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Research report

A niche for adult neurogenesis in social behavior

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ABSTRACT

The structural and functional changes occurring into the brain is the hallmark of its tremendous capacity for dealing with the complexity that we are facing throughout life. It is also the hallmark of what neuroscientists refer as neuroplasticity. The continuous generation of cohorts of new neurons in some discrete regions of the adult brain, including the olfactory system, is a newly recognized form of neuroplasticity that has been recently the focus of neuroscience studies. Several lines of evidence indicate that this recruitment of newly-generated neurons is extremely sensitive to the overall neuronal activity of the host circuits. Therefore, adult neurogenesis represents, not only a constitutive replacement mechanism for lost neurons, but also a process supporting a capacity of neural plasticity in response to specific experience throughout life. The remarkable complexity of the social life offers a host of daily challenges that require a diversity of brain mechanism to make sense of the ever-changing social world.

This review describes some recent findings which have begun to define reciprocal relationships between the production and integration of newborn neurons in the adult brain and social behavior. These studies demonstrate how this domain of research has the potential to address issues in the functional contribution of adult neurogenesis in the expression of some social traits as well in the role of some social contexts to finely regulate the production, survival and integration of adult newborn neurons.

1. Introduction

The first claims of neurogenesis occurring in the adult mammalian brain met strong resistance from neuroscientists [24,48,55]. Historically, the first unambiguous evidence of the existence of adult neurogenesis in a vertebrate brain also demonstrated that the production of newborn cells in the adult brain could be a dedicated support for social information. These elegant experiments were carried out under the leadership of Fernando Nottebohm who aimed to investigate the neural basis of song learning in birds. The vocal control nucleus HVC (nucleus hyperstriatalis ventralis, pars caudalis) supported the first unambiguous example of adult neurogenesis. This has been achieved by demonstrating that individual cells that have incorporated a mitotic marker responded to stimulation with unmistakable action potentials. The song of male birds plays a key role in attracting females and stimulating their reproductive physiology and behavior. Thus, much of what we have clearly learned about the functional significance of adult neurogenesis comes first from these seminal studies on songbirds [41,78,79,82]. Since these pioneering works, one could consider that the domain of social communication would be a privileged framework for the studies of the functional relevance of adult neurogenesis. However, this has not been the case and we will see that the number of studies which have examined the contribution of newly-generated neurons in the adult brain in a social context are still scarce. This is even more obvious and rather surprising regarding the field of olfactory neurogenesis when one considers the major role played by olfaction in the social communication in many species of mammals.

We now know that neuronal replacement during adulthood occurs in some specific brain regions, is widely distributed across species and is probably common to all vertebrates (however, see [3]). However, since these seminal studies pointing out the contribution of avian neurogenesis in the context of social communication, very few studies have been designated to examine the relationships between adult neurogenesis and social interactions in other groups of vertebrates. Undoubtedly this is due to the difficulty to apprehend the high complexity and variability of social environments and social responses. Despite such obstacles, substantial breakthroughs have been made, both in the understanding of social behavior and social neuroscience, indicating that the functional significance of adult neurogenesis in different social contexts of various mammalian species is tractable. In turn, this should provide

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important insight into whether the production of newly-generated neurons represents a functional part of the social brain in different species.

The aim of this review is to point out that the social complexity should be added to the list of factors that regulate the rate of new neurons in the adult vertebrate (mammal) brain and studies may reveal old and new underlying mechanisms (pathway use, neurotrophic and neurohormonal factors) that support the production of new neurons (Table 1). Here we focus on a few examples which illustrate the emerging field of the relations between adult neurogenesis and social behavior, with special attention to the relations between pheromone perception and olfactory neurogenesis. Classically, two main approaches have been developed. The first concerns how social contexts can regulate the birth, fate and integration of neuronal precursors in the adult brain. The second approach aims to examine how much adult neurogenesis contributes to the ability of individuals to make sense of social information and respond in an appropriate way during social interactions. Given the range and richness of social behaviors, further studies using behavioral paradigms reflecting realistic social situations are necessary and represent a critical challenge to understand the relations between adult neurogenesis and social behavior.

