Review

Adult Neurogenesis and the Future of the Rejuvenating Brain Circuits

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For a long time, the mammalian brain has been perceived to be a static organ. However, the discovery of adult neurogenesis in most mammalian species, including humans, monkeys, and rodents, has disrupted this view. As this continuous regeneration has an effect on established behavioral patterns, it holds promising therapeutic potential. However, before harnessing this potential regenerative power, we must understand what effects new neurons have on existing brain circuits. Ongoing research contributes to several important steps toward bridging the gap between adult-born neurons, circuits, and behavior. The study of adult neurogenesis in different neurogenic regions from a systems neuroscience perspective will pave the way to understanding how it supports adaptive behavior and why its dysfunction correlates with some human brain disorders.

1. Introduction

The finding that neurogenesis continues throughout life in the mammalian brain has generated enormous interest among neurobiologists and clinicians. While initially viewed with skepticism, this process is now accepted to occur in most mammalian species, including rodents, monkeys, and humans. Adult neurogenesis is restricted to specific neurogenic zones where neuroblasts are continuously produced and migrate to reach their targeted circuits and differentiate into neurons, integrating into the network. In mammals, this process occurs primarily in two regions: the subventricular zone of the lateral ventricles (SVZ) (Lledo et al., 2006) and in the subgranular zone of the dentate gyrus (DG) in the hippocampus (Ming and Song, 2011; Gage and Temple, 2013). While the latter gives rise to new glutamatergic granule cells (GCs) that mature locally in the DG, the former produces new cells that migrate rostrally to reach the first central relay of the olfactory system, the olfactory bulb (OB), where they differentiate mostly into GABAergic local interneurons, also called GCs. Some rare adult-born neurons have also been reported in other regions, notably the hypothalamus, striatum, amygdala, and olfactory cortex (reviewed in Arisi et al., 2012), although the extent and the functional impact of this limited neurogenesis still remains debated.

Recent progress in the field of adult neurogenesis has greatly advanced two different, yet complementary, research goals. The first aim is to explore how the adult brain encodes and stores representations of our external environment and of our internal body states. In the two main neurogenic brain areas, the continuous addition of new neurons represents an alternative mechanism of neuronal plasticity that acts in parallel to the conventional molecular, synaptic, and connectivity mechanisms of plasticity. From a different perspective, interest in adult neurogenesis has flourished because a growing number of clinical studies have correlated mental and neurological disorders with changes in the degree of adult neurogenesis (Jessberger and Gage, 2014). For example, drug abuse and addiction; major mood disorders such as chronic stress syndrome and depression; epilepsy; and neurodegenerative diseases (such as Alzheimer's disease

and Parkinson's disease, AD and PD, respectively) correlate with reduced adult neurogenesis (DeCarolis and Eisch, 2010; Danzer, 2012; Ruan et al., 2014).

The second aim in the field is to decipher how new neurons impact the functioning of pre-existing circuits. In the past decade, evidence from physiological and behavioral studies suggested that adult-born neurons are a unique neural type that possesses peculiar physiology and connectivity (Carleton et al., 2003; Marín-Burgin et al., 2012; Gu et al., 2012; Dieni et al., 2013; Valley et al., 2013). The functional consequences of continuously recruiting adult-born neurons in brain circuits partially originate from the higher excitability, unique connectivity, and distinct synaptic plasticity. Recent work also suggests that adult neurogenesis may produce not only young and excitable new neurons but also completely new neuronal subtypes (Merkle et al., 2014). In addition, adult neurogenesis appears to be essential for structural maintenance of the OB circuit (Ninkovic et al., 2007; Imayoshi et al., 2008).

These new insights have shed light on how adult neurogenesis contributes to circuit operation, how adult neurogenesis-dependent circuit function correlates with cognitive-behavioral outcomes, and how adult-born neurons respond to sensory experience in healthy and diseased brains. Rather than being comprehensive, this review intends to cover the major discoveries and future research that highlight the functional meaning of adult neurogenesis from a systems neuroscience standpoint. These new insights and emerging ideas highlight the function of adult-born neurons in pre-existing brain circuits and point in new directions to bridge the gap between neuron and cognition.

2. How Do Circuits Nurture the Development of Adult-Born Neurons?

What makes neurogenesis in an adult brain so unique? It is probably the richness of content a developing neuron experiences in the functioning brain by receiving fully developed external inputs in combination with top-down contextual feedback. Both OB and DG circuits have to encode novel, complex, and
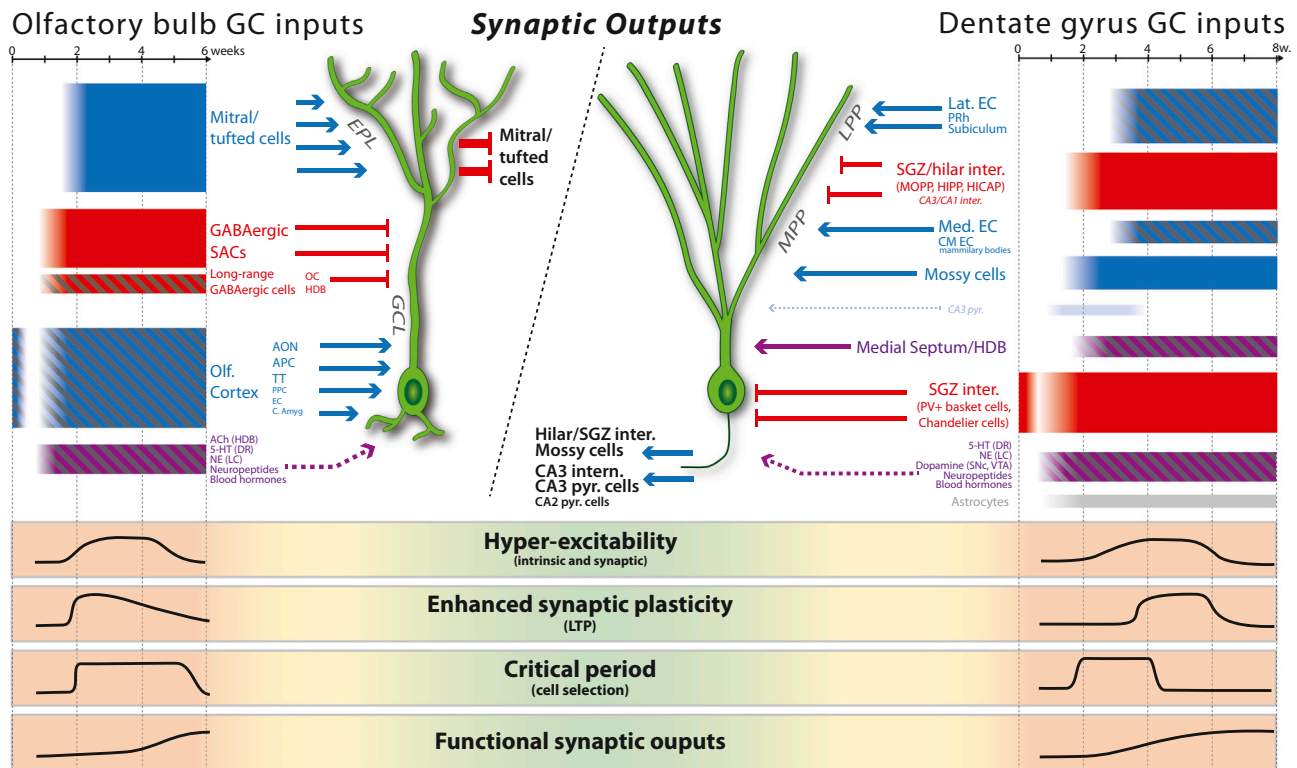
Figure 1. Circuit Development and Functional Maturation of Adult-Born GCs in the OB and DG

Top: identity, relative position, and time course of presynaptic inputs impinging onto adult-born GCs in the OB (left) and DG (right). Excitatory inputs are in blue, inhibitory inputs are in red, and neuromodulatory inputs are in violet. Local inputs are in solid colors, and distant inputs are shaded with black lines. The output targets of adult-born GCs are displayed in the center in bold. Bottom: schematic diagrams representing the relative changes in key maturation parameters such as hyper-excitability, enhanced synaptic plasticity (such as long-term plasticity [LTP]), cell survival, and functional synaptic outputs for adult-born GCs in the OB and the DG.

