the fractions of inputs from mature DG neurons decreased, suggesting that individual inputs probably contribute to distinct steps in the survival, integration, and maturation of adult-born neurons. This connectivity between adult-born neurons and CA3/mature DG neurons was surprising, and it would be interesting to determine how these feedback/feed-forward inputs onto adult-born neurons modulate the integration of adult-born neurons.

Intriguingly, the connectivity of adult newborn neurons also depends on environmental effects. When animals were reared in an enriched environment during the critical period for the development of adult-born neurons, adult-born DG neurons received a considerably higher amount of inputs from local neurons (hilar interneurons, mature DG neurons, mossy cells) as well as distal neurons (cholinergic septal neurons and the entorhinal cortex) (Bergami et al. 2015). More surprisingly, innervations from interneurons in the CA1 and CA3 of the hippocampus and from the mammillary bodies were almost exclusively observed in mice reared in an enriched environment, suggesting that an experience-dependent reorganization of the presynaptic connectivity of adult-born neurons may underlie the effects of environmental enrichment on adult neurogenesis (Kempermann et al. 1997b), and that reorganized neural circuits, including feedback inhibitory inputs from CA1 and CA3 onto adult-born neurons, could modulate synaptic integration and information processing in the DG. Interestingly, physical voluntary exercise shows slightly different effects on the connectivity compared to enriched environment, suggesting that the reorganization of

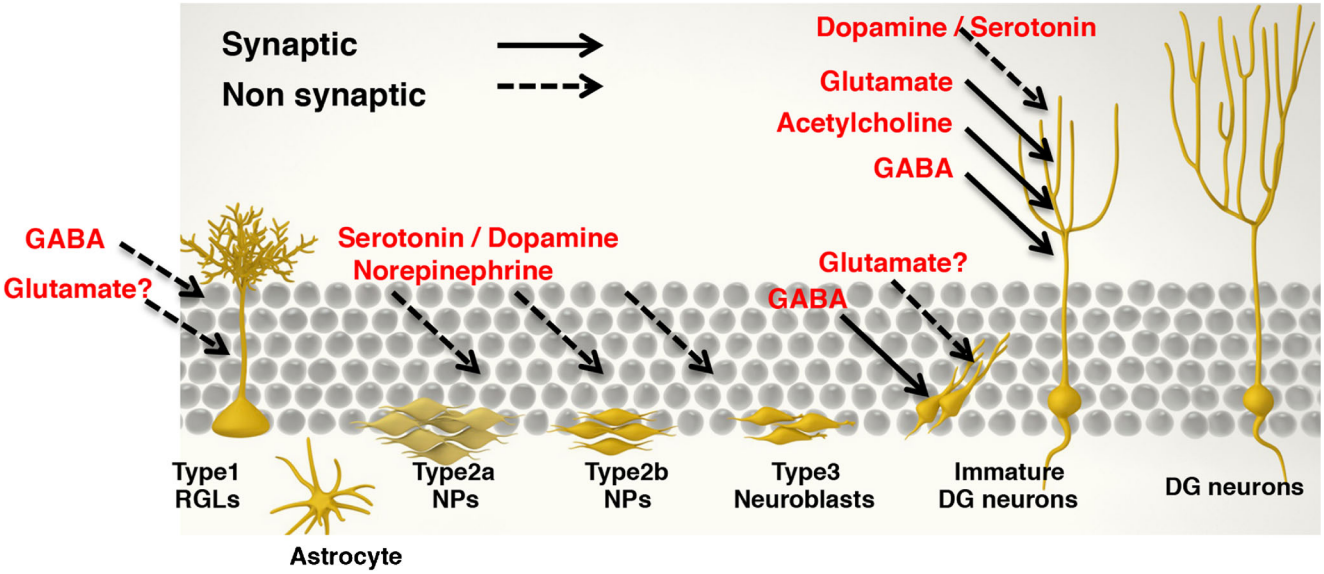

Fig. 2 Synaptic and non-synaptic inputs during adult hippocampal neurogenesis

connectivity onto the adult-born neurons is really context dependent. This finding may also explain the different consequences between the relationship of exercise and enrichment on adult neurogenesis and behavior. Thus, the integration of newborn neurons depends on activity-dependent competitive processes (Tashiro et al. 2006, 2007) and neuronal network activity as well as local release from astrocytes to regulate these processes.

Newborn DG neurons also receive tonic GABA inputs, presumably from ambient GABA, which are thought to be the first synaptic inputs onto adult-born neurons (Esposito et al. 2005); these inputs activate immature neurons due to a higher concentration of intracellular chloride ions in immature neurons (Ge et al. 2006). This GABA-induced excitation of immature neurons regulates the dendritic maturation as well as synaptic integration of immature neurons, but it has been controversial whether GABA inputs actually elicit action potentials in young adult-born neurons (Ge et al. 2006; Mongiat et al. 2009; Overstreet Wadiche et al. 2005). In an elegant recent report, more systematic electrophysiological analyses in GABAergic synaptic inputs onto the young adult-born neurons have been conducted and revealed that GABAergic inputs from the molecular layer actually depolarized doublecortin-positive immature neurons but did not evoke action potentials (Heigele et al. 2016). However, when GABA inputs from both the molecular layer and the granule cell layer were temporally summed in the range of gamma frequency, this combination efficiently evoked action potentials in young adult-born neurons. However, GABA inputs that were too strong inversely interfered with the initiation of action potentials, suggesting that young adult-born neurons responded to GABA inputs in a biphasic manner (Heigele et al. 2016). Furthermore, the study revealed the spatial and temporal integration dynamics of GABAergic and glutamatergic inputs to elicit action potentials in young adult-born DG neurons. This finding is quite striking, since gamma waves have been implicated in seeking behavior as well as memory association (Igarashi 2015). Thus, these findings suggest that the physiological state of the hippocampus could regulate the recruitment of young DG neurons into neuronal networks as well as their integration into the hippocampal circuits through GABAergic signaling. It would be interesting to compare the neuronal activity of young DG neurons and the power of gamma waves in a different environment such as an enriched environment or physical voluntary running.

In agreement with this line of research, the power of hippocampal gamma waves was found to be greater in animals housed in an enriched environment (Shinohara et al. 2013); more recently, researchers using optogenetics and chemogenetics have shown that GABAergic inputs from parvalbumin-positive interneurons, which are thought to be responsible for generating gamma waves, were found to be essential for enriched environments to enhance the integration and maturation of young DG neurons (Alvarez et al. 2016). GABA released from parvalbumin-positive interneurons also regulated the maintenance of quiescent RGLs through γ2-subunit-containing GABAA receptors (Song et al. 2012), as well as supporting the survival of newborn neurons (Song et al. 2013). A recent report has shown that diazepam binding inhibitor, an endogenous negative modulator of GABAA receptor, was enriched in RGLs and regulated the proliferation of RGLs and intermediate neural progenitors (Dumitru et al. 2017), suggesting that GABA signaling is tightly tuned to new neurons, responding to local neuronal activity and experience.

Importantly, in addition to the higher excitability of adult-born DG neurons compared to mature DG neurons, immature neurons exhibited NR2B receptor-dependent higher synaptic plasticity between 4 and 6 weeks of cellular age, a so-called critical period for the development of adult-born neurons (Ge et al. 2007).

These characteristic features of adult-born DG neurons allow them to respond to a broad range of synaptic inputs and to compete with mature neurons to be integrated into the existing neural circuits. Local network activity in the hippocampus regulates the proliferation and integration rates of neural stem cells/immature DG neurons through both glutamatergic and GABAergic signals. The newly integrated DG neurons project feed-forward excitation into the CA3 pyramidal neurons, mossy cells and hilar interneurons (Gu et al. 2012; Toni et al. 2008; Zhao et al. 2006), which is critical for memory retrieval, as well as providing feedback inhibition into the mature DG neurons to control the spare coding in the DG (Temprana et al. 2015), which plays prominent roles in the structural plasticity of hippocampal circuits and the entire hippocampal network activity. Recent studies reported that DG neurons also directly project to the CA2 pyramidal neurons making synaptic contacts, in contrast to previous observations (Kohara et al. 2014; Llorens-Martin et al. 2015). The CA2 pyramidal neurons innervate the deep layer of CA1, suggesting the existence of an alternate to the tri-synaptic circuit in the hippocampus (Kohara et al. 2014) (Fig. 1). Furthermore, adult-born DG neurons project to the CA2 region (Llorens-Martin et al. 2015), and the CA2 region plays key roles in social memory and contextual discrimination (Hitti and Siegelbaum 2014; Wintzer et al. 2014). It would be intriguing to investigate the functional difference and convergence between the classical tri-synaptic circuit and the novel CA2-mediated synaptic circuit.

Intrinsic factors regulating adult neurogenesis

Extrinsic signals activate stage-specific transcription factors (Fig. 1) that are fundamental to regulating cell type-specific gene expression and eventually proliferation, differentiation, cell fate specification, and functional maturation.

One of the prominent transcription factors is a sex-determining region Y box2 (Sox2), which is highly expressed in type1 and type 2a cells and acts as a mediator of Notch signaling and regulator of Shh expression (Ehm et al. 2010; Favaro et al. 2009). Sox2 also regulates the expression of Notch signaling components (Bani-Yaghoub et al. 2006), so these factors constitute a feedback loop to maintain the state of neural stem cells. Sox2 also works as a hub to recruit co-transcriptional regulators, and transcriptional factors such as Prx1, Brn2 (Lodato et al. 2013; Shimozaki et al. 2013) as well as epigenetic regulators HDAC1, MeCP2, Chd7 and *RMST* have been found to cooperate with Sox2 in neural stem cells (Engelen et al. 2011; Kuwabara et al. 2009; Ng et al. 2013; Szulwach et al. 2010). Sox2 regulates other critical transcription factors such as the nuclear orphan receptor Tlx (Shimozaki et al. 2012), which is critical for the regulation of adult neurogenesis as well as hippocampus-dependent learning and memory (Shi et al. 2004; Zhang et al. 2008). We recently found that one of the nuclear pore complex proteins, Nup153, interacts and cooperates with Sox2 to maintain the cellular state of neural stem cells, supporting the idea that a Sox2 partnership plays a central role in maintaining the identity of neural stem cells (Toda et al. 2017).

