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Review

Newborn neurons in the adult olfactory bulb: Unique properties for specific odor behavior

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ABSTRACT

The generation of new cells in the adult brain reveals a new form of plasticity in the neuronal network. New cells are constantly migrating to and integrating into the pre-existing neuronal network in the olfactory bulb. The exact role of new neurons in the adult olfactory bulb and in odor behavior remains elusive despite continuous progress. The unique properties of these adult-born interneurons that distinguish them from pre-existing bulbar neurons allow them to adapt the processing of odor information in the neuronal network of the olfactory bulb in response to sensory experience. The combination of diverse methods for modulating neurogenesis levels with distinct behavioral paradigms has revealed that interneurons generated during adulthood play a role in olfactory behavior. In this review we provide an overview of the unique properties of adult-born neurons that integrate into the olfactory bulb as well as their role in odor behavior.

Contents

1. Introduction

The olfactory system is one of the oldest sensory modalities and is essential for the survival of many animal species. Olfaction provides vital information about food location, and influences social and sexual behaviors. In mammals, odors are detected by olfactory sensory neurons (OSNs) in the olfactory epithelium. The sensory information is transferred to the olfactory bulb (OB) where the axons of the OSNs make synapses with the primary dendrites of mitral and tufted cells (hereafter, we refer only to mitral cells for simplicity), the principal neurons in the bulbar network [1]. From the OB, the information is conveyed to the piriform cortex and other brain areas such as the amygdala, hippocampus, and enthorinal cortex [2,3]. Unlike other sensory modalities, odor information processing occurs without a thalamic relay. It is assumed that the OB "substitutes" thalamus in terms of processing odor information

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and relaying it to higher cortical areas [4]. The processing of odor stimuli in the OB is orchestrated by two populations of interneurons: periglomerular cells (PGCs) and granule cells (GCs). PGCs are located around the glomeruli of the OB, the site of synaptic contacts between OSNs and mitral cells, and form synapses within and between the glomeruli. This strategic positioning of PGCs allows them to control the activity of different glomeruli and take part in odor detection and discrimination processes [5–8]. Different subpopulations of PGCs have developed to perform these complex and variable functions at the initial stages of odor processing in the OB. For example, PGCs can express GABA, calretinin, calbindin and parvalbumin [9–11]. In addition, some GABAergic PGCs co-express tyrosine hydroxylase, a rate limiting enzyme for dopamine synthesis [12]. The chemical makeup of GCs is mostly GABAergic, although some GCs also express calretinin [13]. GCs form dendro-dendritic synapses on the lateral dendrites of mitral cells, providing recurrent and lateral inhibition of these principal neurons [14–19]. This inhibition is mediated through reciprocal synapses, where glutamate is released from the lateral dendrites of the mitral cells onto the spine of a GC, which in turn induces the release of GABA back onto the mitral cell dendrites [14,15,20]. The inhibition provided by the GCs synchronizes mitral cell activity, allowing for fine spatiotemporal tuning of the responses of these principal cells to an odor [16,19,21].

The two populations of interneurons in the OB are, in part, generated during adulthood from neural stem cells in the subventricular zone (SVZ) bordering the lateral ventricle (Fig. 1) [22–24]. Neuronal precursors travel in chains toward the OB along the blood vessels in the rostral migratory stream (RMS) [25–27]. Once in the OB, neuronal precursors mature and acquire the electrophysiological properties of fully developed neurons within 2–3 weeks [28–30]. Neurons generated during adulthood form functional synapses with the principal cells of the OB [31,32] and are activated by odor stimulations [33,34]. Of the large number of cells arriving in the OB, only 3% differentiate into PGCs while the others (97%) become GCs [35]. In this review, we discuss the exclusive functions of adult-born GCs in the olfactory neuronal network. We then discuss how these distinct functions affect olfactory behavior. Lastly, we try to understand why neurogenesis exists in the OB.