In the early phases, OB neuroblasts in the RMS are regulated by ambient glutamate released by surrounding regions such as the olfactory cortex. Once in the OB, adult-born GCs first receive synaptic inputs in the GC layer (GCL) from distant projections originating from the olfactory cortex (mainly from the anterior olfactory nucleus [AON]; anterior piriform cortex [APC]; tenia tecta [TT]; and, to a lesser extent, from posterior piriform cortex [PPC], entorhinal cortex [EC], and cortical amygdala [C. Amyg; this latter structure mainly targets the accessory OB]), as well as from local GABAergic short-axon cells (SACs), which are bulbar interneurons inhibiting others interneurons. They may also receive some non-synaptic neuromodulatory inputs releasing acetylcholine (Ach) from the diagonal band of Broca (HDB), serotonin (5-HT) from the dorsal raphe (DR), and noradrenaline (NE) from the locus coeruleus (LC). In the second week, adult-born GCs start to extend dendrites in the EPL, where they receive dendritic inputs from OB projection neurons, namely, M/T cells. Adult-born GCs then progressively start to release GABA from their dendrites back onto M/T cells.

In the DG, early steps of maturation are regulated by extrasynaptic GABA, released from local DG interneurons. Then, DG adult-born GCs first receive synaptic inputs from local GABAergic interneurons of the sub-granular zone (SGZ), such as parvalbumin-positive (PV+) basket cells and chandelier cells, followed by inputs from local excitatory mossy cells.

As they extend their apical dendrites, adult-born neurons receive inputs from dendritic-targeting interneurons (such as somatostatin-positive hilar perforant path [HIPP] interneurons, hilar commissural-associational pathway [HICAP] interneurons, and interneurons of the molecular perforant path [MOPP]), followed by excitatory inputs from distant structures; from layer II lateral entorhinal cortex (Lat. EC; and, to a lesser extent, from perirhinal cortex [PRh] and subiculum) in the lateral perforant path (LPP); and from the medial entorhinal cortex (MEC; and, to a lesser extent, from caudo-medial EC [CM EC] and mammillary bodies of the hypothalamus) in the medial perforant path (MPP). Adult-born GCs also receive synaptic inputs from cholinergic cells of the medial septum and the Diagonal band of Broca (HDB) as well as non-synaptic inputs from neuromodulatory centers, in particular dopamine from the substantia nigra pars compacta (SNc) and from the ventral tegmental area (VTA). Various studies have also described some transitory inputs from CA3 pyramidal cells.

fine-detailed information, usually with contextual components (Lepousez et al., 2013; Konefal et al., 2013). Since birth, adult-born neurons are surrounded by developmental cues that nurture their growth and orient their fate. Various cell types, from ependymal cells that support neuronal proliferation to microglia that sculpt their dendritic arbor and eventually remove apoptotic-pruned neurons, orchestrate these adult neurodevelopmental processes (Figure 1).

2.1. Who Talks to Newborn Neurons?

In the OB, the vast majority (~95%) of adult-born neurons mature morphologically and functionally into GABAergic GCs within

about 4 weeks (Petreanu and Alvarez-Buylla, 2002; Belluzzi et al., 2003; Carleton et al., 2003), when the rate of synaptogenesis is maximal (Kelsch et al., 2008). It is interesting that these juvenile cells sense and react to many brain areas, and many types of experiences could influence their integration. In the OB, recent efforts sought to identify all the synaptic partners and to precisely describe the sequence of events of synapse formation onto newborn neurons during their maturation. To tackle these questions, a plethora of methods have been used: classical immunocytochemistry (Whitman and Greer, 2007; Pallotto et al., 2012), patch-clamp electrophysiology (Carleton et al.,

2003; Belluzzi et al., 2003; Panzanelli et al., 2009; Katagiri et al., 2011), viral expression of fluorescent synaptic markers (Kelsch et al., 2008) and retrograde *trans*-synaptic tracers (Arenkiel et al., 2011; Deshpande et al., 2013). From these studies, a picture of this orchestrated integration process has started to emerge (Figure 1).

Along their migration in the so-called rostral migratory stream (RMS), neuroblasts already express unclustered neurotransmitter receptors (e.g., NMDA and GABA$_A$ receptors) that sense extrasynaptic glutamate and GABA (Young et al., 2011). A large portion of the RMS is surrounded by olfactory neocortical structures, opening the interesting possibility that neuroblast migration and survival may be regulated by olfactory cortex neuronal activity. Once an immature neuron arrives into the OB, it immediately receives GABAergic and glutamatergic synapses from local and distant cells (mainly from the olfactory cortex). New neurons start their maturation in the deep layers of the OB that contain the highest density of top-down projecting inputs from cortical, limbic, and subcortical areas (Lepousez et al., 2014). During the first days of a young neuron's life in the OB, the predominant synaptic activity is driven by the distant cortical structures (Katagiri et al., 2011; Arenkiel et al., 2011), as well as from local and long-projecting GABAergic cells (Panzanelli et al., 2009; Pallotto et al., 2012; Deshpande et al., 2013). In less than 2 weeks, the new cells extend their apical dendrites toward the external plexiform layer (EPL) and receive dendro-dendritic apical synaptic inputs from OB projection neurons, namely, mitral/tufted (M/T) cells (Carleton et al., 2003; Whitman and Greer 2007; Nissant et al., 2009). Therefore, in the OB, adult-born GCs first are guided by remote cortical structures before connecting with local intrinsic OB neurons.

In the DG, the sequence of these choreographed synaptic events is almost completely opposite. The first synaptic input reaching young maturing GCs cells originates from local GABAergic interneurons (Figure 1). At this immature stage, these GABAergic synapses have a depolarizing effect (Espósito et al., 2005; Ge et al., 2006), unlike in the OB (Mejia-Gervacio et al., 2011). The local inhibitory inputs in the DG also influence earlier phases of adult hippocampal neurogenesis through dual regulation of both stem cell activation and neuroblast survival (Song et al., 2012, 2013). The first excitatory contacts are made a few days later but originate from local excitatory mossy cells (Kumamoto et al., 2012; Chancey et al., 2014; Deshpande et al., 2013; Vivar et al., 2012). On the other hand, the first extrinsic inputs from the enthorinal cortex arrive much later, at between 2 and 5 weeks after cell birth. As a result, DG GCs appear to sense the local network before listening to more remote brain areas whose inputs gradually strengthen with age (Vivar et al., 2012; Mongiat et al., 2009; Bergami et al., 2015). Although local interneurons are among the first inputs onto adult-born neurons, 4-week-old GCs receive weak functional feedforward and feedback inhibition (Marín-Burgin et al., 2012; Temprana et al., 2015). This transient high excitation/inhibition balance in 4-week-old GCs coupled to an enhanced Hebbian plasticity of their inputs makes adult-born neurons hyper-excitable and more responsive to inputs compared to the surrounding mature neurons (Li et al., 2012; Marín-Burgin et al., 2012). In parallel to synaptic integration, astrocytes establish perisynaptic processes during neuronal maturation, regardless of the target neuron's age (Krzisch et al., 2014); microglial cells participate in the phagocytosis of apoptotic cells (Sierra et al., 2010), which may have further impact on adult-born cell development. Recent studies have also uncovered some functional heterogeneity within the maturing adult-born cell population regarding their relative excitation/inhibition balance and their input-output function (Dieni et al., 2013; Brunner et al., 2014).