The other prominent transcription factor is the repressor element 1-silencing transcription (REST) and its co-factors. These factors have been reported to regulate multipotency and play indispensable roles in adult neurogenesis (Ballas et al. 2005; Gao et al. 2011; Mukherjee et al. 2016). REST is expressed from type 1 to mature DG neurons; it controls quiescent RGLs to retain neural stem cell pools and directly regulates several downstream pathways, including neurogenic genes as well as ribosome biogenesis and cell cycle. REST also non-cell-autonomously regulates neuronal differentiation through the secretion of Secretogranin II (Kim et al. 2015).

Other transcription factors that are intensively expressed in adult neural stem cells to regulate quiescence and proliferation are basic helix–loop–helix (bHLH) transcription factors such as Hes1, Hes5, Ascl1 (Mash1), Neurog1, Neurog2, Ids, Olig1, and Olig2. These factors are downstream mediators of Notch signaling, and research in embryonic neural stem cells has revealed that the oscillatory expression of bHLH factors is vital to maintaining a proliferative state and that sustained expression of single bHLH factors results in differentiation into neurons, astrocytes or oligodendrocytes (Imayoshi et al. 2013; Imayoshi and Kageyama 2014; Kageyama et al. 2015). Therefore, it will be intriguing to examine whether bHLH factors also oscillate in the quiescent adult neural stem cells. In the context of adult neurogenesis, Ascl1 has been found to have multiple functions. Originally, it was shown that Ascl1 promoted neurogenesis (Tomita et al. 1996). Subsequently, it was reported that Ascl1 was expressed in type 2a intermediate progenitors, which in turn mostly give rise to DG neurons. However, overexpression of Ascl1 in the dividing neural progenitor in the DG gives rise to oligodendrocytes (Jessberger et al. 2008), showing that adult hippocampal progenitors possess substantial cellular plasticity in vivo. In addition, a recent report found that a small subset of type 1 RGLs also expressed moderate levels of Ascl1, and about 30% of proliferating RGLs were Ascl1-positive (Andersen et al. 2014). Furthermore, neurogenic stimuli, such as kainite acid administration or conditional knockout of *RBPJk,* induced the expression of Ascl1. Additionally, the study found that the induction of Ascl1 in RGLs was essential to activate quiescent RGLs, and

conditional knockout of *Ascl1* in RGLs strongly blocked neurogenesis due to the failure to exit from a quiescent state. The study also found that Ascl1 directly bound to several cell cycle regulator genes such as *Ccnd2* and *Rm2 to* regulate their expression, providing direct evidence for the regulation of cell cycle by the expression of Ascl1 (Andersen et al. 2014). The same group also found that the destabilization of Ascl1 by E3-ubiquitin ligase Huwe1 in proliferating neural stem cells was necessary for the cells to return to a quiescent state, and conditional knockout of Huwe1 resulted in the increase in Ascl1 and depletion of adult neural stem cell pools (Urban et al. 2016). Taken together, these studies indicate that not only the regulation at the transcriptional level but also the proteostatic regulation of bHLH factors are critical to maintaining adequate levels of adult neurogenesis throughout life.

The other transcription factors regulating adult neurogenesis are FoxOs, Tbr2, and CREB (Hodge et al. 2012; Jagasia et al. 2009; Nakagawa et al. 2002; Renault et al. 2009). At the stage of fate specification, NeuroD1 and Prox1 play prominent roles in the specification of DG neurons. Activation of canonical Wnt signaling up-regulates the expression of NeuroD1 through the activation of the β-catenin/TCF/LEF complex (Gao et al. 2009; Kuwabara et al. 2009), which subsequently activates the expression of Prox1 (Karalay et al. 2011). Prox1 is an essential factor for acquiring the characteristic features of dentate granule neurons, and loss of Prox1 in post-mitotic immature DG neurons misdirects them to differentiate into CA3-like neurons (Iwano et al. 2012). Importantly, the expression of Prox1 is maintained even after the maturation of DG neurons, implying that the sustained expression of Prox1 is also essential to maintain the identity and function of DG neurons. After fate determination, Krüppel-like factor 9 (Klf-9) is a transcriptional factor regulating the functional maturation of DG neurons (Scobie et al. 2009). The expression of Klf-9 is induced by neuronal activity, and loss of Klf-9 affected the survival of adult-born neurons as well as neurogenesis-dependent synaptic plasticity (Scobie et al. 2009), suggesting that Klf-9 works as a downstream mediator of synaptic inputs onto maturating adult-born DG neurons. Taken together, these well-organized transcriptional cascades are tightly regulated from the activation of RGLs to the maturation of DG neurons through a combination of environmental and synaptic inputs.

In addition to transcription factors, accumulating evidence has shown that a number of epigenetic factors, such as histone modifiers, DNA methylase/demethylase, and microRNA, are involved in the regulation of adult neurogenesis. Histone modifications are often associated with the transcriptional status of genes, and the N-terminal tails of histones receive several post-translational modifications, such as acetylation, methylation, and phosphorylation. Histone deacetylases (HDACs) have pleiotropic roles in the gene regulation of neurogenesis. Selective knockout of HDAC2 in adult neural stem cells resulted in mis-expression of Sox2 in immature neurons and impaired the survival of adult-born neurons (Jawerka et al. 2010). HDAC1 interacts with Sox2 and presumably represses the expression of NeuroD1 as well as LINE-1 retrotransposons (Kuwabara et al. 2009).

DNA methylation has been intensively studied and plays significant roles in the regulation of temporal genes during development and genomic stability, as well as in the context of adult neurogenesis. Methyl-CpG binding proteins are major readers of DNA methylation, and they bind to methylated DNA to recruit other factors to modulate gene expression. Methyl-CpG binding protein 1 (MBD1)-knockout mice show impairments in neurogenesis and the maintenance of RGLs in the adult brain (Jobe et al. 2017; Zhao et al. 2003). Mechanistically, MBD1 directly binds the regulatory genome regions of *FGF-2*, miR-184, and miR-195, and represses their expression to regulate the proliferation and differentiation of adult neural stem cells (Li et al. 2008; Liu et al. 2013, 2010). Methyl-CpG binding protein (MeCP2) is another well-studied factor, since mutations in MeCP2 have been found to be associated with Rett syndrome (Amir et al. 1999; Guy et al. 2001). In MeCP2-knockout mice, the maturation of adult-born neurons such as spinogenesis is perturbed (Smrt et al. 2007), and the phosphorylation of MeCP2 also modulates adult neurogenesis (Li et al. 2014). MeCP2 has multiple functions in gene regulation and interacts with several other factors, including the key transcription factor Sox2, the HDAC complex, the NCoR repressors, and the microprocessor Drosha complex (Lyst et al. 2013; Nan et al. 1998; Szulwach et al. 2010; Tsujimura et al. 2015), and they work together as a hub for epigenetic regulation. MeCP2 also maintains genome stability by inhibiting L1 retrotransposition (Muotri et al. 2010). Interestingly, recent findings indicate that DNA methylation involves many more dynamic processes than previously thought (Guo et al. 2011; Zeng et al. 2016), and that neuronal activation of DG neurons by electroconvulsive stimulation induces Gadd45b in mature neurons, which mediates active DNA demethylation, and induces Gadd45b to demethylate the promoter of *FGF1* and *BDNF* genes. This demethylation eventually increases the expression of target genes, and this activity-induced gene expression presumably promotes the proliferation and morphogenesis in a non-cell-autonomous manner (Ma et al. 2009). A recent study that has systemically examined the histone modification and DNA methylation among excitatory neurons, and two types of interneurons revealed that different neural cell types possess distinct DNA methylation profiles in addition to gene expression (Mo et al. 2015). Surprisingly, the study found that non-CpG methylation within intragenic regions associated well with gene expression compared to CpG methylation, suggesting that another layer regulating DNA methylation is in place to regulate cell-type-specific gene regulation. It would be intriguing to investigate the role of non-CpG methylation in the context of adult neurogenesis.

In addition to these canonical epigenetic factors, our group has recently discovered that one of the nuclear pore complex proteins, Nup153, interacts with Sox2 and regulates the maintenance of neural progenitors through direct gene regulation (Toda et al. 2017). Although a classical role of nuclear pore complex proteins is the regulation of nuclear-cytoplasmic transport, accumulating evidence suggests that nuclear pore proteins also play prominent roles in gene regulation. Thus, our finding highlights another layer of epigenetic gene regulation by the nuclear pore proteins, which could be associated with non-random genome distribution in the nucleus or nuclear structure, the so-called nuclear architecture.

Environmental effects on adult neurogenesis

One of the intriguing and fundamental features of adult neurogenesis is that the processes of neurogenesis are regulated by an individual's behavior, experience, and emotional/biological status. This on-demand neurogenesis in response to physiological and environmental signals provides an additional layer of plasticity in the hippocampal circuits. An enriched environment has been shown to induce structural and functional changes in the brain (Bartoletti et al. 2004; Fiala et al. 1978; Rosenzweig et al. 1962). Our group tested whether environmental enrichment could lead to a higher number of neurons in the DG. Strikingly, exposure to an enriched environment significantly increased the number of newborn cells and the volume of the granule cell layer and improved the speed of spatial learning (Kempermann et al. 1997b). Subsequently, studies revealed that voluntary running selectively increased the number of newborn cells, whereas environmental enrichment promoted the survival of newborn cells (van Praag et al. 1999). Still, it remains unclear how environmental enrichment and voluntary running can increase proliferation and survival; one possibility is, as described above, that environmental signals could change the neural network activity in the hippocampus that modulates synaptic inputs on immature neurons as well as epigenetic regulation.