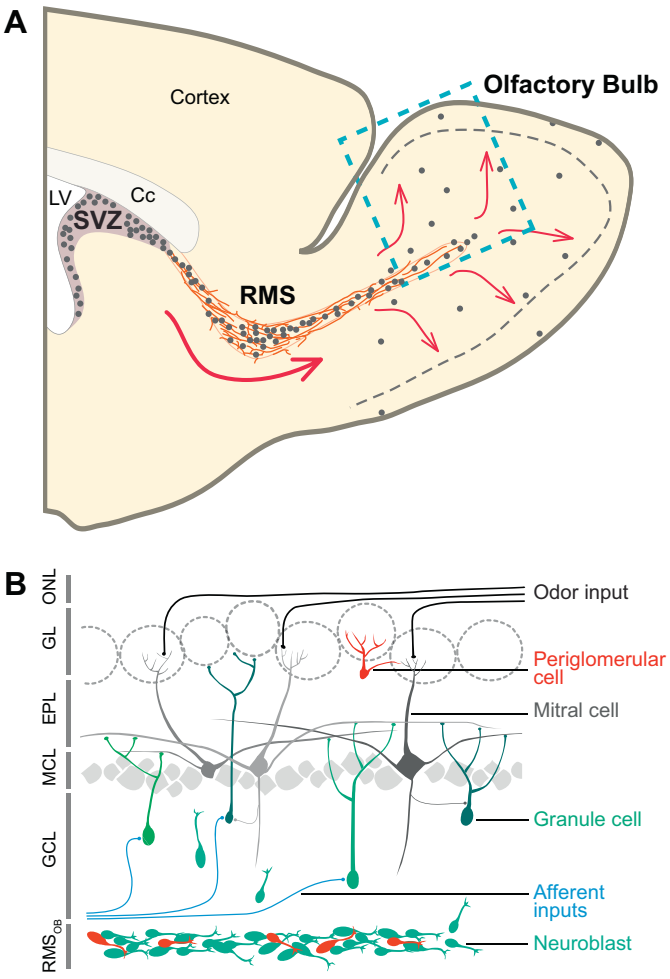

Fig. 1. Adult-generated cells are constantly arriving into the olfactory bulb (OB). (A) Illustration representing the adult OB neurogenesis. Adult-born cells migrate tangentially, using blood vessels, from their site of generation (subventricular zone: SVZ) to the OB via the rostral migratory stream (RMS). In the OB, they migrate radially and integrate into the pre-existing neural network. LV: lateral ventricle; Cc: corpus callosum. (B) View of boxed area in A representing the laminar organization of the OB. Adult-born cells differentiate into the bulbar interneurons, granule and periglomerular cells. RMS$_{OB}$: RMS of the OB; GCL: granule cell layer; MCL: mitral cell layer; EPL: external plexiform layer; GL: glomeruli; ONL: olfactory nerve layer.

2. The unique nature of adult-born granule cells in the OB

The constant arrival of adult-born GCs provides the OB with a substantial pool of flexible neurons that can adapt to the operational needs of the pre-existing neuronal network in response to the environmental demands. Studies using BrdU and [^{3}H]-thymidine to count adult-born cells have indicated that approximately 20 000–30 000 granule cell precursors arrive every day to the OB [28,35]. However, DNA base analogs such as BrdU and [^{3}H]-thymidine only label small cohorts of adult-born cells, which underestimates the true proportion of new neurons integrating into the OB network on a daily basis. To overcome this caveat, genetic fate mapping experiments to permanently label and monitor most of the adult-generated neurons have been performed [36–38]. Based on this technique, the number of adult-born granule cells in the OB 3 months after Cre recombination have been show to be equal to or less than 10% of the total cell density in the granule cell layer [36,37]. Similar experiments performed using another nestin-Cre inducible line revealed that the proportion of adult-born GCs in the OB is approximately 40% after 6 months and 50–60% after 12–18 months [38]. While genetic [38] or pharmacological [39] ablation of adult neurogenesis for 1 month does not result in any measurable differences in the number of GCs, impairing neurogenesis for 6–12 weeks disrupts the structural integrity of the OB [38]. However, physiological alterations in the bulbar network following ablation of neurogenesis can be observed much earlier [39], indicating that adult-born neurons have a considerable impact on the functioning of the bulbar network shortly after their integration into the OB. Almost half of the dendro-dendritic inhibition of mitral cells is provided by GCs born over a period of 28 days [39]. This in turn controls the synchronized activity of the principal neurons of the OB and leads to proper execution of behavioral odor tasks [39]. We hypothesize that adult-born cells have a considerable impact on the functioning of the OB network because of the specific morphological and physiological characteristics that distinguish them from pre-existing GCs. Here, we present some of the evidence for such a unique nature of adult-born GCs.

2.1. Survival, targeting, and synaptic maturation of adult-born GCs are different from their pre-existing counterparts

The continuous supply of the OB network with adult-born neurons is accompanied by a massive cell elimination [28,35,40]. A two-fold reduction in the number of BrdU+ or [^{3}H]-thymidine+ adult-born cells was observed between 15 and 45 days after labeling [28,35]. The second wave of reduction in the number of

adult-born neurons of about 25% was documented in the adult mice from 135 days to 1 year after labeling [28]. This reduction was not observed in rats, where the adult-born cells that survived the first 3 months persist for up to 19 months [35]. Overall these results demonstrate that at least 50% of the adult-born neurons stay in the bulbar circuitry for a limited amount of time, which contrast sharply with the survival profile of the neonatal GCs. No changes in the population of GCs generated during the first postnatal week can be found in the OB from 22 until 60 days after labeling [40]. This data suggest that essentially entire population of GCs generated during early postnatal week may survive until adulthood. Interestingly, however, GCs produced during the early postnatal week are preferentially located in the superficial granule cell layer [40], while the percentage of adult-born cells that develop into the mature NeuN+ phenotype is higher in the deep granule cell layer [38] (Fig. 2A). Indeed, the genetic ablation of adult neurogenesis leads to the elimination of GCs in the deep, but not the superficial granule cell layer [38], implying that neonatal GCs positioned in the superficial granule cell layer persist throughout life, whereas those positioned in the deep granule cell layer are constantly replaced [38]. The differential targeting and replacement of neonatal and adult-born GCs may lead to different functional outcomes. Since the lengths of the