2.2. Activity-Dependent Control of Cell Development/Survival

How does neuronal activity influence the process of adult neurogenesis? The first attempts to answer this question were conducted by manipulating the global activity within the whole networks. Since the OB is the first central relay of the olfactory system, it can be directly manipulated by changing the olfactory environment. Using olfactory enrichment or deprivation, early studies demonstrated that the level of sensory activity highly correlates with cell survival (Rochefort et al., 2002; Petreanu and Alvarez-Buylla, 2002; Winner et al., 2002; Mandairon et al., 2006; Bovetti et al., 2009) and influences synapse formation and structural dynamics (Kelsch et al., 2009; Livneh et al., 2009). Moreover, genetically increasing adult-born neuron excitability increases survival and restores normal synaptic integration of the cells while under sensory deprivation (Kelsch et al., 2009; Lin et al., 2010).

The activity-dependent wiring of newborn GCs relies on the ability of newborn neurons to dynamically connect highly active presynaptic elements from M/T-cell and from top-down inputs (Livneh and Mizrahi, 2011; Chow et al., 2012; Lepousez et al., 2013). As a result, adult-born neurons display enhanced sensitivity to network activity restricted to a specific critical window (Magavi et al., 2005; Belnoue et al., 2011; Moreno et al., 2009). Activity-dependent survival is controlled when the cells are between 2 and 4 weeks old (Mouret et al., 2008) and activity-dependent synaptic remodeling peaks between 1 and 2 months, and it may extend for several months after birth (Livneh and Mizrahi, 2011; Figure 1). During that critical period, adult-born neurons receive inputs from cortical and subcortical areas that might convey important top-down information. Therefore, certain studies have increased the sophistication of network manipulation by controlling the behavioral contexts of neuronal maturation. Survival of newborn neurons is significantly increased when animals are subjected to reward associated olfactory discrimination (Alonso et al., 2006; Mouret et al., 2008) or olfactory perceptual learning (Moreno et al., 2009). Lesion studies suggest that these behavioral paradigms are dependent on the integrity of top-down projections to the OB (Martin et al., 2004; Kiselycznyk et al., 2006; Mandairon et al., 2014).

In the hippocampus, manipulating activity by enriching the environment, promoting voluntary exercise, or engaging spatial learning increases the number of adult-born GCs integrating the DG (Kempermann et al., 1997; van Praag et al., 1999) and increases the innervation of both local and distant inputs (Bergami et al., 2015). Direct in vivo high-frequency stimulation of the enthorinal cortex or the perforant path also promotes cell survival (Bruel-Jungerman et al., 2006; Kitamura et al., 2010; Stone et al., 2011). As in the OB, activity-dependent cell survival is
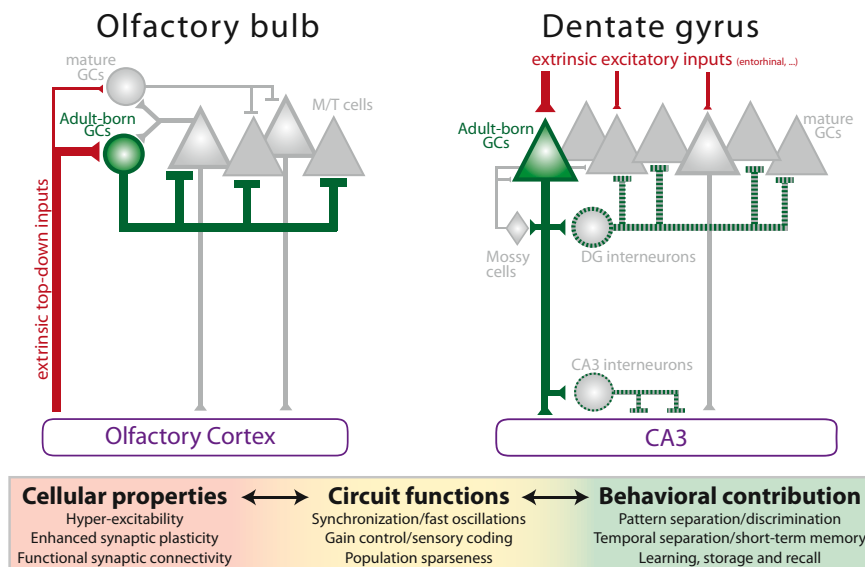
Figure 2. Adult-Born Neuron Functions in Networks: Toward a New Paradigm to Study Adult Neurogenesis at the Systems Level

Comparative analysis of adult-born neuron impact on their surrounding network in the OB (top left) and DG (top right).

In the OB, adult-born GCs (in green) are GABAergic interneurons (circles) that provide feedback and lateral inhibition onto M/T cells, the excitatory output neurons (triangles) of the OB. Adult-born GCs are also at the center of feedforward inhibitory circuits driven by excitatory top-down cortical inputs (in red). Mature GCs are indicated in gray circles.

In the DG, adult-born GCs (in green) are excitatory output cells (triangles) and received extrinsic excitatory inputs that exhibit long-term plasticity (in red). Adult-born GCs drive local excitatory mossy cells (gray diamond) and local interneurons (circles), providing feedback and lateral inhibition onto mature GCs (in gray) but not onto themselves. From one viewpoint, DG adult-born GCs are thus positioned to efficiently transmit information to CA3 while escaping to local DG inhibition. From another viewpoint, the indirect net output of DG adult-born neurons could be considered as GABAergic inhibition, as in the OB. As a result, OB and DG adult-born neurons support comparable functions at the circuit level, such as pacing network synchronization and fast oscillations, controlling the network excitation/inhibition balance, shaping network responsiveness and sensory coding, and increasing the sparseness of the representation at the output cell population level. A new paradigm to analyze the impact of adult neurogenesis at the circuit level in behaving animals is, therefore, needed to bridge the gap between cellular properties and behavioral outcomes (bottom). Thus, from a systems neuroscience perspective, adult neurogenesis represents a unique chance to decipher the role of neuron and neuronal circuits in behavior.

restricted to a critical period (2–3 weeks), but during this period, excitatory synapses have not yet formed (Figure 1). This effect is likely to be mediated indirectly through network activity (Ge et al., 2006; Song et al., 2012). On the other hand, experience-dependent structural plasticity persists for several months (Lemaire et al., 2012).