In contrast, stress and aging decrease the number of adult-born neurons in the DG through corticosteroid signaling (Cameron and McKay 1999; Gould et al. 1997; Kuhn et al. 1996). These studies highlight the fact that the rate of adult neurogenesis and/or that of the integration of newborn neurons could be regulated by environmental and biological factors in both a positive and a negative direction, and its consequences could affect brain function. These studies serve as a basis for follow-up studies to investigate how environmental stimuli and pathological conditions regulate and affect adult neurogenesis, how adult-born neurons contribute to brain function, and how we can implement the accumulating knowledge to develop medicines to treat people.

Functional impacts of adult-born neurons

Since the discovery of adult neurogenesis, the central question has been how adult-born neurons influence cognition and behavior. To address this question, several methodologies have been applied to ablate adult neurogenesis or silence adult-born neurons. Accumulating evidence has suggested that adult-born neurons play significant roles in cognition, learning and memory, although the results of studies have also shown inconsistencies depending on the methodology used to ablate/reduce adult-born neurons, the species and strains used, the experimental design for the behavioral assessment, and the timing of tests after the manipulation of adult neurogenesis; all these factors have made it difficult to obtain a consensus regarding the basic principles of the functional roles of adult neurogenesis. In this section, we summarize the experimental observations based on different strategies and discuss future directions for research.

Learning, memory and cognitive flexibility

One common strategy used to study the function of adult neurogenesis is to ablate adult-born neurons and examine the cognitive performance of animals. To assess the functional roles of hippocampal adult neurogenesis, many studies have investigated hippocampus-dependent cognitive abilities such as contextual and spatial memories after the ablation of adult-born neurons. Initially, antimitotic reagents such as methylazoxymethanol acetate (MAM) or temozolomide (TMZ) were used to reduce adult neurogenesis in the adult rat and mouse (Garthe et al. 2009; Shors et al. 2001). Treatment by MAM reduced adult neurogenesis in the hippocampus and resulted in deficits in hippocampus-dependent trace eyeblink conditioning but not in hippocampus-independent delay eyeblink conditioning tasks (Shors et al. 2001). After withdrawal of MAM, as adult neurogenesis recovered, the trace eyeblink conditioning recovered (Shors et al. 2001), suggesting that adult neurogenesis plays a role in hippocampus-dependent contextual memory. Similarly, MAM treatment canceled out the beneficial effect of environmental enrichment on long-term memory during a novel-object recognition task in the adult rat but made no changes in contextual fear memory (Bruel-Jungerman et al. 2005; Shors et al. 2002). Interestingly, the ablation of adult neurogenesis by TMZ in mice affected not only the speed of learning but also the flexibility in the Morris water maze test (Garthe et al. 2009). Thus, adult-born neurons may function not only in learning processes but also in the plasticity of learning strategies.

Since the chemical ablation of adult neural stem cells could involve other side effects, several groups subsequently developed novel strategies to selectively ablate adult neurogenesis, such as focal X-ray irradiation and genetic ablation based on

transgenic animals using neural progenitor-specific promoters (Clelland et al. 2009; Deng et al. 2009; Imayoshi et al. 2008; Meshi et al. 2006; Saxe et al. 2006, 2007). As opposed to the results using MAM in rats (Shors et al. 2002), focally irradiated mice, depleted of adult neurogenesis, showed impairments in contextual fear conditioning and a formation of long-term potentiation (LTP) in the DG but not in cued fear conditioning and spatial memory 3 months after irradiation (Saxe et al. 2006). Similarly, although MAM blocked the effect of enriched environment on novel-object recognition test in rats (Bruel-Jungerman et al. 2005), the ablation of adult-born neurons by focal X-ray irradiation onto the mouse hippocampus did not alter the effects of an enriched environment on spatial learning with the Morris Water maze (Meshi et al. 2006). In another study, 11 days after X-ray irradiation of the whole brain, the magnitude of LTP was not altered but the retention of LTP was enhanced in the DG of rats (Kitamura et al. 2009), suggesting that learning-induced LTP in the DG might be reversed by adult-born DG neurons, which might be the basis of the decay of the hippocampus-dependent memory as well as hippocampus-dependent cognitive flexibility (Garthe et al. 2009). Since the feedback inhibition from young adult-born DG neurons suppresses the activity of mature DG neurons (Temprana et al. 2015), the ablation of newborn neurons may temporarily increase the excitability of mature DG neurons. In line with this notion, a recent study reported the role of adult neurogenesis in the clearance of hippocampus-dependent memory and infantile amnesia (Akers et al. 2014; Epp et al. 2016). However, another study reported that an episodic memory during the infantile amnesia period was not completely cleared but stored as a latent memory for long periods of time. (Travaglia et al. 2016). The study also showed that, although recent fear contextual memory was slightly impaired in the irradiated mice 5 weeks after irradiation, remote fear contextual memory was not perturbed in the irradiated mice (Kitamura et al. 2009). Interestingly, the study found that adult neurogenesis modulated the speed of memory transfer from the hippocampus to elsewhere, most likely into the neocortex, suggesting that adult neurogenesis could also modulate the relocation and long-term storage of memory in the brain.

As an independent approach to specifically ablate neural stem cells, or temporally control the rate of adult neurogenesis, transgenic animal models were developed: Nestin-CreER^{T2,} in which a tamoxifen-inducible Cre recombinase is expressed under the control of a neural stem cell-specific nestin promoter (Imayoshi et al. 2008), or Nestin-tk and GFAP-tk mice, in which a thymidine kinase is expressed under the control of neural stem cell/glial cell-specific promoters (Deng et al. 2009; Saxe et al. 2007). Ablation of adult-born neurons by the combination of Nestin-CreER^{T2} and NSE-DTA (diphtheria toxin A) mice impaired spatial learning and memory with the Barnes maze test (Imayoshi et al. 2008). Treatment of Nestin-tk or GFAP-tk mice by ganciclovir (GCV) allowed researchers to temporally reduce adult neurogenesis. After a 6-week GCV treatment, GFAP-tk mice exhibited a deficit in contextual fear conditioning but not in cued conditioning (Saxe et al. 2006). On the other hand, the reduction of adult neurogenesis by a 2-week treatment of Nestin-tk mice with GCV impaired spatial long-term memory in the Morris water maze but did not affect learning processes and memory extinction (Deng et al. 2009). In the same mouse model with the contextual fear memory test, extinction of short-term memory was impaired but not learning itself, and the effect reverted after the recovery of neurogenesis (Deng et al. 2009), suggesting a specific role for adult neurogenesis in the process of learning and memory.

Overall, a number of studies support the idea that adult hippocampus neurogenesis plays significant roles in hippocampus-dependent cognitive functions, including learning, memory, and cognitive flexibility, although the results and interpretations vary depending on the method used to ablate adult-born neurons, the species used in the studies, and the behavioral assays; therefore, further investigations are required. It has been noted that the genetic background and ages of animals strongly influence the rate of adult neurogenesis (Kempermann et al. 1997a; Kuhn et al. 1996), and thus the impacts of adult neurogenesis on hippocampal function may vary among different species and strains; we need to carefully take this point into account when comparing different studies.

Pattern separation

In addition to contextual memory, hippocampal adult neurogenesis has been postulated to function in the process of pattern separation, a computational process that is employed to discriminate inputs from entorhinal cortex to separate information and to encode that information as distinct memories, based on the firing patterns of groups of neurons. Due to its anatomical and physiological features (Aimone et al. 2014; Deng et al. 2010), the DG has been considered to be a pattern separator, and this notion has been experimentally tested (Leutgeb et al. 2007; McHugh et al. 2007). The addition of highly excitable newborn DG neurons could impact the process of pattern separation and may shape spatial and temporal pattern separation. The details of pattern separation combined with adult neurogenesis are reviewed in Aimone et al. (2014) and Deng et al. (2010). To experimentally test the pattern separation hypothesis, focally irradiated mice exhibited impaired spatial pattern separation. Therefore, the DG was suggested to function as a pattern separator for spatial or episodic memory (Clelland et al. 2009). Similarly, attenuation of adult neurogenesis by treatment with TMZ or GCV in Nestin-tk mice impaired spatial pattern separation and

CA3 population coding (Niibori et al. 2012). Complementary approaches that increased adult neurogenesis with voluntary running or inhibited programmed cell death by ablating *Bax* improved pattern separation (Creer et al. 2010; Sahay et al. 2011) and also supported the idea that adult-born neurons were in place to regulate spatial pattern separation. However, in contrast, another study showed that ablation of neurogenesis by X-ray irradiation improved working memory in a low-memory load/high interference radial maze-task (Saxe et al. 2007). Thus, depending on the temporal and spatial information, immature neurons may have distinct functions in pattern separation.

Recent advanced transgenic approaches also allowed researchers to compare the functions of mature and immature DG neurons using cell-type-specific expression of tetanus toxin (Nakashiba et al. 2012). When the synaptic transmission from mature DG neurons was inhibited, the ability to discriminate different contexts in the contextual fear memory test was enhanced, but this enhancement was blocked by ablating adult-born neurons with irradiation, supporting the idea that immature DG neurons are responsible for spatial pattern separation. Another study investigated the functional impact of adult-born DG neurons from a different angle by increasing the integration of adult-born neurons. The study found that, as the integration of adult-born neurons increased, local connectivities involved in adult-born neurons were reorganized and the precision of contextual fear memory was improved in both young and old mice, suggesting that a fraction of integrated adult-born DG neurons is crucial for pattern separation (McAvoy et al. 2016).