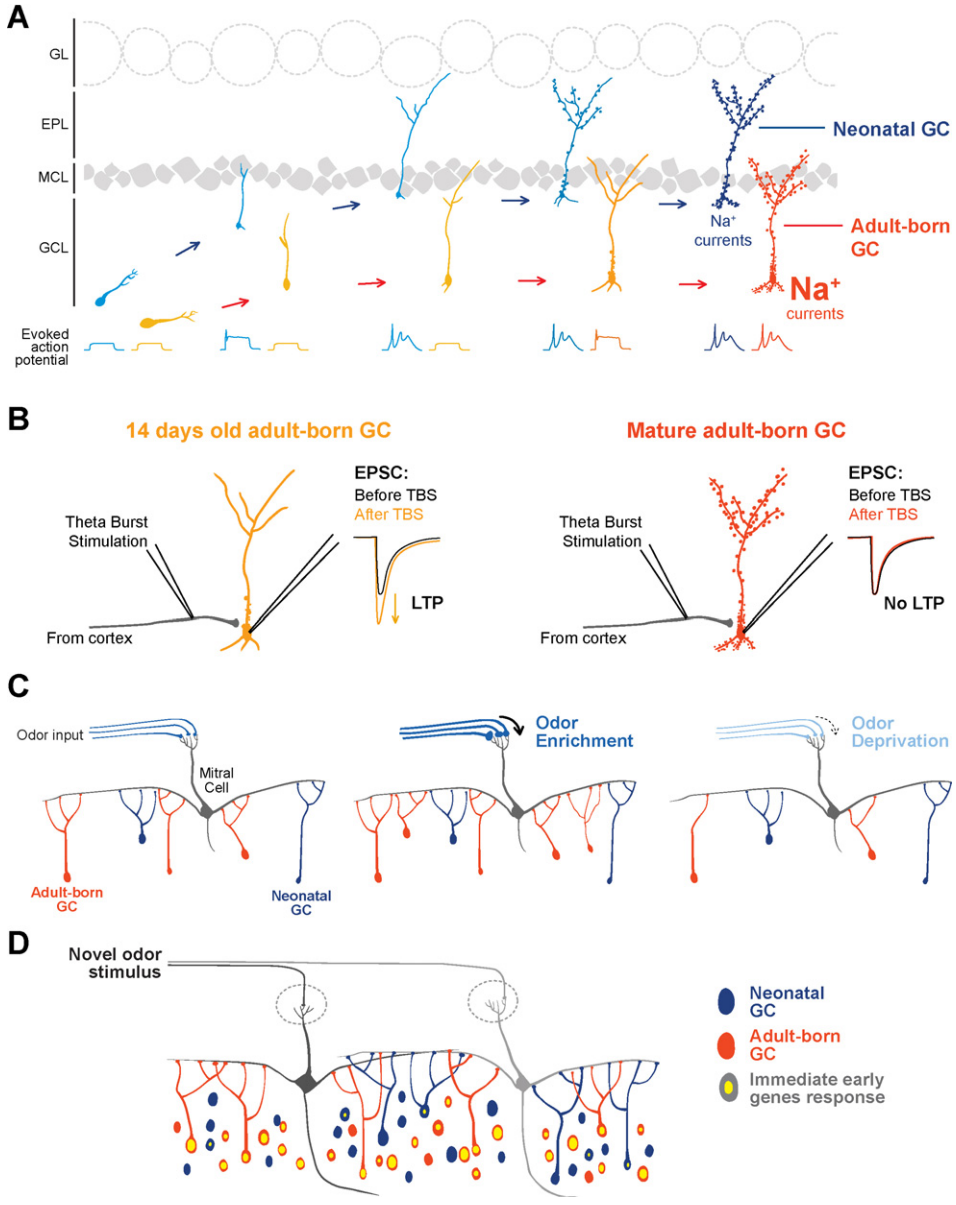

Fig. 2. Illustration showing the distinct properties of the adult-born granule cells. (A) Model of the maturation of neonatal versus adult-born granule cells. The different shading of red (neonatal) and blue (adult-born) represent the granule cells at their different stage of maturation. Adult-born cells exhibit differences in: location, timing of synaptic input formation and sodium channel properties. Adult-born cells tend to have their soma located in the deeper layer of the OB whereas the neonatal cells are placed in the superficial layer (closer to the mitral cell layer). As a result, their dendritic arborization is reaching different part of the external plexiform layer (EPL). In contrast to neonatal granule cells, interneurons generated during adulthood receive synaptic input before forming synaptic output with mitral cell dendrites. In addition, adult-born granule cells fire action potentials at later maturational stages and tend to have stronger sodium currents when they are fully mature. (B) Shortly after arriving into the adult OB (14 days), theta burst stimulation (TBS) induces long-term potentiation (LTP) at the glutamatergic synapses between cortical projections and adult-born GCs. This feature is lost with maturation of adult-born GCs. (C) Effect of odor enrichment and deprivation on adult-born cells survival and morphology. After odor enrichment there is an increase in the number of adult-born cells surviving in the OB. Odor deprivation on the other hand decreases the survival and number of spine of the adult-born GCs. The pre-existing population of GCs remains intact. (D) Greater amount of adult-born cells respond to novel odors, as assessed by the expression of immediate early genes, compared to the pre-existing population of interneurons. GL: glomeruli; EPL: external plexiform layer; MCL: mitral cell layer; GCL: granule cell layer.

primary dendrites of superficial and deep GCs remains relatively constant [41], these two subpopulations can preferentially target the dendrites of mitral or tufted cell, respectively [1,42]. This, in turn, implies that the activity of tufted cells is under the preferential control of neonatal GCs, while interneurons produced during adulthood provide an inhibitory drive to both mitral and tufted cells.

GCs produced at different developmental ages not only have distinct targeting and likely survival profiles, they also differ in the development of their input–output synaptic connections (Fig. 2A). Adult-born GCs integrating into the OB network receive the first synaptic input on their soma and basal dendrites before forming their output via dendro-dendritic synapses with mitral cells, on their distal dendrites [31,43]. This maturational profile of GCs generated during adulthood is completely different that of GCs generated during early development, where input and output synapses are formed simultaneously on proximal and distal dendrites [43]. Such particular sequential acquisition of input synapses on the proximal dendrites of adult-born GCs before forming the output synapses on the distal dendrites allows these cells to be silently integrated into the bulbar network. Adult-born bulbar interneurons thus behave in a "*first listen then act*" mode. However, when output dendro-dendritic synapses are being formed, the number of spines on the dendrites of adult-born GCs increases until day 28, remains stable until day 42, and subsequently decreases by day 56 [31]. This indicates that adult-born GCs overproduce spines during their integration process [31]. If these overproduced spines are part of the functional dendro-dendritic synapses, it also suggests that adult-born GCs provide greater inhibition of principal neurons at an early stage of their bulbar life. The developmental profile of output synapses of neonatal GCs remains to be elucidated. Analysis of synaptophysis-GFP retrovirally labeled neonatal GCs revealed that the number of output synapses increases until day 28 [43]. It remains unclear, however, if neonatal GCs display the same decrease in the number of output synapses as adult-born interneurons at day 56 and if overproduction of spines is a general feature of both populations of interneurons residing in their immaturity.