2.3. Formation of the Synaptic Output of Adult-Born Neurons

In the OB, 3–4 weeks after their arrival, newborn GCs form GABAergic contacts onto M/T cells after having received functional synaptic inputs (Kelsch et al., 2008; Bardy et al., 2010; Figure 1). To phrase this differently, newborn neurons "listen before they talk." However, during their migration, neuroblasts release GABA in a non-synaptic manner (Bolteus and Bordey, 2004), although it is unknown whether the GABAergic volume transmission takes place within the OB. In the OB, neuropeptide expression by some adult-born neurons could be one way to influence the activity of surrounding network even before forming actual output synapses (Lepousez et al., 2010). In addition, because GABA is released from adult-born spines and because GC spines display a high degree of structural plasticity, the functional output of adult-born neurons is highly plastic and sensitive to circuit activity (Livneh and Mizrahi, 2011). GABA release from mature adult-born dendrites is also more reliable than release from early postnatally derived GCs (Valley et al., 2013). If mature adult-born GCs represent a functionally distinct sub-population, this may be one of several unique adaptations made by adult-born neurons to facilitate their integration into adult circuits.

In the hippocampus, adult-born GC axons (i.e., mossy fibers) are fully developed by 21 days after birth, with mossy-fiber bouton density first appearing in the second week and reaching final

maximum density by 21 days post-injection (dpi) (Sun et al., 2013). Adult-born GCs synapse onto inhibitory interneurons of the hilus and onto local interneurons of the DG, providing feedback inhibition to the pre-existing GC population. This recruitment of DG inhibitory circuits progressively increases as the cells mature (Temprana et al., 2015). Within the DG circuit, these hyper-excitable neurons are thus positioned to impose feedback inhibition onto the general GC population while also escaping this inhibition. In the CA3, they activate local CA3 interneurons as well as CA3 pyramidal cells (Toni et al., 2008; Gu et al., 2012), and CA3 activity is altered after reduction of DG neurogenesis (Stone et al., 2011; Denny et al., 2012; Niibori et al., 2012). It is interesting that this transient hyper-excitability between 4 and 6 weeks appears well after mossy-fiber boutons reach their steady-state density (i.e., 3 weeks), suggesting an important dynamic rewiring of the post-synaptic targets along maturation. Though the impact of this feature on network activity deserves additional investigation (e.g., Piatti et al., 2013), we propose that the dynamic connectivity onto the various populations of interneurons may be an important aspect of adult-born GC function (Figure 2).

3. The Contribution of Adult-Born Neurons to Circuit Function

3.1. The Role of Immature Neurons in Network Dynamics and Computation: New Insights on Pattern Separation

Although loss-of-function and gain-of-function experiments have clearly highlighted a role of adult-born OB neurons in different olfactory-related behaviors encompassing perceptual learning, olfactory discrimination, and olfactory short- and long-term memory (Lazarini and Lledo, 2011; Lepousez et al., 2013), a direct involvement of adult-born neurons in neuronal

coding was not explored until recently. Using targeted recording of adult-born periglomerular cells in the OB, Livneh et al. (2014) have found that adult-born neurons' responsiveness increased and peaked at 4 weeks after cell birth. At this point, the receptive field is broader in immature neurons but then sharpens in an experience-dependent manner as they mature (Livneh et al., 2014). These results support previous findings showing that adult-born neurons are more responsive to novel odors (Belnoue et al., 2011; Magavi et al., 2005) and are preferentially activated by recall of an odor-reward memory (Sultan et al., 2010; Figure 2). Altogether, this form of hyper-excitability argues for a supralinear role of adult neurogenesis in dynamically shaping network activity. In the OB, recent progress demonstrated that new interneurons provide both feedforward and feedback inhibition to M/T cells. As such, they may participate in stimulus normalization and promote synchronization of output OB neurons (Chow et al., 2012; Lepousez et al., 2013; Figure 2). Moreover, recordings in behaving mice have shown that the activation of newly generated inhibitory interneurons in the OB can suppress the contribution of spontaneous activity. This provides a dynamic gain control of OB output cell activity (Alonso et al., 2012).

In the DG, recent efforts have assigned several computational functions to adult-born neurons based on the associated behavioral evidence: controlling DG responsiveness and population sparseness (Burghardt et al., 2012; Ikrar et al., 2013), shaping fast network oscillations (Lacefield et al., 2012), facilitating temporal integration (Aimone et al., 2009, 2011), endowing circuits with pattern separation, background suppression (Aimone et al., 2009, 2011; Wojtowicz, 2012), and memory resolution (Aimone et al., 2011). Although DG adult-born GCs are glutamatergic cells, most of these described functions are characteristic of inhibitory networks (Isaacson and Scanziani, 2011), suggesting that DG adult-born neurons predominantly recruit local inhibition (Figure 2).

Regarding the functional consequences of olfactory and hippocampal adult neurogenesis, one well accepted hypothesis is that it enables the decorrelation of evoked activity patterns, also referred as pattern separation. Pattern separation is a computational concept that allows the disambiguation of confounding information by making initially similar patterns of neural activity more distinct over time, using non-overlapping representations (Rolls and Kesner, 2006; Leutgeb and Leutgeb, 2007; Aimone et al., 2011; Sahay et al., 2011; Yassa and Stark, 2011; Nakashiba et al., 2012; Gu et al., 2012; Déry et al., 2013). Although, only a small fraction of DG and OB neurons are activated by physiological stimuli (Piatti et al., 2013), pattern separation is a way to recode cortical or glomerular inputs, respectively, into a sparse and orthogonal representation (Treves and Rolls, 1992). As such, this process may benefit learning and memory by enabling the distinct storage of similar experiences (Aimone et al., 2011). In other words, pattern separation is critical for adapting the subject to a complex and changing environment characterized by confounding signals.

Remarkably, both olfactory neurogenesis and hippocampal neurogenesis seem to improve their respective neuronal networks for discriminating between ambiguous and complex stimuli. Since behavioral pattern separation has always been analyzed using learning protocols, it is difficult to dissociate sensory pattern discrimination per se from learning-associated sensory representation. Studies of adult neurogenesis have revealed that new GCs of the DG and the OB facilitate behavioral discrimination. Recent data suggest that adult-born neurons are critical for making fine discriminations between similar visual, contextual, and spatial information in tests involving working memory and for discriminating between similar odorants. In the OB, direct optogenetic activation of adult-born OB neurons enhanced olfactory discrimination learning only for a difficult task (Alonso et al., 2012). Ablating adult DG neurogenesis impairs mouse performance on a discrimination task between two simultaneously presented adjacent stimuli (Niibori et al., 2012; Clelland et al., 2009; Kheirbek et al., 2012). In contrast, increasing the proportion of adult-born GCs in the DG enhances spatial and contextual discrimination (Sahay et al., 2011; Nakashiba et al., 2012). Recent evidence suggests that young and mature DG GCs may, in fact, hold opposite roles in pattern separation (Nakashiba et al., 2012). These findings demonstrate that changing the ratio between young and mature GCs has important functional consequences on information processing.

Up to now, pattern separation has only been addressed at the computational and behavioral levels. Current research now challenges its role at the cellular and network levels. Current hypotheses link pattern separation with the period of hyper-excitability for newborn neurons and their associated synaptic plasticity. The hyper-excitability for a given neuron might originate from intrinsic cell properties and/or from network attributes. The latter has been demonstrated by neurophysiological approaches highlighting enhanced activity-dependent potentiation of the synaptic inputs onto new neurons, thereby enhancing their plasticity (Figure 1; Snyder et al., 2001; Ge et al., 2007; Schmidt-Hieber et al., 2004; Nissant et al., 2009). In the DG, enhanced synaptic plasticity results from the formation of new synapses endowed with unique functions and from a delay in receiving proximal inhibitory activity (Ge et al., 2006, 2007). Both events could lead to a high excitation/inhibition ratio that endows immature neurons with low activation thresholds and weak input specificity (Marín-Burgin et al., 2012; Piatti et al., 2013; but see also Dieni et al., 2013).