Overall, adult-born neurons in the DG seem to be functionally important in many different aspects of hippocampus-dependent function such as short-term and long-term memory formation, the flexibility of learning strategies, and pattern separation.

Emotional control by adult neurogenesis

In addition to learning and memory, accumulating evidence suggests that adult neurogenesis in the DG regulates emotional status, such as anxiety and depression, in conjunction with cognitive flexibility. It has been shown that hippocampal adult neurogenesis is very sensitive to the effects of stress from the perinatal period to adulthood (Gould et al. 1997; Lehmann et al. 2013; Lemaire et al. 2000; Mirescu et al. 2004), and that adult neurogenesis is required for some of the beneficial effects of antidepressants through $5HT_{1A}$ receptors (Santarelli et al. 2003). Interestingly, most studies have shown that the ablation of adult-born neurons does not affect the baseline levels of anxiety (David et al. 2009; Kitamura et al. 2009; Saxe et al. 2006), suggesting that adult neurogenesis is important for the stress response but not in every case (Bessa et al. 2009). It is not yet clear how adult hippocampal neurogenesis regulates anxiety levels, but some evidence indicates that adult-born neurons buffer the stress responses, and that the depletion of adult-born neurons augments stress responses and increases anxiety and depression-like behavior (Snyder et al. 2011). Since the ventral subiculum in the hippocampus inhibits the activity of the hypothalamo-pituitary-adrenocortical axis, a critical adaptive system against physical and psychological challenges (Jankord and Herman 2008), adult-born neurons may somehow balance the activity levels of the ventral subiculum. Recent optogenetic approaches have revealed that the ventral hippocampus is associated with social memory and anxiety, and that the activation of the ventral DG neurons can reduce anxiety levels (Kheirbek et al. 2013; Okuyama et al. 2016), suggesting that differential circuits along the dorsoventral axis of the hippocampus may process distinct information. However, it is possible that the dorsal hippocampus could also regulate anxiety-/depression-related behavior through the amygdala (Ramirez et al. 2015). Further investigation will be required to figure out how adult-born neurons buffer stress responses at the circuit levels.

Future directions

As summarized above, since adult neurogenesis was "rediscovered", the molecular mechanisms underlying adult hippocampal neurogenesis have been intensively studied. A number of intrinsic and extrinsic factors regulate the maintenance, proliferation, and differentiation of adult neural stem cells/progenitors. In addition, spatially and temporally organized synaptic/non-synaptic inputs onto adult-born neurons regulate the integration of adult-born neurons into the existing neural circuits, which provides substantial structural plasticity into the tri-synaptic hippocampal circuits. Since the number of adult-born neurons and the integrated numbers of neurons into the existing circuits are regulated by several intrinsic and environmental factors, as summarized above, these observations suggest that the degree of hippocampal plasticity, which is adult hippocampal neurogenesis-dependent meta-plasticity, can also be regulatable. It would be intriguing to investigate to what extent the adult-hippocampal neurogenesis-dependent meta-plasticity can be regulated in physiological and pathological conditions. Importantly, it is not yet clear how adult-born neurons modify the network activity and contribute behaviorally to hippocampal functional plasticity in vivo. Most of our knowledge about the function of adult neurogenesis comes from behavioral studies using the ablation of adult-born neurons or from electrophysiological analysis in vitro. Therefore, we do not yet know how adult-born neurons contribute to hippocampal functions in the natural context. Several groups, including ours, have been developing novel live-imaging methodology to measure neuronal activity in the DG in awake, behaving mice using a multi-photon

microscopy or microendoscopy (Danielson et al. 2016, 2017; Goncalves et al. 2016a; Kirschen et al. 2017; Pilz et al. 2016). In combination with cell type-specific expression of calcium indicators, these methods allow us to track neural activity in young adult-born DG neurons, mature DG neurons, mossy cells, and interneurons in the hilus over time, and enable us to measure the impact of adult-born neurons on hippocampal plasticity. Although current methodologies require the removal of the neocortex and/or the CA1 regions for imaging the DG, in vivo imaging will likely uncover more precisely the functions of adult-born DG neurons depending on the timing of maturation, the state of the neural network, and the history of neuronal activity. Further technical developments, such as 3-photon microscopy, may one day allow intact imaging of the DG (Ouzounov et al. 2017).

Looking back on the relatively short history since the rediscovery of adult neurogenesis, remarkable progress in our understanding of the structure and function of this most plastic process in the adult nervous system has been made, and new technologies are promising a deeper understanding.

Acknowledgments We thank M.L. Gage and S. Marshall for comments on the manuscript. This work was supported by NIH R01 MH095741, NIH U01 MH106882, The G. Harold and Leila Y. Mathers Charitable Foundation, The Leona M. and Harry B. Helmsley Charitable Trust (grant #2012-PG-MED00), Annette C. Merle-Smith, JPB Foundation and The McKnight Foundation, The Kanae foundation for the Promotion of Medical Science. T.T. was supported by Japan Society for the Promotion of Science. We thank Mary Lynn Gage for editorial comments and Veronika Mertens for illustrations.

Compliance with ethical standards

Conflict of interests The authors declare no conflict of interests.

References

Ables JL, Breunig JJ, Eisch AJ, Rakic P (2011) Not(ch) just development: notch signalling in the adult brain. Nat Rev Neurosci 12:269–283

Ables JL, Decarolis NA, Johnson MA, Rivera PD, Gao Z, Cooper DC, Radtke F, Hsieh J, Eisch AJ (2010) Notch1 is required for maintenance of the reservoir of adult hippocampal stem cells. J Neurosci 30:10484–10492

Ahn S, Joyner AL (2005) In vivo analysis of quiescent adult neural stem cells responding to sonic hedgehog. Nature 437:894–897

Aimone JB, Li Y, Lee SW, Clemenson GD, Deng W, Gage FH (2014) Regulation and function of adult neurogenesis: from genes to cognition. Physiol Rev 94:991–1026

Akers KG, Martinez-Canabal A, Restivo L, Yiu AP, De Cristofaro A, Hsiang HL, Wheeler AL, Guskjolen A, Niibori Y, Shoji H, Ohira K, Richards BA, Miyakawa T, Josselyn SA, Frankland PW (2014) Hippocampal neurogenesis regulates forgetting during adulthood and infancy. Science 344:598–602

Altman J (1962) Are new neurons formed in the brains of adult mammals? Science 135:1127–1128

Altman J (1963) Autoradiographic investigation of cell proliferation in the brains of rats and cats. Anat Rec 145:573–591

Altman J, Das GD (1965) Autoradiographic and histological evidence of postnatal hippocampal neurogenesis in rats. J Comp Neurol 124: 319–335

Altman J, Das GD (1966) Autoradiographic and histological studies of postnatal neurogenesis. I. A longitudinal investigation of the kinetics, migration and transformation of cells incorporating tritiated thymidine in neonate rats, with special reference to postnatal neurogenesis in some brain regions. J Comp Neurol 126:337–389

Alvarez DD, Giacomini D, Yang SM, Trinchero MF, Temprana SG, Buttner KA, Beltramone N, Schinder AF (2016) A disynaptic feedback network activated by experience promotes the integration of new granule cells. Science 354:459–465

Amaral DG, Scharfman HE, Lavenex P (2007) The dentate gyrus: fundamental neuroanatomical organization (dentate gyrus for dummies). Prog Brain Res 163:3–22

Amir RE, Van den Veyver IB, Wan M, Tran CQ, Francke U, Zoghbi HY (1999) Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpG-binding protein 2. Nat Genet 23:185–188

Andersen J, Urban N, Achimastou A, Ito A, Simic M, Ullom K, Martynoga B, Lebel M, Goritz C, Frisen J, Nakafuku M, Guillemot F (2014) A transcriptional mechanism integrating inputs from extracellular signals to activate hippocampal stem cells. Neuron 83:1085–1097

Ashton RS, Conway A, Pangarkar C, Bergen J, Lim KI, Shah P, Bissell M, Schaffer DV (2012) Astrocytes regulate adult hippocampal neurogenesis through ephrin-B signaling. Nat Neurosci 15:1399–1406

Ballas N, Grunseich C, Lu DD, Speh JC, Mandel G (2005) REST and its corepressors mediate plasticity of neuronal gene chromatin throughout neurogenesis. Cell 121:645–657

Bani-Yaghoub M, Tremblay RG, Lei JX, Zhang D, Zurakowski B, Sandhu JK, Smith B, Ribecco-Lutkiewicz M, Kennedy J, Walker PR, Sikorska M (2006) Role of Sox2 in the development of the mouse neocortex. Dev Biol 295:52–66

Bartoletti A, Medini P, Berardi N, Maffei L (2004) Environmental enrichment prevents effects of dark-rearing in the rat visual cortex. Nat Neurosci 7:215–216

Bergami M, Masserdotti G, Temprana SG, Motori E, Eriksson TM, Gobel J, Yang SM, Conzelmann KK, Schinder AF, Gotz M, Berninger B (2015) A critical period for experience-dependent remodeling of adult-born neuron connectivity. Neuron 85:710–717

Bergmann O, Liebl J, Bernard S, Alkass K, Yeung MS, Steier P, Kutschera W, Johnson L, Landen M, Druid H, Spalding KL, Frisen J (2012) The age of olfactory bulb neurons in humans. Neuron 74:634–639

Bessa JM, Ferreira D, Melo I, Marques F, Cerqueira JJ, Palha JA, Almeida OF, Sousa N (2009) The mood-improving actions of antidepressants do not depend on neurogenesis but are associated with neuronal remodeling. Mol Psychiatry 14(764–773):739