2.2. GCs generated during adulthood display delayed acquisition of firing activity but greater excitability when fully matured

While morphological distinctions between neonatal and adult-born GCs have different implications for the functional circuitry of the OB, electrophysiological differences between these two subpopulations of GCs have also been observed. The first electrophysiological assessments of newborn interneurons in the adult OB have revealed dissimilarities in terms of spiking activity and the development of sodium conductance (Fig. 2A) [29,30]. Neonatal GCs can fire action potentials around the time they finish migrating [43]. In contrast, interneurons generated during adulthood acquire sodium conductance and fire action potentials at later maturational stages, just before the emergence of output synapses and only after receiving synaptic inputs at their proximal dendrites [29,30,43], but see also [44]. When both adult-born GCs and PGCs acquire their synaptic inputs, they tend to develop significantly larger sodium currents than their neonatal counterparts [29,30,45], with steeper conductance-voltage relationships and more negative activation thresholds [29]. This may result in a greater excitability of newcomers than of neonatal GCs, which would enhance their overall inhibitory drive on the principal cells of the bulbar network. Moreover, the excitability of adult-born GCs might be further increased by the modulation of the level of sensory activity [45]. While odor deprivation induces a shift in the voltage dependency of the sodium currents toward more hyperpolarized values leading to the increased excitability of adult-born GCs, neonatal GCs remain unaffected [45]. As such, adult-born cells display a distinct level of adaptation, which is not present in other interneurons in the OB.

2.3. Long-term potentiation can be transiently induced in adult-born GCs

Glutamatergic inputs on the proximal dendrites of GCs, which originate mainly from cortical feedback projections or mitral cell axon collaterals, can be specifically potentiated (Fig. 2B) [46,47]. This, in turn, increases the excitatory postsynaptic potential of the GCs and, consequently, mitral cell inhibition [46]. Nissant et al. reported that the plasticity in these synapses can be reliably induced only in young adult-born interneurons, 2 weeks after viral labeling in the RMS [47]. Theta-burst stimulation (TBS) did not induce long-term potentiation 12 weeks after viral labeling and in unlabeled GCs [47]. Gao and Strowbridge also demonstrated that TBS or pairing focal stimulation near the proximal dendrites of GCs with postsynaptic action potentials reliably induces potentiation in GCs in slices prepared mostly from P14 to P21 and in a few cases from P30 rats [46]. Since about 55% and 18% of granule cells are generated during the first and second postnatal weeks, respectively [48], it is likely that most of the recorded cells in juvenile rats were approximately of 2–3 weeks old. Therefore, it is conceivable that adult-born and neonatal GCs might both display experience-dependent modifications in the synaptic efficacy at their proximal glutamatergic synapses at the early stages of their life. It seems that, as adult-born neurons, neonatal GCs also lose their capacity for experience-dependent modification at their proximal synapses at later stages, since recording of nonGFP+ cells in the adult OB did not reveal LTP at these synapses [47]. This remains to be proven directly by labeling neonatal GCs and recording them in the adult OB. If young adult-born neurons are more prone to plastic changes at their glutamatergic proximal synapses as compared to old adult-born or neonatal GCs, transiently potentiating these cells provides an immediate way for higher brain areas to modulate the OB neuronal network by increasing the inhibition of mitral cells. This would suggest that adult-born cells adapt more promptly than pre-existing cells.

2.4. Adult-born GCs generated during 28 days provide 45% of inhibition received by mitral cells

The morphological and electrophysiological data highlighted above suggest that adult-born neurons may influence the bulbar network in a very specific and time-restricted manner. The ablation of adult neurogenesis for 28 days induces drastic changes in the adult OB network and reduces the frequency of spontaneous inhibitory postsynaptic currents (IPSCs) in mitral cells by 45% [39]. These data strongly suggest that adult-born interneurons provide more inhibition to mitral cells as compared to neonatal GCs. Ablation of neurogenesis for 28 days also decreases the evoked dendro-dendritic currents [39], whereas there is no difference in rise and decay times or IPSCs amplitudes in mitral cells recorded from control and neurogenesis-ablated animals [39]. These results suggest that the functioning and content of postsynaptic $GABA_A$ receptors is normal but that there is a lower number of GABA release sites on mitral cell dendrites. This hypothesis is supported by the decrease in the number of gephyrin+ puncta, which is anchoring protein for GABA receptors on mitral cell lateral dendrites [39]. Interestingly, while the frequency of miniature IPSCs is reduced by 45%, the number of inhibitory synapses is reduced only by 20% [39]. These data imply, among other possibilities discussed elsewhere [39], that adult-born GCs may display a higher probability of GABA release than their neonatal counterparts and thus provide a greater inhibitory drive on the lateral dendrites of mitral

cells. This remains to be proven directly by imaging the vesicular GABA release in adult-born and pre-existing cells using FM dyes.