In the OB, hyper-excitable new interneurons inhibit circuit output. Because of this arrangement, sensory representations are sparse (Rinberg et al., 2006) and thus amenable to pattern separation (Rolls and Kesner, 2006; Leutgeb and Leutgeb, 2007). However, the principle of pattern separation raises a challenge in the hippocampus, where new immature excitatory GCs with poor input specificity cannot contribute to sparse coding in the DG. This could be explained by investigating the nature of the message conveyed by adult-born neurons and by determining how adult-born neurons recruit local inhibition (Figure 2). A recent computational modeling suggests that the transition from low to high inhibition coupling during cell maturation together with a low input selectivity are a key feature for pattern discrimination and encoding of novel inputs (Temprana et al., 2015). In this circuit context, adult-born neurons turn out to be preferential computational units for encoding and transmitting information to downstream regions. From another viewpoint, immature adult-born cells may impact the overall excitability of the DG network by driving a significant portion of the feedback

and lateral inhibition onto the GC layer while escaping from it, due to transient uncoupling to the inhibitory network (Marín-Burgin et al., 2012; Temprana et al. 2015). Increased activity in mature GCs and enhanced gamma oscillations have been observed after adult neurogenesis ablation (Lacefield et al., 2012; Burghardt et al., 2012; Ikrar et al., 2013). These observations support the hypothesis that the indirect net output of these hyper-excitable neurons of the DG would be GABAergic inhibition, a circuit feature that would ultimately reduce the general activity of mature GCs, modulate the timing of inhibition and the network synchronization, maintain some network homeostasis, and increase the sparseness of the representation (Figure 2).

3.2. Adult Neurogenesis and Memory Engram

Another common feature of olfactory and hippocampal adult neurogenesis is their facilitation of both learning and memory processes. In the OB, ablation of adult neurogenesis using chemical, irradiation-based, and genetic strategies have led to heterogeneous results, with at least one common behavioral impairment in olfactory memory (Lazarini and Lledo, 2011). Recent optogenetic gain-of-function strategies have confirmed that the selective activation of adult-born neurons improves the speed of olfactory associative discrimination learning and facilitates long-term memory recall (Alonso et al., 2012). Olfactory learning has also been shown to enhance input-specific synaptic strength onto adult-born neurons (Lepousez et al., 2014), further bridging synaptic plasticity in adult-born neurons and learning.

Consistent with the previous hypothesis that the DG is principally involved in memory encoding (Hasselmo et al., 1996), a number of approaches have highlighted the role of new neurons in encoding new memories (Shors et al., 2001; Zhang et al., 2008; Dupret et al., 2008; Winocur et al., 2006). To date, there are conflicting results in the literature showing that the ablation of adult neurons can either impair or have no effect on the acquisition during spatial learning. Most studies suggest that short-term/long-term retention and recall are altered following adult neurogenesis reduction in spatial learning or in an associative memory task (contextual fear conditioning, etc.). It is interesting that, when dentate newborn neurons were optogenetically silenced at 4 weeks of age, but not at 2 or 8 weeks, the retrieval of previously learned spatial locations on the water maze and the retrieval of learned fear-conditioned contexts were both impaired (Gu et al., 2012; see also Denny et al., 2012). More work is needed to characterize this restricted time window for adult-born neurons and to determine the role that 4-week-old neurons might play and that cannot be fulfilled by younger or older neurons. Additionally, indirect stimulation of adult neurogenesis (using enrichment, running, etc.) leads to spatial and associative memory enhancement, but the causal link between these observations is still missing (Koehl and Abrous, 2011; Marín-Burgin and Schinder, 2012).

If adult-born GCs act to separate ensemble patterns in the DG, how would this pattern separation impact memory storage? The answer relies on the fact that memory formation in the CA3 depends on sparse coding and that memory discrimination at the time of recall relies on adult neurogenesis. As a result, the pattern separation ensuing from adult neurogenesis reduces the probability that a new episodic memory will interfere with existing memories. This temporal separation partially results from the ongoing recruitment of adult-born neurons, which may encode new recent events during their transient window of hyper-excitability, whereas mature cells encode older memories (Aimone et al., 2011; Rangel et al., 2014). Once events have been encoded, the memory traces transfer from the hippocampus to the cortex. Consolidation of memory occurs at this stage. Remarkably, this process relies partly on hippocampal adult neurogenesis (Kitamura and Inokuchi, 2014). Together, these studies support the hypothesis that hippocampal neurogenesis impacts different stages of memory formation. Lastly, adult-born GCs have been shown to project to CA2 (Llorens-Martín et al., 2015), a hippocampal field selectively involved in social memory (Hitti and Siegelbaum, 2014). In addition to spatial and contextual memories, hippocampal neurogenesis may influence other forms of hippocampal-dependent memories.

3.3. Subregional Differences in Adult-Born Circuit Contribution

Consistent with an early distinction between the "cognitive" and "emotive" hippocampus (Bannerman et al., 2004; Fanselow and Dong, 2010), the discovery of adult neurogenesis in the DG was initially thought, and then progressively demonstrated, to participate both in learning and memory, as well as in emotion and mood regulation.

Anatomical projections to the ventral and dorsal hippocampus arise largely from non-overlapping downstream regions of the entorhinal cortex and reach distinct subregions of the DG (Dolorfo and Amaral, 1998; Ohara et al., 2013). In rodent, the dorsal subregion of the hippocampus receives multimodal information originating from dorsolateral entorhinal cortices and is mostly involved in spatial relational learning and memory (Moser et al., 1995). This region is also highly active and contains a larger pool of adult-born GCs (Piatti et al., 2011). Alternatively, the ventral subregion in rodent shows less basal activity, with fewer adult-born neurons that exhibit delayed maturation compared to dorsal ones (Piatti et al., 2011). The ventral region receives massive connections from affective brain areas, including the medial prefrontal cortex, amygdala, and hypothalamus and is intimately involved in anxiety, fear, and stress responses (Bannerman et al., 2004). At the output level, differential axon targeting within CA3 between dorsal and ventral adult-born GCs (Sun et al., 2013), as well as differential learning-induced recruitment of CA3 interneurons by GC mossy-fiber terminals in ventral and dorsal hippocampus (Ruediger et al., 2012), has been reported. Notably, the transient high excitation/inhibition balance observed in 4-week-old GCs of dorsal hippocampus (Marín-Burgin et al., 2012) has not been observed in the ventral hippocampus (Dieni et al., 2013), suggesting that the coupling to the inhibitory network may also be different in these two subregions. At the behavioral level, selective activation and inactivation of these dentate sub-regions (Kheirbek et al., 2013) or subregional adult neurogenesis ablation (Wu and Hen, 2014) indicates that the dorsal domain is preferentially involved in modulation of exploratory behavior, whereas the ventral part is more suited for regulation of anxiety-related behavior. Nevertheless, this dichotomy might be oversimplified, since it was recently demonstrated that exposing rats to moderate acute stress increased neurogenesis only in the dorsal subregion (Kirby et al., 2013). Also, in challenging contexts such as chronic exposure to

glucocorticoids, both populations of adult-born GCs (ventral and dorsal) contribute to the fluoxetine-induced anxiolytic effect (Wu and Hen, 2014).