Bonaguidi MA, McGuire T, Hu M, Kan L, Samanta J, Kessler JA (2005) LIF and BMP signaling generate separate and discrete types of GFAP-expressing cells. Development 132:5503–5514

Bonaguidi MA, Peng CY, McGuire T, Falciglia G, Gobeske KT, Czeisler C, Kessler JA (2008) Noggin expands neural stem cells in the adult hippocampus. J Neurosci 28:9194–9204

Bonaguidi MA, Song J, Ming GL, Song H (2012) A unifying hypothesis on mammalian neural stem cell properties in the adult hippocampus. Curr Opin Neurobiol 22:754–761

Bonaguidi MA, Wheeler MA, Shapiro JS, Stadel RP, Sun GJ, Ming GL, Song H (2011) In vivo clonal analysis reveals self-renewing and multipotent adult neural stem cell characteristics. Cell 145:1142–1155

Bond AM, Peng CY, Meyers EA, McGuire T, Ewaleifoh O, Kessler JA (2014) BMP signaling regulates the tempo of adult hippocampal progenitor maturation at multiple stages of the lineage. Stem Cells 32:2201–2214

Bredenoord AL, Clevers H, Knoblich JA (2017) Human tissues in a dish: the research and ethical implications of organoid technology. Science 355:eaaf9414

Breunig JJ, Sarkisian MR, Arellano JI, Morozov YM, Ayoub AE, Sojitra S, Wang B, Flavell RA, Rakic P, Town T (2008) Primary cilia regulate hippocampal neurogenesis by mediating sonic hedgehog signaling. Proc Natl Acad Sci U S A 105:13127–13132

Brooker SM, Gobeske KT, Chen J, Peng CY, Kessler JA (2017) Hippocampal bone morphogenetic protein signaling mediates behavioral effects of antidepressant treatment. Mol Psychiatry 22: 910–919

Bruel-Jungerman E, Laroche S, Rampon C (2005) New neurons in the dentate gyrus are involved in the expression of enhanced long-term memory following environmental enrichment. Eur J Neurosci 21: 513–521

Cameron HA, McKay RD (1999) Restoring production of hippocampal neurons in old age. Nat Neurosci 2:894–897

Castellano JM, Mosher KI, Abbey RJ, McBride AA, James ML, Berdnik D, Shen JC, Zou B, Xie XS, Tingle M, Hinkson IV, Angst MS, Wyss-Coray T (2017) Human umbilical cord plasma proteins revitalize hippocampal function in aged mice. Nature 544:488–492

Clelland CD, Choi M, Romberg C, Clemenson GD Jr, Fragniere A, Tyers P, Jessberger S, Saksida LM, Barker RA, Gage FH, Bussey TJ (2009) A functional role for adult hippocampal neurogenesis in spatial pattern separation. Science 325:210–213

Corriveau RA, Huh GS, Shatz CJ (1998) Regulation of class I MHC gene expression in the developing and mature CNS by neural activity. Neuron 21:505–520

Creer DJ, Romberg C, Saksida LM, van Praag H, Bussey TJ (2010) Running enhances spatial pattern separation in mice. Proc Natl Acad Sci U S A 107:2367–2372

Curtis MA, Kam M, Nannmark U, Anderson MF, Axell MZ, Wikkelso C, Holtas S, van Roon-Mom WM, Bjork-Eriksson T, Nordborg C, Frisen J, Dragunow M, Faull RL, Eriksson PS (2007) Human neuroblasts migrate to the olfactory bulb via a lateral ventricular extension. Science 315:1243–1249

Danielson NB, Kaifosh P, Zaremba JD, Lovett-Barron M, Tsai J, Denny CA, Balough EM, Goldberg AR, Drew LJ, Hen R, Losonczy A, Kheirbek MA (2016) Distinct contribution of adult-born Hippocampal granule cells to context encoding. Neuron 90:101–112

Danielson NB, Turi GF, Ladow M, Chavlis S, Petrantonakis PC, Poirazi P, Losonczy A (2017) In vivo imaging of dentate Gyrus mossy cells in behaving mice. Neuron 93:552–559 e554

David DJ, Samuels BA, Rainer Q, Wang JW, Marsteller D, Mendez I, Drew M, Craig DA, Guiard BP, Guilloux JP, Artymyshyn RP, Gardier AM, Gerald C, Antonijevic IA, Leonardo ED, Hen R (2009) Neurogenesis-dependent and -independent effects of fluoxetine in an animal model of anxiety/depression. Neuron 62:479–493

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

Deng W, Saxe MD, Gallina IS, Gage FH (2009) Adult-born hippocampal dentate granule cells undergoing maturation modulate learning and memory in the brain. J Neurosci 29:13532–13542

Deshpande A, Bergami M, Ghanem A, Conzelmann KK, Lepier A, Gotz M, Berninger B (2013) Retrograde monosynaptic tracing reveals the temporal evolution of inputs onto new neurons in the adult dentate gyrus and olfactory bulb. Proc Natl Acad Sci U S A 110:E1152–E1161

Dumitru I, Neitz A, Alfonso J, Monyer H (2017) Diazepam binding inhibitor promotes stem cell expansion controlling environment-dependent Neurogenesis. Neuron 94:125–137 e125

Eckenhoff MF, Rakic P (1988) Nature and fate of proliferative cells in the hippocampal dentate gyrus during the life span of the rhesus monkey. J Neurosci 8:2729–2747

Ehm O, Goritz C, Covic M, Schaffner I, Schwarz TJ, Karaca E, Kempkes B, Kremmer E, Pfrieger FW, Espinosa L, Bigas A, Giachino C, Taylor V, Frisen J, Lie DC (2010) RBPJkappa-dependent signaling is essential for long-term maintenance of neural stem cells in the adult hippocampus. J Neurosci 30:13794–13807

Encinas JM, Michurina TV, Peunova N, Park JH, Tordo J, Peterson DA, Fishell G, Koulakov A, Enikolopov G (2011) Division-coupled astrocytic differentiation and age-related depletion of neural stem cells in the adult hippocampus. Cell Stem Cell 8:566–579

Engelen E, Akinci U, Bryne JC, Hou J, Gontan C, Moen M, Szumska D, Kockx C, van Ijcken W, Dekkers DH, Demmers J, Rijkers EJ, Bhattacharya S, Philipsen S, Pevny LH, Grosveld FG, Rottier RJ, Lenhard B, Poot RA (2011) Sox2 cooperates with Chd7 to regulate genes that are mutated in human syndromes. Nat Genet 43:607–611

Epp JR, Silva Mera R, Kohler S, Josselyn SA, Frankland PW (2016) Neurogenesis-mediated forgetting minimizes proactive interference. Nat Commun 7:10838

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

Ernst A, Alkass K, Bernard S, Salehpour M, Perl S, Tisdale J, Possnert G, Druid H, Frisen J (2014) Neurogenesis in the striatum of the adult human brain. Cell 156:1072–1083

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

Favaro R, Valotta M, Ferri AL, Latorre E, Mariani J, Giachino C, Lancini C, Tosetti V, Ottolenghi S, Taylor V, Nicolis SK (2009) Hippocampal development and neural stem cell maintenance require Sox2-dependent regulation of Shh. Nat Neurosci 12:1248–1256

Fiala BA, Joyce JN, Greenough WT (1978) Environmental complexity modulates growth of granule cell dendrites in developing but not adult hippocampus of rats. Exp Neurol 59:372–383

Gage FH, Coates PW, Palmer TD, Kuhn HG, Fisher LJ, Suhonen JO, Peterson DA, Suhr ST, Ray J (1995) Survival and differentiation of adult neuronal progenitor cells transplanted to the adult brain. Proc Natl Acad Sci U S A 92:11879–11883

Gao Z, Ure K, Ables JL, Lagace DC, Nave KA, Goebbels S, Eisch AJ, Hsieh J (2009) Neurod1 is essential for the survival and maturation of adult-born neurons. Nat Neurosci 12:1090–1092

Gao Z, Ure K, Ding P, Nashaat M, Yuan L, Ma J, Hammer RE, Hsieh J (2011) The master negative regulator REST/NRSF controls adult neurogenesis by restraining the neurogenic program in quiescent stem cells. J Neurosci 31:9772–9786

Garthe A, Behr J, Kempermann G (2009) Adult-generated hippocampal neurons allow the flexible use of spatially precise learning strategies. PLoS ONE 4:e5464

Ge S, Goh EL, Sailor KA, Kitabatake Y, Ming GL, Song H (2006) GABA regulates synaptic integration of newly generated neurons in the adult brain. Nature 439:589–593

Ge S, Yang CH, Hsu KS, Ming GL, Song H (2007) A critical period for enhanced synaptic plasticity in newly generated neurons of the adult brain. Neuron 54:559–566

Goncalves JT, Bloyd CW, Shtrahman M, Johnston ST, Schafer ST, Parylak SL, Tran T, Chang T, Gage FH (2016a) In vivo imaging of dendritic pruning in dentate granule cells. Nat Neurosci 19:788–791

Goncalves JT, Schafer ST, Gage FH (2016b) Adult Neurogenesis in the hippocampus: from stem cells to behavior. Cell 167:897–914

Gould E, Beylin A, Tanapat P, Reeves A, Shors TJ (1999) Learning enhances adult neurogenesis in the hippocampal formation. Nat Neurosci 2:260–265

Gould E, McEwen BS, Tanapat P, Galea LA, Fuchs E (1997) Neurogenesis in the dentate gyrus of the adult tree shrew is regulated

by psychosocial stress and NMDA receptor activation. J Neurosci 17:2492–2498

Gu Y, Arruda-Carvalho M, Wang J, Janoschka SR, Josselyn SA, Frankland PW, Ge S (2012) Optical controlling reveals time-dependent roles for adult-born dentate granule cells. Nat Neurosci 15:1700–1706