2.5. Adult-born GCs are highly sensitive to olfactory activity

The morphological and electrophysiological evidence discussed above indicates that adult-born GCs have unique properties and reveals some of the differences between them and their neonatal counterparts. These differences suggest that adult-born GCs might exert specific and time-restricted influences on odor information coding in the OB. If this is the case, then this population of interneurons should be also susceptible to changes induced by sensory stimulation. This is born out by the fact that the number of adult-born cells can be modulated by odor enrichment (Fig. 2C) [49–53], odor deprivation (Fig. 2C) [28,45,54–57], pheromones [58,59], and associative tasks based on olfaction [52,60–64] (see also section 3 for further discussions). In addition, the morphology and spine number of adult-born cells are modulated by olfactory activity [45,55,65,66]. On the other hand, the neonatal neurons likely persists over time in the OB, and their initial survival depends greatly on the early olfactory experience occurring at the time of their generation and integration [40]. However, while the modulation of sensory activity occurs shortly after the integration of neonatal GCs into the bulbar network, their number and morphology remains unchanged [45]. This contrasts with the properties of GCs born during adulthood. At this stage, the level of sensory activity modulates not only the population of adult-born GCs during their integration process, but also the population of adult-born interneurons present in the bulbar network before sensory deprivation [56]. This indicates that GCs that are integrated into the bulbar network remain tuned to changes in the level of sensory information. Adult-born GCs thus seem to be more sensitive to odor stimulations than pre-existing interneurons. In line with this hypothesis, the presentation of novel odors induces a greater immediate early gene expression in adult-born GCs than in pre-existing GCs (Fig. 2D) [34], again suggesting that adult-born and pre-existing GCs undergo different experience-dependent modifications [34].

Altogether, these data highlight the unique function of adult-born neurons in the OB. This population of interneurons expresses several morphological and electrophysiological features that make them well suited to exert rapid, time-restricted and efficient modulations in the neuronal network in response to changing environmental conditions. The overproduction of dendritic spines, increase in sodium currents and excitability, potentiation of the proximal glutamatergic synapse, and likely many other yet undiscovered characteristics of adult-born GCs, distinguish these cells from their older counterparts and suggest that they exert specific roles in odor encoding.

3. Role of adult neurogenesis in olfactory behavior

As mentioned above, adult-born GCs form reciprocal synapses with the lateral dendrites of mitral cells. GCs control the responses of mitral cells to an odor by lateral and recurrent inhibitions through this dendro-dendritic synapse [16,19,21]. By selectively attenuating or boosting dendro-dendritic inhibition in the OB, the latency of odor discrimination can be increased or decreased, respectively [67]. The synchronization of mitral cells in the OB is crucially dependent on the inhibition provided by the dendro-dendritic reciprocal synapse [68,69] and decrease in the number of adult-born GCs impairs the oscillatory activity of the principal bulbar neurons [39]. The massive arrival and integration of new cells in the OB network suggests that adult neurogenesis plays a role in olfactory behavior.

Studies on the behavioral impact of adult OB neurogenesis on olfaction have provided, however, many contradictory results. This is likely due to the use of different animal models of neurogenesis modulation including enhancement of neurogenesis by odor enrichment [49,50,52,59–62,64,70], genetic models that indirectly target neurogenesis [38,71–75]; and specific ablation of neurogenesis via inducible genetic models, pharmaceutical agents or irradiation [39,52,59,62,76–78]. Many of these models are correlative and far from being specific. The odor stimulation and learning do not only induce changes in the number and morphology of adult-born neurons [49,50,52,59–62,64,70], but also affect the sensory neurons turnover [79] and the structural plasticity in the glomeruli [80]. Constitutive gene knock-out and knock-in models [38,71–75] might affect the development and the function of the olfactory system and, thus, lead indirectly to changes in the level of neurogenesis. Therefore, in order to get a better understanding on the role of adult-born neurons in the bulbar circuitry and the odor behavior, the number of these cells should be modulated specifically in adults and far away from the OB, where sensory-induced changes in the neuronal network might affect behavioral outcome in a neurogenesis-independent manner. This is achieved by using inducible genetic models, infusion of antimitotic drugs into the lateral ventricle or irradiation of SVZ [39,52,59,62,76–78]. In addition to the different models to study neurogenesis, distinct paradigms to study olfaction were used. The various behavioral paradigms employed were either based on spontaneous olfactory behavior [39,49,50,52,71,73–77] or associative olfactory tasks [38,39,60–64,72,76–78] generally using single odor molecules or mixtures of two odorants. The involvement of adult neurogenesis in ethologically relevant olfactory behavior has also been studied [38,58,59,70,81,82]. Since the role of adult neurogenesis may differ significantly depending on the behavioral paradigm employed, we distinguish between the results obtained with these different tests.

3.1. Role of adult neurogenesis in spontaneous odor behavior

The simplest odor behavior test involves presenting a novel neutral odor to an animal and measuring the sniffing time during the presentation of that odorant. This type of behavior, hereafter called spontaneous odor behavior, does not rely on the active involvement of higher brain areas as in associative or ethologically relevant odor tasks. The ability of an animal to discriminate an odor can be assessed using repeated presentations of an odor (habituation) followed by the presentation of a novel odor (dishabituation). The sniffing time during the habituation phase normally decreases between each presentation, and then increases during the dishabituation phase if the animal is able to discriminate between the two odors. The performance of an animal during the habituation/dishabituation phases can be tested using either chemically related odors (enantiomers, *n*-aliphatic aldehydes, acids, alcohols), hereafter called similar odors, or two completely different chemical cues differing in composition and chemical properties, hereafter called dissimilar odors [52,83,84]. Spontaneous odor behavior can also be used to assess the short-term olfactory memory of an animal by comparing the sniffing time during two exposures to the same odor with different time intervals between presentations. At the second presentation of the odor, an animal remembering the odor investigates the odor for a shorter period of time. The short-term memory refers to the memory of an odor within a time interval that is less than four hours [75] as opposed to long-term memory, which is tested over a period equal or exceeding 24 h and is typically assessed using associative tasks. Spontaneous odor behavior can be used to evaluate the odor detection threshold of an animal by comparing sniffing times during the presentation of the same odor at different concentrations. All these tests can be used to probe the role of adult neurogenesis in simple spontaneous odor behavior

tasks that largely rely on odor detection in the sensory epithelium and odor information processing in the OB.