Similar to the subregional action of new hippocampal neurons, OB neurogenesis occurs not only in the main OB but also in the accessory OB (AOB). This brain region is a smaller structure embedded within the main OB and is dedicated to encoding pheromonal signals. In the AOB, SVZ-derived neuroblasts differentiate into GCs that are localized within the inner region of the GCL (Oboti and Peretto, 2014). Recent efforts have been pursued to understand the contribution of adult-born cells in social behavior or with endocrine modulators (Gheusi et al., 2009; Feierstein et al., 2010).

Given the precise role of the hippocampal and olfactory subnetworks, the aforementioned findings shed new light on the variety of roles that adult neurogenesis may play in cognitive and affective functions.

4. Bridging the Gap between Adult Neurogenesis and Behavioral Outcomes

4.1. Adult Neurogenesis in the Hippocampus: Where Are We Standing?

Collectively, hippocampal studies aiming at suppressing adult-born neurons have yielded conflicting results on cognitive and emotional impairments. The inconsistent findings and hypotheses relate, in part, to the heterogeneity of experimental models used. When deciphering the impact of adult-born neurons on behavioral responses, adult neurogenesis has been altered using a number of different techniques including genetic ablation, focal irradiation, and chemical tools that differ considerably in efficacy, specificity, and the nature of the targeted cells (e.g., Jessberger et al., 2009; Dupret et al., 2005; Monje et al., 2002) and their respective off-target or compensatory effects. Furthermore, variability between species, for instance between rats and mice, makes it difficult to draw generalizable conclusions from distinct models (Ray and Gage, 2006; Snyder et al., 2009). Recently, the use of a rat genetic model to delete newborn neurons showed no significant difference from controls in spatial pattern separation on the radial maze, spatial learning in the water maze, and contextual or cued fear conditioning (Groves et al., 2013). This absence of effect is in contradiction to previous observations that demonstrated the need of adult neurogenesis when animals discriminated between similar stimuli (discussed in the earlier section "The Role of Immature Neurons in Network Dynamics and Computation"). However, when Groves et al. (2013) conducted a meta-analysis of all published results, they found no significant effects in ablation of adult neurogenesis on spatial memory, cue conditioning, or ethological measures of anxiety. Their meta-analysis revealed remarkably high levels of heterogeneity among studies of hippocampal function, indicating that only very sensitive tasks may capture the functional relevance of adult-born neurons. For instance, altering adult DG neurogenesis impaired spatial pattern separation learning in a contextual discrimination learning task (Sahay et al., 2011) and in a delayed non-matching to place radial arm maze task (Clelland et al., 2009). However, it did not impair it in a water maze task (Wojtowicz et al., 2008). This heterogeneity suggests that, in addition to sensory and contextual information, adult-born GCs integrate

multiple parameters, such as the level of stress and vigilance (Wu and Hen, 2014) that may affect their functional impact. On that line, stress, which usually reduces neurogenesis, can also increase neurogenesis when it persists after chronic social defeat (Lagace et al., 2010). Further studies are necessary to identify precisely the source of this heterogeneity and reveal unique interaction pathways between behaviorally relevant parameters.

Most studies have focused on the functional roles of neurogenesis in memory acquisition, in particular, during early phases of memory formation (Shors et al., 2001; Zhang et al., 2008; Dupret et al., 2008; Winocur et al., 2006). However, theoretical studies have postulated that the continuous integration of newborn neurons into existing adult circuits could potentially disturb the memory traces of previously stored contextual information in the DG (Meltzer et al., 2005). For example, a study with genetically modified mice lacking enrichment-induced neurogenesis in the DG showed that adult-born neurons play a key role in hippocampal memory clearance (Feng et al., 2001). Recently, a study revealed the retrograde function for adult neurogenesis in forgetting. After a group of adult mice learned how to find a hidden platform in a water maze, their neurogenesis was 2- to 3-fold enhanced. When tested later, mice with boosted adult neurogenesis performed much worse than their non-manipulated peers (Frankland et al., 2013; Akers et al., 2014). Endowing adults with a high rate of neurogenesis deteriorates otherwise stable memories, recapitulating the infantile amnesia that accompanies early postnatal development (Frankland et al., 2013). Increased neurogenesis may also support the consolidation process during adulthood in which a memory trace becomes progressively independent from the hippocampus (McClelland et al., 1995). The decay of hippocampal dependency is an active process that plays a role in clearing old memories out of the hippocampus once the memory has been stored in cortical networks, thereby allowing the hippocampus to continuously store new events (McClelland et al., 1995). This erasing process may also be part of a more general systems-level memory process in which information stored in the hippocampus is progressively transferred to distribute the cortical network (Maviel et al., 2004).

4.2. Adult-Born Neurons in OB Circuits: A Hub that Links Brain States with Sensory Representations

In the olfactory system, the OB is not merely a relay for olfactory information. In addition to receiving sensory inputs from the olfactory epithelium, it receives numerous "centrifugal" inputs from different brain areas, such as cortical regions of the olfactory cortex and limbic and neuromodulatory subcortical regions (Figure 1). GCs are, therefore, perfectly located to integrate both sensory and top-down information, adapting sensory processing to the behavioral/internal context.

In which contexts do top-down inputs act on adult-born neurons? Coarse lesioning of centrifugal afferents to the OB impairs the animal's ability to perform reward-associated olfactory discrimination tasks or perceptual learning (Gray and Skinner, 1988; Martin et al., 2004; Kiselycznyk et al., 2006; Mandairon et al., 2014). Active olfactory learning can enhance the survival of adult-born cells (Alonso et al., 2006; Mouret et al., 2008; Sultan et al., 2011), and adult-born GCs are selectively activated by

memory recall (Belnoue et al., 2011). Reward-associated olfactory learning induces a specific structural and synaptic remodeling of cortico-bulbar inputs onto adult-born GCs, resulting in the strengthening of top-down inputs (Lepousez et al., 2014). Along the same line, slow-wave sleep has also been associated with the specific activation of the cortico-bulbar top-down inputs and to adult-born cell selection (Yokoyama et al., 2011). Recently, the cortico-bulbar projection system has been shown to link internal nutritional states (i.e., hunger) to olfactory perception and to modulate feeding behavior (Soria-Gómez et al., 2014). These results illustrate that adult-born GCs are not only sensitive to the sensory environment but may also be highly influenced by internal variables such as valence, sleep/arousal, stress, nutrition status, attention, and motivation. These states impact the development, synaptic function, and (ultimately) survival of adult-born neurons, producing an additional level of metaplasticity. By encoding olfactory and contextual information through the detection of the occurrence between sensory inputs and top-down signaling, adult-born GCs thus act as efficient coincidence detectors between the content of a message and the context associated with it.

If GCs are key players in the cortico-bulbar loop, do adult-born GCs hold a unique role in accepting this feedback? Adult-born GCs exhibit distinct higher cell excitability, higher dynamic connectivity, enhanced synaptic plasticity, and enhanced activity-dependent survival (Figure 1). The expression of each of these features in specific temporal windows could have precise functional outcomes. For example, the olfactory cortex drives both direct excitation and feedforward inhibition onto GCs (Boyd et al., 2012; Markopoulos et al., 2012). The relative strength and timing of excitation versus inhibition will strongly impact the precision of spike timing and related plasticity rules in a manner similar to what has been demonstrated for entorhinal cortex inputs onto new neurons of the DG (Marín-Burgin et al., 2012). Thereby, long-term modification of the synaptic strength or connectivity could support learning and act as an enduring mark to protect cells from death. Consequently, coincident sensory and centrifugal inputs may be detected by newborn GCs and be critical to their survival.