2. Neurogenesis in the adult brain

The observation that the adult brain retains the ability to generate new neurons has led to the discovery of neural stem cells located in some specific areas of the brain, also called neurogenic zones. These neural stem cells constitute a special cell type that has the potential for self-renewal and generating any or all of the three main cell lineages of the brain, i.e. neurons, astrocytes and oligodendrocytes. Each neural stem cell gives birth to another stem cell and a progeny that, if it survives (about 50% of them die before they mature into neurons), will become a neuron or a glial cell. Two germinal zones have been defined in the mammalian brain: the subventricular zone (SVZ) and the subgranular zone (SGZ) (Fig. 1) (reviewed in [1,30,68,73]). The former lies adjacent to the wall of the lateral ventricle and generates olfactory bulb interneurons. The latter is located in the granule cell layer (GCL) of the dentate gyrus and gives rise to dentate granule cells. In the SVZ stem cell astrocytes (B, GFAP-positive cells) divide and generate rapidly dividing type C transit amplifying cells which in turn give rise to type A migrating neuroblasts [29]. These neuroblasts migrate along the rostral migratory stream (RMS) before reaching the olfactory bulb where they differentiate into granule and periglomerular neurons. In the SGZ, new granule cells are also produced from mitotically active neural precursors/stem cells. Newborn cells migrate a short distance into the GCL, develop neuronal markers and granule cell morphology, integrate into the existing circuitry and receive functional synaptic input. There have also been reports referring to constitutive adult neurogenesis in other brain areas such as the substantia nigra [101], the vagal complex of the brain stem [10], the hypothalamus [54,59,60], the amygdala [14,35], the piriform cortex [84], the striatum [13,26] and the neocortex [26,44,46]. However, some of these reports have been called into question regarding the very low rate of production of newborn cells found in some of these brain areas and/or lack of evidence of co-labelling with mitotic and neuronal markers, while other reports have been challenged by negative results [15,32,37,58,61,67]. The significant progress made during the past few years has provided evidence that the local microenvironment (i.e. SVZ and SGZ) represents a key factor which determines the behavior of precursors and their capac-

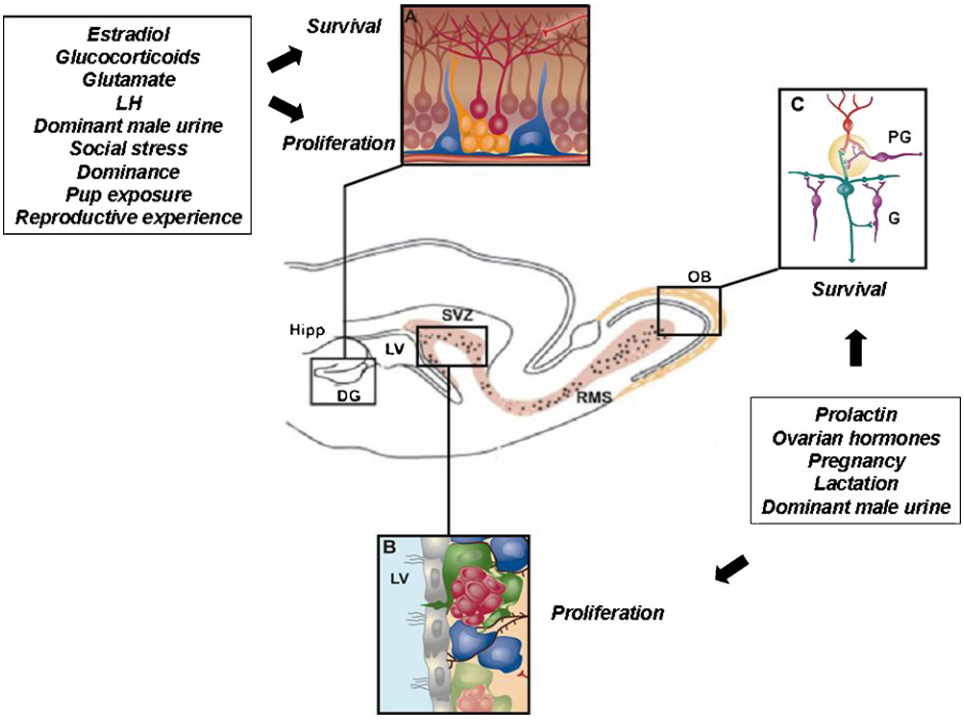

Fig. 1. Neurogenesis in the subventricular zone (SVZ)/olfactory bulb (OB) and in the hippocampal system (DG). A sagittal view of a rodent brain showing the sites of neurogenesis including the physiological and social factors regulating *in vivo* cell proliferation and survival in the SVZ/OB system and in the DG of the hippocampus. Inset A: in the hippocampus (Hipp), stem cells (blue) located in the subgranular zone of the dentate gyrus (DG) produce transient precursors (orange) which give rise to new granule neurons (red). Inset B: proliferation in the subventricular zone (SVZ) takes place in the medial wall of the lateral ventricule (LV), where stem cells (blue) divide to generate transient amplifying cells (green), which in turn, give rise to neuroblasts (red) that migrate in the rostral migratory stream (RMS) to their final destination in the olfactory bulb (OB). Inset C: basic circuitry of the olfactory bulb (OB). Olfactory sensory neurons (red) send their axon to specific glomeruli where they synapse with the dendrite of mitral cells (green) and local interneurons (periglomerular cells – PG). The lateral dendrites of mitral cells contact the apical dendrites of granule cells (G). Periglomerular cells and granule cells represent the two types adult-born OB interneurons.