Many studies have used spontaneous odor tasks to evaluate the behavior of rodents where neurogenesis is either reduced or enhanced. Olfactory stimulation by odor enrichment increases the survival of adult-born interneurons in the OB [49,50,52,60–62]. Placing mice in an enriched environment for 40 days enhances the number of adult-born GCs in the OB and improves spontaneous short-term memory of odors [49,50]. In addition to the effects on the cell survival and short-term memory with odor enrichment, it has been demonstrated that olfactory perceptual learning is accompanied by an increased number of adult-born cells in the OB [52,60–62]. Enrichment with two chemically similar odors boosts adult-born cell survival, which improves the ability of an animal to discriminate pairs of odors which activates partially overlapping regions of the OB [52]. As expected, blocking neurogenesis by infusing antimitotic drug AraC (arabinofuranosyl cytidine) during the period of odor enrichment prevents the improvement in the discriminative abilities of mice [52]. This effect is specific to pairs of chemically similar odorants, since the ablation of neurogenesis has no impact on the discrimination of odors that are chemically dissimilar [39]. These results suggest that adult-born neurons are mainly involved in short-term odor memory and the discrimination of perceptually similar odors, but not in the discrimination of dissimilar odor cues.

Different transgenic mouse models leading to the affected number of newborn cells were also used to assess the contribution of neurogenesis to spontaneous olfactory behavior [71,73,75]. These studies have resulted in the contrasting data. The impairment of the migration process in neural cell adhesion molecule (NCAM)-deficient mice, and the survival rate in variant brain-derived neurotrophic factor (Val66Met) mutant mice, leads to a decrease in the overall number of adult-born cells in the OB and reduces the ability of the mice to discriminate between dissimilar odors [71,73] while leaving short-term memory intact [73]. In contrast, the removal of β2-containing nicotinic acetylcholine receptors leads to an increase in adult-born cell survival and a decrease in short-term memory [75]. However, this behavioral effect might be due to the direct modulatory role of cholinergic afferents in olfactory processing and not neurogenesis *per se*. This possibility is supported by the fact that the injection of scopolamine, a cholinergic receptor antagonist, in the OB impairs short-term olfactory memory [85]. Overall, the impairment of neurogenesis using constitutive gene knock-out or knock-in models is far from specific. Possible compensatory mechanisms such as a change in OB size, defects in the formation of neuronal circuitry during embryogenesis and neonatal life, and possible functional alterations in the bulbar circuitry of an adult animal may distort the actual effect. As such, the use of models that only alter adult neurogenesis, leaving the rest of the brain intact, seem to be the most appropriate approach for studying neurogenesis.

Several models in which adult neurogenesis is specifically affected have been introduced in recent years [38,39,62,76,78]. In the studies examining the role of adult-born GCs in spontaneous odor behavior, neurogenesis was altered either by irradiation or by using antimitotic drugs [39,52,76]. Focal irradiation of the subventricular zone impairs cell proliferation and thus disrupts the production of OB interneurons for a period up to 180 days [76,78,86]. Depending on the intensity of the irradiation, the number of migrating cells arriving in the OB can be reduced by 70–96%, leaving proliferation in the hippocampus intact [76,78]. In one study where focal irradiation induced a 70% decrease in the number of doublecortin+ cells, no changes in spontaneous discrimination or short-term memory were noted [76]. However, in this study, a major compensatory effect on the survival of the remaining 30% of adult-born cells in the OB was observed [76]. Indeed, the cells that arrived in the OB of irradiated animals survived significantly longer [76]. The disruption of adult neurogenesis may be compensated for by changes in the remaining population of adult-born GCs, which ensure the proper functioning of the bulbar circuitry [45]. It is thus conceivable that the negative spontaneous odor behavior results obtained with irradiated mice can be explained by compensatory changes in the bulbar network. Therefore, in order to understand the role of adult-born neurons in odor coding and olfaction, a careful evaluation of physiological changes, at both cellular and network levels, in the OB following affected neurogenesis is required.

The infusion of the antimitotic drug AraC into the lateral ventricle stops proliferation [72] and completely abolishes the arrival of cells in the OB [39,52,59,62]. The effect on hippocampal neurogenesis appears to be minimal [39,52,59,62]. The number, morphology, and spine density of interneurons generated before the infusion of AraC do not change, indicating that the compensatory changes in the survival of GCs observed in the irradiation model do not occur in AraC-treated mice. Ablating neurogenesis for 1 month using AraC affects the odor detection threshold and the short-term memory of odors, but leaves the discrimination of chemically dissimilar odorants unaffected [39]. As outlined above, the reduced inhibitory drive on bulbar principal neurons that leads to the alteration of synchronized activity following sensory stimuli thus appears to be the cellular basis of odor behavior deficits [39]. These findings imply that short-term memory depends on the constant formation of inhibitory reciprocal synapses in the OB.

3.2. Role of adult neurogenesis in olfactory associative learning

Associative learning of an odor is another paradigm that has been extensively used to evaluate the function of neurogenesis in the OB. Rather than measuring the natural exploration time of an animal, these tests evaluate the capacity of an animal to associate an odor with a food or water reward or noxious stimuli [38,39,60–64,72,76–78]. Use of these tests in different animal models displaying altered neurogenesis has given rise, however, to conflicting results.