5. Some Open Issues: The Human Case

Understanding the extent of new neuron production and integration in the human brain is one of the most controversial topics in the field of adult neurogenesis. Here, we discuss the status of human adult neurogenesis in the healthy and diseased brain.

5.1. Adult Neurogenesis in Humans

The first direct evidence supporting the notion of human adult neurogenesis was discovered in 1998, when a chemical label that permanently integrates into the DNA of dividing brain cells, bromodeoxyuridine (BrdU), was given to cancer patients for diagnostic purposes (Eriksson et al., 1998). However, since the BrdU technique for newborn neuron identification does not provide quantitative information on the number of new neurons generated and is no longer possible in humans due to safety concerns, it has been difficult to compare neurogenesis in humans to the same extent as previously reported in other mammals. However, a new technique has been developed to determine the aggregate neuronal age in brain subregions using the natural

C^{14} abundance in genomic DNA in deceased patients (Spalding et al., 2013). This study demonstrated that hippocampal neurogenesis occurs throughout adulthood, with a modest decline during aging, in sharp contrast to rodents. In addition, the C^{14} data also revealed a nearly 100% turnover of dentate neurons in humans, compared to the 10% reported in rodents (Spalding et al., 2013).

When the same retrospective dating technique was applied to quantify adult OB neurogenesis in postmortem brains, only a few, if any, OB adult-born neurons were detected. In infants, however, a small but significant level of postnatal bulbar neurogenesis was reported (Sanai et al., 2004, 2011; Bergmann et al., 2012). It is noteworthy that the declining healthy status of the human subjects and the resolution of these techniques could be confounding factors of reduced neurogenesis. Proliferating neuroblasts have been reported in the adult human SVZ using BrdU, histological markers, and neurosphere generation (Curtis et al., 2007; Wang et al., 2011; Sanai et al., 2011). Since adult-born neurons are not detectable in the OB, the fate of SVZ neuroblasts is still an unresolved issue. There is compelling evidence that the RMS migratory pathway is organized differently than in the rodent forebrain and substantially reduced after infancy (Sanai et al., 2004, 2011). In contrast, other works have shown an existence of functional RMS (e.g., Curtis et al., 2007; Wang et al., 2011) and were able to identify progenitors within the OB itself (Pagano et al., 2000). An anatomical study of the human OB indicates that it has a fundamentally distinct glomerular organization compared to rodents (Maresh et al., 2008), additionally questioning the functional homology between human and rodent olfactory system. Thus, existence and functional significance of adult neurogenesis in the human SVZ warrants further investigation. In this quest, researchers will have to take into account that the natural fate for SVZ neuroblast neurons might be either cell death or migration into a different region. Using histological and C^{14} dating, Frisén and colleagues have found that new neurons integrate in the human striatum, a brain region adjacent to the SVZ and involved in movement and cognition (Ernst et al., 2014). This shows that neuronal turnover in the striatum is restricted to interneurons. Remarkably, this study also demonstrates that postnatally generated striatal neurons are preferentially depleted in patients with Huntington's disease, thus linking impairment of adult neurogenesis with neurodegenerative diseases.

5.2. Altered Adult Neurogenesis and Human Brain Disorders

Some cognitive impairments and mental disorders have been hypothesized to rely on the malfunction of neuronal production in the hippocampus and on the adult neurogenesis-dependent pattern separation. Not only does pattern separation play a well-established role in spatial learning and memory, but mounting evidence supports its role in mood control (i.e., Kheirbek et al., 2012). According to the neurogenic hypothesis of mood disorders, new hippocampal neurons are required for proper mood control and for the action of certain antidepressant drugs (Eisch and Petrik, 2012). Insufficiency of new neurons results in an altered pattern separation that might generate difficulties in distinguishing threatening from similar safe situations. This difficulty in discrimination may contribute to anxiety and to an over-generalization of fear perception observed in

posttraumatic stress disorder. Because the expression of fear responses and the regulation of stress responses are mediated by other brain regions, such as the prefrontal cortex, the amygdala, and the hypothalamus, future experiments will have to use a systems-level approach to address how changes in hippocampal neurogenesis affect communication with brain regions outside the hippocampus.

While more work must be done in the field of adult neurogenesis and mood control, it is already noteworthy that the most commonly prescribed antidepressant drugs today promote hippocampal neurogenesis, and some of the effects of antidepressants in animal models are strictly dependent on increased neurogenesis (Santarelli et al., 2003). This neurogenic hypothesis of mood disorders might explain why depressed patients exhibit decreased hippocampal volume (Small et al., 2011; Fotuhi et al., 2012; Boldrini et al., 2012) and decreased neural progenitor cells in the hippocampus (Boldrini et al., 2012, 2013). It might also account for the increases in the prevalence of depression in the elderly, since neurogenesis rates slowly decline with aging. Accumulating evidence makes this framework very promising for conceptualizing depression mechanisms, which eventually may lead to the path for novel therapeutic strategies. Future studies should elucidate how adult-born neurons, especially those in the ventral hippocampal region, might impact the neural pathways mediating emotional experience and affective states.

Similarly, impaired adult neurogenesis has been linked with neurological disorders (and their animal models) such as AD, stroke, epilepsy, and HD (DeCarolis and Eisch, 2010; Danzer, 2012; Ruan et al., 2014). For instance, while adult hippocampal neural stem cells have lifelong activity in healthy humans, their numbers diminish in AD patients (Haughey et al., 2002), thus possibly accelerating learning and memory decline. Along these lines, striatum neurogenesis is also reduced in patients with HD (Ernst et al., 2014). Although the literature reporting on human cases is sparse, numerous studies conducted in mice have already highlighted several pathophysiological conditions in which adult neurogenesis is concerned, including addiction, epilepsy, and neurodegenerative and neuropsychiatric disorders. Currently, it is still unclear whether alteration of adult neurogenesis is a cause or a consequence of these pathologies.

The inflammatory status of the brain also strongly influences the process of adult neurogenesis. Neurogenic zones show a high density of microglia that phagocytose apoptotic adult-generated neurons (Sierra et al., 2010). It is now also clear that resting and activated microglia exert diverse (even adverse) effects on adult neurogenesis through the action of anti-inflammatory or pro-inflammatory cytokines (Fuster-Matanzo et al., 2013). The interaction between microglia and adult-generated neurons appears to be extremely complex. One of the greatest challenges of the coming years is understanding the meaning of this communication at every stage of the young neuron's life. Also, we will need to define the role of other glial or immune cells, such as astrocytes or macrophages, as well as circulating factors related to immune or allergic responses. With aging, microglial regulation of oxidative stress also declines, while neuroinflammation increases (Fuster-Matanzo et al., 2013), which could partially contribute to age-dependent reduction of neurogenesis. Recently, a striking study revealed that old mice in

heterochronic parabiosis with young animals developed some juvenile brain features, in particular, the restoration of high levels of neurogenesis in the SVZ-OB (Katsimpardi et al., 2008). This recent finding is yet another example of how adult neurogenesis integrates internal body states.

6. Key Questions and Future Directions
Understanding the role of adult neurogenesis in brain function has been a major challenge and has recently benefited from new technologies and new concepts. In this section, we point to a number of important key questions and future directions that will bring us closer to understanding the function of adult neurogenesis from a systems neuroscience perspective.