Guo JU, Su Y, Zhong C, Ming GL, Song H (2011) Hydroxylation of 5-methylcytosine by TET1 promotes active DNA demethylation in the adult brain. Cell 145:423–434

Guy J, Hendrich B, Holmes M, Martin JE, Bird A (2001) A mouse Mecp2-null mutation causes neurological symptoms that mimic Rett syndrome. Nat Genet 27:322–326

Han YG, Spassky N, Romaguera-Ros M, Garcia-Verdugo JM, Aguilar A, Schneider-Maunoury S, Alvarez-Buylla A (2008) Hedgehog signaling and primary cilia are required for the formation of adult neural stem cells. Nat Neurosci 11:277–284

Heigele S, Sultan S, Toni N, Bischofberger J (2016) Bidirectional GABAergic control of action potential firing in newborn hippocampal granule cells. Nat Neurosci 19:263–270

Hitti FL, Siegelbaum SA (2014) The hippocampal CA2 region is essential for social memory. Nature 508:88–92

Hodge RD, Nelson BR, Kahoud RJ, Yang R, Mussar KE, Reiner SL, Hevner RF (2012) Tbr2 is essential for hippocampal lineage progression from neural stem cells to intermediate progenitors and neurons. J Neurosci 32:6275–6287

Huh GS, Boulanger LM, Du H, Riquelme PA, Brotz TM, Shatz CJ (2000) Functional requirement for class I MHC in CNS development and plasticity. Science 290:2155–2159

Igarashi KM (2015) Plasticity in oscillatory coupling between hippocampus and cortex. Curr Opin Neurobiol 35:163–168

Imayoshi I, Isomura A, Harima Y, Kawaguchi K, Kori H, Miyachi H, Fujiwara T, Ishidate F, Kageyama R (2013) Oscillatory control of factors determining multipotency and fate in mouse neural progenitors. Science 342:1203–1208

Imayoshi I, Kageyama R (2014) bHLH factors in self-renewal, multipotency, and fate choice of neural progenitor cells. Neuron 82:9–23

Imayoshi I, Sakamoto M, Ohtsuka T, Takao K, Miyakawa T, Yamaguchi M, Mori K, Ikeda T, Itohara S, Kageyama R (2008) Roles of continuous neurogenesis in the structural and functional integrity of the adult forebrain. Nat Neurosci 11:1153–1161

Inestrosa NC, Arenas E (2010) Emerging roles of Wnts in the adult nervous system. Nat Rev Neurosci 11:77–86

Iwano T, Masuda A, Kiyonari H, Enomoto H, Matsuzaki F (2012) Prox1 postmitotically defines dentate gyrus cells by specifying granule cell identity over CA3 pyramidal cell fate in the hippocampus. Development 139:3051–3062

Jagasia R, Steib K, Englberger E, Herold S, Faus-Kessler T, Saxe M, Gage FH, Song H, Lie DC (2009) GABA-cAMP response element-binding protein signaling regulates maturation and survival of newly generated neurons in the adult hippocampus. J Neurosci 29:7966–7977

Jankord R, Herman JP (2008) Limbic regulation of hypothalamo-pituitary-adrenocortical function during acute and chronic stress. Ann N Y Acad Sci 1148:64–73

Jawerka M, Colak D, Dimou L, Spiller C, Lagger S, Montgomery RL, Olson EN, Wurst W, Gottlicher M, Gotz M (2010) The specific role of histone deacetylase 2 in adult neurogenesis. Neuron Glia Biol 6: 93–107

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

Jhaveri DJ, O'Keeffe I, Robinson GJ, Zhao QY, Zhang ZH, Nink V, Narayanan RK, Osborne GW, Wray NR, Bartlett PF (2015) Purification of neural precursor cells reveals the presence of distinct, stimulus-specific subpopulations of quiescent precursors in the adult mouse hippocampus. J Neurosci 35:8132–8144

Jobe EM, Gao Y, Eisinger BE, Mladucky JK, Giuliani CC, Kelnhofer LE, Zhao X (2017) Methyl-CpG-binding protein MBD1 regulates neuronal lineage commitment through maintaining adult neural stem cell identity. J Neurosci 37:523–536

Kageyama R, Shimojo H, Imayoshi I (2015) Dynamic expression and roles of Hes factors in neural development. Cell Tissue Res 359: 125–133

Kaplan MS (1985) Formation and turnover of neurons in young and senescent animals: an electronmicroscopic and morphometric analysis. Ann N Y Acad Sci 457:173–192

Karalay O, Doberauer K, Vadodaria KC, Knobloch M, Berti L, Miquelajauregui A, Schwark M, Jagasia R, Taketo MM, Tarabykin V, Lie DC, Jessberger S (2011) Prospero-related homeobox 1 gene (Prox1) is regulated by canonical Wnt signaling and has a stage-specific role in adult hippocampal neurogenesis. Proc Natl Acad Sci U S A 108:5807–5812

Kempermann G, Gast D, Gage FH (2002) Neuroplasticity in old age: sustained fivefold induction of hippocampal neurogenesis by long-term environmental enrichment. Ann Neurol 52:135–143

Kempermann G, Kuhn HG, Gage FH (1997a) Genetic influence on neurogenesis in the dentate gyrus of adult mice. Proc Natl Acad Sci U S A 94:10409–10414

Kempermann G, Kuhn HG, Gage FH (1997b) More hippocampal neurons in adult mice living in an enriched environment. Nature 386: 493–495

Kempermann G, Kuhn HG, Gage FH (1998) Experience-induced neurogenesis in the senescent dentate gyrus. J Neurosci 18:3206–3212

Kheirbek MA, Drew LJ, Burghardt NS, Costantini DO, Tannenholz L, Ahmari SE, Zeng H, Fenton AA, Hen R (2013) Differential control of learning and anxiety along the dorsoventral axis of the dentate gyrus. Neuron 77:955–968

Kim HJ, Denli AM, Wright R, Baul TD, Clemenson GD, Morcos AS, Zhao C, Schafer ST, Gage FH, Kagalwala MN (2015) REST regulates non-cell-autonomous neuronal differentiation and maturation of neural progenitor cells via Secretogranin II. J Neurosci 35:14872–14884

Kirschen GW, Shen J, Tian M, Schroeder B, Wang J, Man G, Wu S, Ge S (2017) Active dentate granule cells encode experience to promote the addition of adult-born Hippocampal neurons. J Neurosci 37: 4661–4678

Kitamura T, Saitoh Y, Takashima N, Murayama A, Niibori Y, Ageta H, Sekiguchi M, Sugiyama H, Inokuchi K (2009) Adult neurogenesis modulates the hippocampus-dependent period of associative fear memory. Cell 139:814–827

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

Kohara K, Pignatelli M, Rivest AJ, Jung HY, Kitamura T, Suh J, Frank D, Kajikawa K, Mise N, Obata Y, Wickersham IR, Tonegawa S (2014) Cell type-specific genetic and optogenetic tools reveal hippocampal CA2 circuits. Nat Neurosci 17:269–279

Kuhn HG, Dickinson-Anson H, Gage FH (1996) Neurogenesis in the dentate gyrus of the adult rat: age-related decrease of neuronal progenitor proliferation. J Neurosci 16:2027–2033

Kuwabara T, Hsieh J, Muotri A, Yeo G, Warashina M, Lie DC, Moore L, Nakashima K, Asashima M, Gage FH (2009) Wnt-mediated activation of NeuroD1 and retro-elements during adult neurogenesis. Nat Neurosci 12:1097–1105

Lacar B, Linker SB, Jaeger BN, Krishnaswami S, Barron J, Kelder M, Parylak S, Paquola A, Venepally P, Novotny M, O'Connor C, Fitzpatrick C, Erwin J, Hsu JY, Husband D, McConnell MJ,

Lasken R, Gage FH (2016) Nuclear RNA-seq of single neurons reveals molecular signatures of activation. Nat Commun 7:11022

Lehmann ML, Brachman RA, Martinowich K, Schloesser RJ, Herkenham M (2013) Glucocorticoids orchestrate divergent effects on mood through adult neurogenesis. J Neurosci 33:2961–2972

Lemaire V, Koehl M, Le Moal M, Abrous DN (2000) Prenatal stress produces learning deficits associated with an inhibition of neurogenesis in the hippocampus. Proc Natl Acad Sci U S A 97: 11032–11037

Leutgeb JK, Leutgeb S, Moser MB, Moser EI (2007) Pattern separation in the dentate gyrus and CA3 of the hippocampus. Science 315:961–966

Li G, Fang L, Fernandez G, Pleasure SJ (2013) The ventral hippocampus is the embryonic origin for adult neural stem cells in the dentate gyrus. Neuron 78:658–672

Li G, Pleasure SJ (2005) Morphogenesis of the dentate gyrus: what we are learning from mouse mutants. Dev Neurosci 27:93–99

Li H, Zhong X, Chau KF, Santistevan NJ, Guo W, Kong G, Li X, Kadakia M, Masliah J, Chi J, Jin P, Zhang J, Zhao X, Chang Q (2014) Cell cycle-linked MeCP2 phosphorylation modulates adult neurogenesis involving the notch signalling pathway. Nat Commun 5:5601

Li X, Barkho BZ, Luo Y, Smrt RD, Santistevan NJ, Liu C, Kuwabara T, Gage FH, Zhao X (2008) Epigenetic regulation of the stem cell mitogen Fgf-2 by Mbd1 in adult neural stem/progenitor cells. J Biol Chem 283:27644–27652