Most associative learning tasks influence the level of neurogenesis in the OB [60–62,64]. The survival of adult-born cells increases when mice are tested with an odor discrimination task in which they have to distinguish between two odors to receive a reward [60,62–64]. The discrimination task mainly increases the survival of 3–4 weeks old GCs [64]. However, the survival of adult-born cells generated 5 weeks before performing the learning task decreases [61,64]. The complexity of the task (similar or dissimilar odors) appears to abolish this reduction in survival [61]. The proportion of activated BrdU+ cells co-expressing immediate early gene marker *cfos* was evaluated over the age of adult-born cells in order to understand the involvement of adult-born neurons in the associative learning [63]. It has been shown that odor stimulation preferentially recruit young 2 weeks old adult-born neurons, whereas associative learning based on odor-discrimination recruit more mature 5 weeks old BrdU/*cfos*+ adult-born neurons [63]. These results suggest that olfactory learning may increase either the integration/elimination or the activation of adult-born GCs depending on cell age, and indicates that there is a critical period for learning-induced integration and activation of adult-born neurons into the bulbar circuitry. Newly recruited neurons are more sensitive to associated odors [60–63], and an increase in cell number appears to upregulate the overall inhibition received by mitral cells [52]. We still do not completely understand how adult-born neurons affect the cellular and neuronal network in the OB to influence bulbar circuitry involved in associative odor discrimination and learning.

The exact role of increased neurogenesis following odor associative learning in modulating olfactory behavior also remains unclear. It appears that blocking neurogenesis during the odor

conditioning of an animal does not impair the acquisition of the associative olfactory task [62]. Moreover, associative odor discrimination and memory are also unaffected when adult-born neuron survival is increased by caspase inhibitor zVAD [77]. On the other hand, it has been recently suggested that the increase in the number of adult-born neurons following learning paradigms may be necessary for the retrieval of long-term memories [62,76]. However, this is contradicted by the data obtained in an inducible transgenic model showing long-lasting impairment in adult neurogenesis [38]. In this model, there were no differences between control animals and neurogenesis-ablated mice in terms of odor-associated learning tasks, suggesting that adult neurogenesis is not required for odor-associated memory. In addition, normal long-term associative memory has been reported in two other models of altered neurogenesis [39,74]. The reasons for this discrepancy are unclear, but likely results from the type of associative learning task used in the studies. The associative learning tasks can be sub-divided into operant and non-operant conditioning tasks that should be clearly defined in order to avoid an additional confusion in the field. The operant conditioning task depends on the active learning of the behavioral paradigm, where the behavior of the animal during the training phase determines whether it receives a reward or not. In contrast, non-operant associative task relies on a passive association of a reward with odor stimuli during the training phase. However, it should be noted, that the level of "active behavior" of the mouse during the passive association of the reward with odor stimuli could be a matter of debate and thus classification of some of the tests used in the recent studies as operant conditioning tasks. We think that Sultan et al. [62] and Lazarini et al. [76] used operant conditioning task since the behavior of the animal during the training phase determined whether it receives a reward or not. In contrast, our group [39], Imayoshi et al. [38] and Kim et al. [74] used non-operant associative tasks that relied on a passive association of a reward with odor stimuli during the training phase. Our classification of operant and non-operant conditioning tasks is in line with that of several other groups. After the initial submission of our review, the group of Dr. Pierre-Marie Lledo has published a review article where it was implicitly stated that "*. . .it is worth noting that some studies have employed non-operant tasks (Imayoshi et al., 2009; Breton-Provencher et al., 2009) whereas other studies have used operant tasks (Lazarini et al., 2009; Sultan et al., 2010)*" [87]. Sultan et al. [62] have also classified the test performed by Imayoshi and colleagues as non-operant conditioning task. Thus, several groups agree that the discrepancy in the behavioral studies using associative learning paradigms could result from the use of operant vs. non-operant associative tasks. Each of these behavioral paradigms has advantages and disadvantages. The operant go/no-go conditioning test provides precise control over odor concentration, but requires extensive active learning, whereas non-operant conditioning tasks provide little control over odor concentration and the timing of olfactory stimulation, but depend on passive association of an odor with the reward [4]. Lastly, a completely different approach to assessing OB function suggests that blocking neurogenesis alters the fear response created by the association of an odor with a noxious stimulus [78].

The major drawback of all these behavioral paradigms is, however, the requirement for the involvement of higher brain areas such as the hippocampus, amygdala and piriform cortex to execute these tasks [3]. Long-term olfactory memory is largely attributed to the potentiation of synapses in the piriform cortex [88–92]. Fear conditioning paradigms mainly evaluate the interaction between the OB and the amygdala [93]. The involvement of different centrifugal projections in the distinct associative paradigms (operant vs. non-operant) can also be different, thus leading to different functional outcomes [94–96]. It is known that centrifugal inputs projecting to the OB modulate adult neurogenesis [75,97,98], adding another level of complexity. Because of all these "interferences", it is difficult to determine whether changes in the level of neurogenesis and the reported, but controversial, involvement of adult-born neurons in the learning paradigm are caused by influences from higher brain areas or by the preferential recruitment and survival of adult-born GCs in the bulbar circuitry by odor learning. However, the fact that the ablation of neurogenesis during the acquisition phase does not influence associative memory and that adult-born neurons are involved in the retrieval of memory [62] favors a top-down effect of higher brain areas on the survival of adult-born neurons. In order to fully understand the implication of adult-born neurons in the formation of associative memory, more detailed analyses of physiological changes, both at cellular and network levels, in the OB following associative odor learning paradigms are required. The results of such studies, combined with morphological analyses of adult-born neurons and behavioral outcomes, will make it possible to determine the exact function of adult-born neurons in associative odor behaviors.