6.1. Functional Connectivity
Thanks to the continuous addition of new computational units, adult neurogenesis dynamically reformats the wiring of the bulbar and hippocampal circuits. Notably, adult-born neurons progressively integrate both inhibitory and excitatory inputs from local interneurons as well as from distant structures. During the critical period, experience can strongly remodel this presynaptic connectivity (Bergami et al., 2015). From this general wiring diagram (Figure 1), several questions emerge: How does the dynamic sequence of inhibitory and excitatory inputs shape the development and the activity of adult-born neurons? How does experience-dependent remodeling of presynaptic inputs influence adult-born neuron activity? What types of messages are conveyed by long-range versus local connections? How does distant activity interact with the local network to shape the development and function of new neurons? What are the consequences of such different wiring sequences between DG and OB neurogenesis?

Regarding the synaptic output of adult-born neurons, we still don't have a clear picture of how and when newborn neurons functionally interact with their post-synaptic partners. How does this connectivity dynamic impact network activity and the excitation/inhibition balance? How do experience- and activity-dependent processes shape postsynaptic connectivity? In the DG, experiments are needed to further analyze the mossy-fiber terminal complex and, particularly, its filopodia that support activity-dependent feedforward inhibition in CA3 and learning-induced inhibitory network plasticity (Caroni et al., 2012). The activity pattern of adult-born GCs may also be a decisive parameter to control the functional recruitment of inhibitory circuits. The use of optogenetics has provided some important answers on adult-born GC output, but further effort is needed to understand the impact of adult neurogenesis at the network level. Adult neurogenesis was shown to have distinct functional impacts according to the subregions of the hippocampus, namely, dorsal versus ventral hippocampus. Identifying the functional, cellular, and/or network differences and the various postsynaptic targets through which these subregions mediate their specific effects constitutes another priority research goal.

6.2. Activity-Dependent Control of Survival
Intrinsic genetic factors and neuronal activity profoundly influence adult-born neuron survival. What are the factors defining the critical periods for cell survival and regulating experience-dependent circuit integration such as presynaptic connectivity? Is it possible to extend or reopen a critical period? How do

genetic and intrinsic factors interact with local and distant networks to control cell survival? To finally understand how widespread neuronal activity orchestrates the development of new neurons, it will be necessary to unravel the precise contribution of all synaptic partners at every stage of the neuron's life. To do so, we will first need to characterize all the connections morphologically and functionally and then manipulate them in vivo. The combination of opto- and pharmaco-genetic strategies with behavioral and electrophysiological monitoring will be needed to achieve these goals.

6.3. Network Computations

Most of the computational functions of adult-born neurons have been derived and validated using behavioral analysis. However, extensive studies are needed to apply these functions to the circuits and system levels. Experimental work in awake, behaving animals combined with state-of-the-art in vivo recording techniques would refine our understanding of how new neurons influence network processing and representations. These techniques may answer questions such as the following: which computational functions are supported by adult neurogenesis in defined behavioral contexts? How do the olfactory and hippocampal newborn neurons shape the excitation/inhibition balance and network synchronization, as well as spontaneous versus evoked activities? What sensory or cognitive computations may be unique to these interactions? In parallel to these experimental approaches, biophysically realistic, large-scale models may also enable new insights on the computational functions of new neurons.

6.4. Behavioral Contribution

The precise contribution of immature adult-born neurons in the memory engram warrants further investigation. Optogenetic activation of a sparse population of dentate GCs active during learning is sufficient for memory recall or false-memory creation (Ramirez et al., 2013). Given their high responsiveness compared to mature neurons, adult-born neurons may have a significant role in this process (Figure 2). In addition, further efforts are required to chronologically analyze the activity of the same adult-born neuron during the different phases of acquisition, retention, consolidation, and recall. For this, chronic imaging of adult-born neurons in behaving animals will be fruitful. Adult neurogenesis has recently been involved in disrupting previous memory traces stored in synaptic connections. At the circuit level, which specific memory-related microcircuits and connectivity patterns are altered by adult-born neurons? In the ventral DG, further efforts are needed to investigate how ventral adult-born GCs and their specific connectivity regulate mood and emotional states. In the OB, a future challenge is to understand how sensory activity and centrifugal inputs naturally interact to support olfactory-driven behavior and control the development and survival of adult-born neurons. To address this, it will be necessary to control both centrifugal and sensory inputs while monitoring GC activity in vivo in various behavioral contexts.

6.5. Human Adult Neurogenesis

New neurons in humans may serve unique functions when compared to those in other mammals. Differences in maturation rates, newborn neuron proportion, destination, lifespan, and anatomy between humans and other animal models are now be-

ing investigated and will re-shape our understanding of human adult neurogenesis over the coming decades. The strong DG turnover observed in humans raises several questions. How could the human DG process information with such a large proportion of adult-born cells? Do human adult-born neurons display an extended maturation phase, including a larger critical window, as observed in macaque (Kohler et al., 2011)? Although cognitive deficits in patients with reduced neurogenesis (following radiation therapy, aging, stress) have provided interesting correlations (Jessberger and Gage, 2014), further evidence is needed to demonstrate causally that human adult-born neurons have a similar role as characterized in rodents and represent a potential target to alleviate cognitive decline in humans. The presence of striatal adult neurogenesis also raise important questions from an evolutionary perspective: In the animal kingdom, which other species share this feature? Is human neurogenesis in the SVZ fundamentally different from that in rodent? Are these adult-born striatal interneurons functionally relevant? Why, in humans, is this local integration conserved in the striatum but not feasible in the OB? For instance, striatal neurogenesis has been observed in rabbit (Luzzati et al., 2006) but not in rodent. In mice, Notch signaling has been shown to prevent striatal neurogenesis (Magnusson et al., 2014), indicating the presence of a latent neurogenic program in the adult brain. However, reactive striatal neurogenesis has been reported in mice following stroke but not in humans (Huttner et al., 2014). To explain these discrepancies, recent studies hypothesized that adult neurogenesis may have evolved to serve new functionalities to the targeted structures due to the socio-ecological pressure (Konefal et al., 2013).

7. Conclusions

The past decade has seen a tremendous increase in regenerative medicine research using stem cells for repairing damaged brain circuits. For example, for PD patients, analysis of clinical trials has identified several features of replacement cells that are essential for favorable outcomes (Wijeyekoon and Barker, 2009; Lindvall and Björklund, 2011). The therapeutic use of stem cells for neurological disorders includes either the modulation of endogenous stem cells that are resident within the brain or the introduction of exogenous stem cells. In this quest, the adult SVZ is a promising source of neural stem cells for generation of different neuronal subtypes (Merkle et al., 2014). In PD, for example, dopaminergic neurons may be used for cell transplantation (Cave et al., 2014). Harvesting adult-born neurons may also be an alternative method to using embryonic stem cells or induced pluripotent stem cells (Jessberger and Gage, 2014). Though highly promising, this strategy still faces several important challenges, including developing protocols with higher efficiency for neuron production and specification, improving migration and survival of engrafted cells, understanding how new connections are formed in a complex brain circuit, and removing the contaminating cell types responsible for tumor or teratoma formation. Since adult neural stem cells can be endogenously harvested from patients, they are a potential autologous source for cell therapy. Nonetheless, there are several basic conceptual frameworks and important technical issues that need to be tackled before creating favorable human clinical outcomes.

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