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

Liu C, Teng ZQ, McQuate AL, Jobe EM, Christ CC, von Hoyningen-Huene SJ, Reyes MD, Polich ED, Xing Y, Li Y, Guo W, Zhao X (2013) An epigenetic feedback regulatory loop involving microRNA-195 and MBD1 governs neural stem cell differentiation. PLoS ONE 8:e51436

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

Llorens-Martin M, Jurado-Arjona J, Avila J, Hernandez F (2015) Novel connection between newborn granule neurons and the hippocampal CA2 field. Exp Neurol 263:285–292

Lodato MA, Ng CW, Wamstad JA, Cheng AW, Thai KK, Fraenkel E, Jaenisch R, Boyer LA (2013) SOX2 co-occupies distal enhancer elements with distinct POU factors in ESCs and NPCs to specify cell state. PLoS Genet 9:e1003288

Lugert S, Basak O, Knuckles P, Haussler U, Fabel K, Gotz M, Haas CA, Kempermann G, Taylor V, Giachino C (2010) Quiescent and active hippocampal neural stem cells with distinct morphologies respond selectively to physiological and pathological stimuli and aging. Cell Stem Cell 6:445–456

Lui JH, Hansen DV, Kriegstein AR (2011) Development and evolution of the human neocortex. Cell 146:18–36

Lyst MJ, Ekiert R, Ebert DH, Merusi C, Nowak J, Selfridge J, Guy J, Kastan NR, Robinson ND, de Lima AF, Rappsilber J, Greenberg ME, Bird A (2013) Rett syndrome mutations abolish the interaction of MeCP2 with the NCoR/SMRT co-repressor. Nat Neurosci 16: 898–902

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

Martynoga B, Mateo JL, Zhou B, Andersen J, Achimastou A, Urban N, van den Berg D, Georgopoulou D, Hadjur S, Wittbrodt J, Ettwiller L, Piper M, Gronostajski RM, Guillemot F (2013) Epigenomic enhancer annotation reveals a key role for NFIX in neural stem cell quiescence. Genes Dev 27:1769–1786

McAvoy KM, Scobie KN, Berger S, Russo C, Guo N, Decharatanachart P, Vega-Ramirez H, Miake-Lye S, Whalen M, Nelson M, Bergami M, Bartsch D, Hen R, Berninger B, Sahay A (2016) Modulating neuronal competition dynamics in the dentate Gyrus to rejuvenate aging memory circuits. Neuron 91:1356–1373

McHugh TJ, Jones MW, Quinn JJ, Balthasar N, Coppari R, Elmquist JK, Lowell BB, Fanselow MS, Wilson MA, Tonegawa S (2007) Dentate gyrus NMDA receptors mediate rapid pattern separation in the hippocampal network. Science 317:94–99

Meshi D, Drew MR, Saxe M, Ansorge MS, David D, Santarelli L, Malapani C, Moore H, Hen R (2006) Hippocampal neurogenesis is not required for behavioral effects of environmental enrichment. Nat Neurosci 9:729–731

Mira H, Andreu Z, Suh H, Lie DC, Jessberger S, Consiglio A, San Emeterio J, Hortiguela R, Marques-Torrejon MA, Nakashima K, Colak D, Gotz M, Farinas I, Gage FH (2010) Signaling through BMPR-IA regulates quiescence and long-term activity of neural stem cells in the adult hippocampus. Cell Stem Cell 7:78–89

Mirescu C, Peters JD, Gould E (2004) Early life experience alters response of adult neurogenesis to stress. Nat Neurosci 7:841–846

Mo A, Mukamel EA, Davis FP, Luo C, Henry GL, Picard S, Urich MA, Nery JR, Sejnowski TJ, Lister R, Eddy SR, Ecker JR, Nathans J (2015) Epigenomic signatures of neuronal diversity in the mammalian brain. Neuron 86:1369–1384

Mongiat LA, Esposito MS, Lombardi G, Schinder AF (2009) Reliable activation of immature neurons in the adult hippocampus. PLoS ONE 4:e5320

Mukherjee S, Brulet R, Zhang L, Hsieh J (2016) REST regulation of gene networks in adult neural stem cells. Nat Commun 7:13360

Muotri AR, Marchetto MC, Coufal NG, Oefner R, Yeo G, Nakashima K, Gage FH (2010) L1 retrotransposition in neurons is modulated by MeCP2. Nature 468:443–446

Nakagawa S, Kim JE, Lee R, Chen J, Fujioka T, Malberg J, Tsuji S, Duman RS (2002) Localization of phosphorylated cAMP response element-binding protein in immature neurons of adult hippocampus. J Neurosci 22:9868–9876

Nakashiba T, Cushman JD, Pelkey KA, Renaudineau S, Buhl DL, McHugh TJ, Rodriguez Barrera V, Chittajallu R, Iwamoto KS, McBain CJ, Fanselow MS, Tonegawa S (2012) Young dentate granule cells mediate pattern separation, whereas old granule cells facilitate pattern completion. Cell 149:188–201

Nan X, Ng HH, Johnson CA, Laherty CD, Turner BM, Eisenman RN, Bird A (1998) Transcriptional repression by the methyl-CpG-binding protein MeCP2 involves a histone deacetylase complex. Nature 393:386–389

Ng SY, Bogu GK, Soh BS, Stanton LW (2013) The long noncoding RNA RMST interacts with SOX2 to regulate neurogenesis. Mol Cell 51: 349–359

Niibori Y, Yu TS, Epp JR, Akers KG, Josselyn SA, Frankland PW (2012) Suppression of adult neurogenesis impairs population coding of similar contexts in hippocampal CA3 region. Nat Commun 3:1253

Okuyama T, Kitamura T, Roy DS, Itohara S, Tonegawa S (2016) Ventral CA1 neurons store social memory. Science 353:1536–1541

Ouzounov DG, Wang T, Wang M, Feng DD, Horton NG, Cruz-Hernandez JC, Cheng YT, Reimer J, Tolias AS, Nishimura N, Xu C (2017) In vivo three-photon imaging of activity of GCaMP6-labeled neurons deep in intact mouse brain. Nat Methods 14:388–390

Overstreet Wadiche L, Bromberg DA, Bensen AL, Westbrook GL (2005) GABAergic signaling to newborn neurons in dentate gyrus. J Neurophysiol 94:4528–4532

Palmer TD, Markakis EA, Willhoite AR, Safar F, Gage FH (1999) Fibroblast growth factor-2 activates a latent neurogenic program in neural stem cells from diverse regions of the adult CNS. J Neurosci 19:8487–8497

Palmer TD, Ray J, Gage FH (1995) FGF-2-responsive neuronal progenitors reside in proliferative and quiescent regions of the adult rodent brain. Mol Cell Neurosci 6:474–486

Palmer TD, Takahashi J, Gage FH (1997) The adult rat hippocampus contains primordial neural stem cells. Mol Cell Neurosci 8:389–404

Paredes MF, James D, Gil-Perotin S, Kim H, Cotter JA, Ng C, Sandoval K, Rowitch DH, Xu D, McQuillen PS, Garcia-Verdugo JM, Huang EJ, Alvarez-Buylla A (2016) Extensive migration of young neurons into the infant human frontal lobe. Science 354:aaf7073

Patzke N, Spocter MA, Karlsson KAE, Bertelsen MF, Haagensen M, Chawana R, Streicher S, Kaswera C, Gilissen E, Alagaili AN, Mohammed OB, Reep RL, Bennett NC, Siegel JM, Ihunwo AO, Manger PR (2015) In contrast to many other mammals, cetaceans have relatively small hippocampi that appear to lack adult neurogenesis. Brain Struct Funct 220:361–383

Pilz GA, Carta S, Stauble A, Ayaz A, Jessberger S, Helmchen F (2016) Functional imaging of dentate granule cells in the adult mouse hippocampus. J Neurosci 36:7407–7414

Rakic P (1985) Limits of neurogenesis in primates. Science 227:1054–1056

Ramirez S, Liu X, MacDonald CJ, Moffa A, Zhou J, Redondo RL, Tonegawa S (2015) Activating positive memory engrams suppresses depression-like behaviour. Nature 522:335–339

Ray J, Gage FH (2006) Differential properties of adult rat and mouse brain-derived neural stem/progenitor cells. Mol Cell Neurosci 31:560–573

Renault VM, Rafalski VA, Morgan AA, Salih DA, Brett JO, Webb AE, Villeda SA, Thekkat PU, Guillerey C, Denko NC, Palmer TD, Butte AJ, Brunet A (2009) FoxO3 regulates neural stem cell homeostasis. Cell Stem Cell 5:527–539

Rosenzweig MR, Krech D, Bennett EL, Diamond MC (1962) Effects of environmental complexity and training on brain chemistry and anatomy: a replication and extension. J Comp Physiol Psychol 55:429–437

Roy NS, Wang S, Jiang L, Kang J, Benraiss A, Harrison-Restelli C, Fraser RA, Couldwell WT, Kawaguchi A, Okano H, Nedergaard M, Goldman SA (2000) In vitro neurogenesis by progenitor cells isolated from the adult human hippocampus. Nat Med 6:271–277

Sahay A, Scobie KN, Hill AS, O'Carroll CM, Kheirbek MA, Burghardt NS, Fenton AA, Dranovsky A, Hen R (2011) Increasing adult hippocampal neurogenesis is sufficient to improve pattern separation. Nature 472:466–470

Sakaguchi H, Kadoshima T, Soen M, Narii N, Ishida Y, Ohgushi M, Takahashi J, Eiraku M, Sasai Y (2015) Generation of functional hippocampal neurons from self-organizing human embryonic stem cell-derived dorsomedial telencephalic tissue. Nat Commun 6:8896