3.3. Role of adult neurogenesis in ethologically relevant odor behavior

A better understanding of the role of adult-born neurons in ethologically relevant odor behaviors has begun to emerge. For instance, the addition of adult-born neurons plays a significant role in pregnancy, mating behavior, male offspring recognition and male–male aggressive behavior [38,58,59,70,81,82]. Pregnancy induces a prolactin-mediated increase in the proliferation of neuronal precursors in the SVZ together with an enhancement in the number of OB interneurons [58]. Inactivation of prolactin receptor gene or ablation of adult-born neurons using genetic models induces defects in the maternal behavior [38,58]. However, opposite results were obtained in focal SVZ irradiated mice, where no defects in the maternal behavior were observed [81]. As discussed elsewhere [38,81], the discrepancy between studies might arise from different models used to ablate adult neurogenesis. While SVZ irradiation leads to 60–70% reduction in the number of Dcx+ cells [76,81], the remaining 30% of adult-born cells might uphold the functioning of the OB neuronal network because of compensatory changes. It has been already demonstrated that compensatory changes brought by adult-born GCs indeed preserve the normal functioning of the bulbar network despite dramatic defects in the number and morphology of adult-born interneurons [45]. This can be directly addressed by performing electrophysiological investigations at both the cellular and network levels, in the OB. To our opinion, the discrepancy between studies could be solved only if we know how the functioning of the bulbar network is affected in different models used to ablate adult neurogenesis.

The number of adult-born cells was also increased when female mice were stimulated for 7 days with pheromones from a dominant male [59]. This increase in neurogenesis is correlated with the female's preference for a dominant male, since blocking neurogenesis during the period where the female is exposed to the dominant male pheromones attenuates this behavioral preference [59]. While these studies point to a role for OB neurogenesis in female behavior, ethologically relevant stimulation increases OB neurogenesis in males [70]. The number of cells in the OB increases in male mice that interact with their offspring in the first seven postpartum days [70]. These adult-born neurons are preferentially stimulated by odors that are specific to the offspring and are involved in offspring recognition [70]. Finally, it has been recently demonstrated that the ablation of neurogenesis in males using inducible genetic models induces defects in male–male aggression and male sexual behavior toward female [38]. All these results provide direct proof for the importance of neurogenesis in the natural and ethologically relevant odor behavior of animals.

4. Adult neurogenesis: a form of plasticity adapted to the needs of the OB

The addition of adult-born cells to the OB network is a captivating process. The OB, unlike other regions of the brain, requires the constant assembly and disassembly of synapses to efficiently compute and integrate the sensory information it relays. The activity of mitral cells in the OB is modulated by interneurons, especially by the GCs. The inhibition provided by GCs is thought to be involved in the spatio-temporal coding of odor information [16–19,99,100]. Spatial coding is characterized by the lateral inhibition of different groups of mitral cells by bulbar interneurons. Temporal coding is characterized by the synchronization of the activity between mitral cells responding to an odor. The constant arrival of adult-born GCs and, consequently, the persistent formation and elimination of dendro-dendritic synapses formed by these cells with the principal neurons allows the OB circuitry to maintain and modulate this spatio-temporal coding of odor information in response to olfactory experiences [39].

Why does the OB network need such an elaborated process for promoting plasticity? Could olfactory processing simply involve the potentiation of an existing synapse between a mitral cell and a GC in order to improve spatio-temporal coding? Given the reciprocal nature of mitral-GC cell synapses [14,15,20], it seems conceptually impossible to induce the potentiation of such synapses to modulate olfactory processing. The main expected outcome of long-term potentiation would be an increase in the efficacy of synaptic transmission. However, the potentiation of a glutamatergic synapse from a mitral cell dendrite to a GC spine would increase the efficacy of synaptic transmission onto the GC which, in turn, would induce greater feedback (the same mitral cell) and feedforward (other mitral cells) inhibition. As such, the activity of a mitral cell that "initiates" the potentiation would be attenuated and the initial increase in synaptic efficacy would be dampened. The formation of new synapses between GCs and mitral cells thus acts to counterbalance the lack of a classic form of plasticity between GCs and the principal cells of the OB. GCs can precisely control the group of mitral cells involved in a particular odor-induced pattern of activity via these newly formed synapses. When the pattern of sensory stimulation inducing these plastic changes disappears, the GCs involved in the stimuli representation would no longer be needed and would be eliminated. It thus appears that the constant recruitment and elimination of new cells provides the OB with a unique pool of flexible neurons that are well suited to the structural organization of the bulbar network and that adapt its functioning to the constantly changing sensory world.

5. Conclusion

Adult neurogenesis plays a critical role in the regulation of the information conveyed by OB mitral cells to higher brain regions. Adult-born interneurons, with their higher level of adaptation, have a considerable impact on the overall inhibition received by mitral cells. Despite the clear role of adult neurogenesis in the structural and functional maintenance of the bulbar network, completely understanding the involvement of adult-born neurons in olfactory behavior remains a challenge. So far, research has resulted in contradictory results. As discussed above, the involvement of adult-born neurons in odor behavior may differ depending on the type of behavioral test used (spontaneous vs. associative; operant vs. non-operant conditioning), and therefore the involvement of higher brain areas in the treatment of sensory information. To fully understand the exact role of adult-born neurons in the different types of odor behavior, a careful examination of physiological changes, at both the cellular and network levels, in the OB following affected neurogenesis is required. We propose that the continuous birth and integration of adult-born cells influences only specific types of behavior requiring fine adjustments of the OB circuitry. It is conceivable that the long-lasting GCs generated during embryonic and early postnatal life are required for fundamental olfactory functions such as general odor perception, whereas new neurons generated during adulthood fine-tune the functioning of the bulbar network to the constantly changing environment.

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