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

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

Saxe MD, Battaglia F, Wang JW, Malleret G, David DJ, Monckton JE, Garcia AD, Sofroniew MV, Kandel ER, Santarelli L, Hen R, Drew MR (2006) Ablation of hippocampal neurogenesis impairs contextual fear conditioning and synaptic plasticity in the dentate gyrus. Proc Natl Acad Sci U S A 103:17501–17506

Saxe MD, Malleret G, Vronskaya S, Mendez I, Garcia AD, Sofroniew MV, Kandel ER, Hen R (2007) Paradoxical influence of hippocampal neurogenesis on working memory. Proc Natl Acad Sci U S A 104:4642–4646

Schafer ST, Han J, Pena M, von Bohlen Und Halbach O, Peters J, Gage FH (2015) The Wnt adaptor protein ATP6AP2 regulates multiple stages of adult hippocampal neurogenesis. J Neurosci 35:4983–4998

Scobie KN, Hall BJ, Wilke SA, Klemenhagen KC, Fujii-Kuriyama Y, Ghosh A, Hen R, Sahay A (2009) Kruppel-like factor 9 is necessary for late-phase neuronal maturation in the developing dentate gyrus and during adult hippocampal neurogenesis. J Neurosci 29:9875–9887

Seki T, Arai Y (1999) Temporal and spacial relationships between PSA-NCAM-expressing, newly generated granule cells, and radial glia-like cells in the adult dentate gyrus. J Comp Neurol 410:503–513

Shi Y, Chichung Lie D, Taupin P, Nakashima K, Ray J, Yu RT, Gage FH, Evans RM (2004) Expression and function of orphan nuclear receptor TLX in adult neural stem cells. Nature 427:78–83

Shimozaki K, Clemenson GD Jr, Gage FH (2013) Paired related homeobox protein 1 is a regulator of stemness in adult neural stem/progenitor cells. J Neurosci 33:4066–4075

Shimozaki K, Zhang CL, Suh H, Denli AM, Evans RM, Gage FH (2012) SRY-box-containing gene 2 regulation of nuclear receptor tailless (Tlx) transcription in adult neural stem cells. J Biol Chem 287:5969–5978

Shin J, Berg DA, Zhu Y, Shin JY, Song J, Bonaguidi MA, Enikolopov G, Nauen DW, Christian KM, Ming GL, Song H (2015) Single-cell RNA-Seq with waterfall reveals molecular cascades underlying adult Neurogenesis. Cell Stem Cell 17:360–372

Shinohara Y, Hosoya A, Hirase H (2013) Experience enhances gamma oscillations and interhemispheric asymmetry in the hippocampus. Nat Commun 4:1652

Shors TJ, Miesegaes G, Beylin A, Zhao M, Rydel T, Gould E (2001) Neurogenesis in the adult is involved in the formation of trace memories. Nature 410:372–376

Shors TJ, Townsend DA, Zhao M, Kozorovitskiy Y, Gould E (2002) Neurogenesis may relate to some but not all types of hippocampal-dependent learning. Hippocampus 12:578–584

Smith LK, He Y, Park JS, Bieri G, Snethlage CE, Lin K, Gontier G, Wabl R, Plambeck KE, Udeochu J, Wheatley EG, Bouchard J, Eggel A, Narasimha R, Grant JL, Luo J, Wyss-Coray T, Villeda SA (2015) beta2-microglobulin is a systemic pro-aging factor that impairs cognitive function and neurogenesis. Nat Med 21:932–937

Smrt RD, Eaves-Egenes J, Barkho BZ, Santistevan NJ, Zhao C, Aimone JB, Gage FH, Zhao X (2007) Mecp2 deficiency leads to delayed maturation and altered gene expression in hippocampal neurons. Neurobiol Dis 27:77–89

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

Song H, Stevens CF, Gage FH (2002) Astroglia induce neurogenesis from adult neural stem cells. Nature 417:39–44

Song J, Sun J, Moss J, Wen Z, Sun GJ, Hsu D, Zhong C, Davoudi H, Christian KM, Toni N, Ming GL, Song H (2013) Parvalbumin interneurons mediate neuronal circuitry-neurogenesis coupling in the adult hippocampus. Nat Neurosci 16:1728–1730

Song J, Zhong C, Bonaguidi MA, Sun GJ, Hsu D, Gu Y, Meletis K, Huang ZJ, Ge S, Enikolopov G, Deisseroth K, Luscher B, Christian KM, Ming GL, Song H (2012) Neuronal circuitry mechanism regulating adult quiescent neural stem-cell fate decision. Nature 489:150–154

Spalding KL, Bergmann O, Alkass K, Bernard S, Salehpour M, Huttner HB, Bostrom E, Westerlund I, Vial C, Buchholz BA, Possnert G, Mash DC, Druid H, Frisen J (2013) Dynamics of hippocampal neurogenesis in adult humans. Cell 153:1219–1227

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

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

Sultan S, Li L, Moss J, Petrelli F, Casse F, Gebara E, Lopatar J, Pfrieger FW, Bezzi P, Bischofberger J, Toni N (2015) Synaptic integration of adult-born Hippocampal neurons is locally controlled by Astrocytes. Neuron 88:957–972

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

Tanapat P, Hastings NB, Reeves AJ, Gould E (1999) Estrogen stimulates a transient increase in the number of new neurons in the dentate gyrus of the adult female rat. J Neurosci 19:5792–5801

Tashiro A, Makino H, Gage FH (2007) Experience-specific functional modification of the dentate gyrus through adult neurogenesis: a critical period during an immature stage. J Neurosci 27:3252–3259

Tashiro A, Sandler VM, Toni N, Zhao C, Gage FH (2006) NMDA-receptor-mediated, cell-specific integration of new neurons in adult dentate gyrus. Nature 442:929–933

Temprana SG, Mongiat LA, Yang SM, Trinchero MF, Alvarez DD, Kropff E, Giacomini D, Beltramone N, Lanuza GM, Schinder AF (2015) Delayed coupling to feedback inhibition during a critical period for the integration of adult-born granule cells. Neuron 85: 116–130

Toda T, Homma D, Tokuoka H, Hayakawa I, Sugimoto Y, Ichinose H, Kawasaki H (2013) Birth regulates the initiation of sensory map formation through serotonin signaling. Dev Cell 27:32–46

Toda T, Hsu JY, Linker SB, Hu L, S.T. Schafer, Mertens J, Jacinto FV, Hetzer MW, Gage FH (2017) Nup153 interacts with Sox2 to enable bimodal gene regulation and maintenance of neural progenitor cells. Cell Stem Cell 21:619–634.e7. (in press)

Tomita K, Nakanishi S, Guillemot F, Kageyama R (1996) Mash1 promotes neuronal differentiation in the retina. Genes Cells 1:765–774

Toni N, Laplagne DA, Zhao C, Lombardi G, Ribak CE, Gage FH, Schinder AF (2008) Neurons born in the adult dentate gyrus form functional synapses with target cells. Nat Neurosci 11:901–907

Toni N, Teng EM, Bushong EA, Aimone JB, Zhao C, Consiglio A, van Praag H, Martone ME, Ellisman MH, Gage FH (2007) Synapse formation on neurons born in the adult hippocampus. Nat Neurosci 10:727–734

Travaglia A, Bisaz R, Sweet ES, Blitzer RD, Alberini CM (2016) Infantile amnesia reflects a developmental critical period for hippocampal learning. Nat Neurosci 19:1225–1233

Tsujimura K, Irie K, Nakashima H, Egashira Y, Fukao Y, Fujiwara M, Itoh M, Uesaka M, Imamura T, Nakahata Y, Yamashita Y, Abe T, Takamori S, Nakashima K (2015) miR-199a links MeCP2 with mTOR signaling and its Dysregulation leads to Rett syndrome phenotypes. Cell Rep 12:1887–1901

Urban N, van den Berg DL, Forget A, Andersen J, Demmers JA, Hunt C, Ayrault O, Guillemot F (2016) Return to quiescence of mouse neural stem cells by degradation of a proactivation protein. Science 353: 292–295

van Praag H, Kempermann G, Gage FH (1999) Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. Nat Neurosci 2:266–270

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

Vivar C, Potter MC, Choi J, Lee JY, Stringer TP, Callaway EM, Gage FH, Suh H, van Praag H (2012) Monosynaptic inputs to new neurons in the dentate gyrus. Nat Commun 3:1107

Wickersham IR, Lyon DC, Barnard RJ, Mori T, Finke S, Conzelmann KK, Young JA, Callaway EM (2007) Monosynaptic restriction of transsynaptic tracing from single, genetically targeted neurons. Neuron 53:639–647

Wintzer ME, Boehringer R, Polygalov D, McHugh TJ (2014) The hippocampal CA2 ensemble is sensitive to contextual change. J Neurosci 34:3056–3066

Yousef H, Morgenthaler A, Schlesinger C, Bugaj L, Conboy IM, Schaffer DV (2015) Age-associated increase in BMP signaling inhibits Hippocampal Neurogenesis. Stem Cells 33:1577–1588

Zeng Y, Yao B, Shin J, Lin L, Kim N, Song Q, Liu S, Su Y, Guo JU, Huang L, Wan J, Wu H, Qian J, Cheng X, Zhu H, Ming GL, Jin P, Song H (2016) Lin28A binds active promoters and recruits Tet1 to regulate gene expression. Mol Cell 61:153–160

Zhang CL, Zou Y, He W, Gage FH, Evans RM (2008) A role for adult TLX-positive neural stem cells in learning and behaviour. Nature 451:1004–1007

Zhao C, Teng EM, Summers RG Jr, Ming GL, Gage FH (2006) Distinct morphological stages of dentate granule neuron maturation in the adult mouse hippocampus. J Neurosci 26:3–11

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