Table 1
Factors regulating *in vivo* cell proliferation and survival in the subventricular zone/olfactory bulb and in the hippocampal systems in different species under various social contexts ((▲) increase; (▼) decrease; SVZ: subventricular zone; OB: olfactory bulb; DG: dentate gyrus; LH: luteinising hormone; F: female; M: male).

Social context	Species	Sex	Stimuli/conditions	Hormones/ neurotransmitters	SVZIOB neurogenesis		Hippocampal neurogenesis		References
					Proliferation	Survival	Proliferation	Survival	
Social stress	Rat (*Rattus norvegicus*)	M	Resident male	Glucocorticoids Glutamate	Not investigated	Not investigated	(▼)	(▼)	[21,36,75]
Social stress	Mouse (*Mus musculus*)	M	Resident male	Glucocorticoids	Not investigated	Not investigated	(▼)	(▼)	[73]
Social stress	Tree Shrew (*Tupaia belangen*)	M	Resident male	Glucocorticoids	Not investigated	Not investigated	(▼)	(▼)	[43]
Social stress	Marmoset monkey (*Callithrix jacchus*)	M	Resident male	Glucocorticoids	Not investigated	Not investigated	(▼)	(▼)	[45]
Dominance hierarchy	Rat (*Rattus norvegicus*)	M	Agonistic interactions	Not investigated	Not investigated	Not investigated	No change	(▲) (Dominant)	[62]
Social isolation	Rat (*Rattus norvegicus*)	M	Lack of social interactions	Not investigated	Not investigated	Not investigated	(▼)	Not investigated	[68,90]
Social isolation	Rat (*Rattus norvegicus*)	M	Stressful experience	Glucocorticoids	Not investigated	Not investigated	(▼)	Not investigated	[90]
Sexual encounter	Prairie voles (*Microtus ochrogaster*)	F	Male odor	Estrogen	(▲)	Not investigated	Not investigated	Not investigated	[89]
Mating	Prairie voles (*Microtus ochrogaster*)	F	Male and copulatory activity	Not investigated	No change	No change	Not investigated	Not investigated	[36]
Mate choice	Mouse (*Mus musculus*)	F	Exposure to dominant male urine	Prolactin (SVZ) LH(DG)	(▲)	(▲)	(▲)	(▲)	[63,69]
Maternal behavior	Mouse (*Mus musculus*)	F	1st week of pregnancy 1st week of lactation	Prolactin	(▲)	(▲)	No change	No change	[88]
Maternal behavior	Mouse (*Mus musculus*)	F	Male pheromones	Prolactin Ovarian hormones	(▲)	Not investigated	Not investigated	Not investigated	[63]
Maternal behavior	Rat (*Rattus norvegicus*)	F	3rd week of pregnancy	Not investigated	(▲)	Not investigated	Not investigated	Not investigated	[39]
Maternal behavior	Rat (*Rattus norvegicus*)	F	Early postpartum period	Glucocorticoids	Not investigated	Not investigated	(▼)	Not investigated	[64]
Maternal behavior	Rat (*Rattus norvegicus*)	F	Reproductive experience	Not investigated	Not investigated	Not investigated	(▼)	(▼) Primiparous (▲) multiparous	[83]
Maternal behavior	Rat (*Rattus norvegicus*)	F	Pup exposure to nulliparous females (sensitization)	Not investigated	Not investigated	Not investigated	(▲)	(▲)	[83]

ity to differentiate into neurons [89]. Adult neurogenesis involves different processes: proliferation, cell fate, migration, differentiation, survival and integration, all of them being highly regulated by intrinsic and extrinsic factors. The functional analysis of the detailed molecular mechanisms involved in the regulation of these different processes is still underway and beyond the scope of the present review [49,50,77]. Regulation operates at different levels and involves among others, cell–cell interactions, neurotransmitters, hormones and extracellular matrix components. Behavioral activities triggered by sensory experience, exercise, stress, reproduction and cognitive functions induce changes in the rate of cell division, survival and integration into the neural circuitry by a host of these regulatory factors [73]. However, the mechanisms underlying these regulations are thus far unknown. It remains to be shown whether some of the changes related to certain behaviors are tightly associated or more loosely coregulated. Unravelling these mechanisms will undoubtedly not only increase our fundamental knowledge of adult neurogenesis, but also may shed light on the etiology, pathophysiology and potential regenerative capacity of the mature brain.

3. Adult neurogenesis and socio-sexual behavior

Smith et al. showed that exposure of female prairie voles (*Microtus ochrogaster*) to a male behind a fine wire mesh induces behavioral estrus and an increase in proliferation of BrdU-labeled cells in the SVZ, along the RMS and in the subependymal zone of the olfactory bulb [91]. No increase in proliferation was observed in ovariectomized females exposed to a sexual partner. Meanwhile, estradiol benzoate treatment was sufficient to restore the increased production of neuronal progenitors in the SVZ, suggesting that estrogen was partly involved in the stimulation of proliferation of SVZ-derived neuroblasts. Whether, in these specific conditions, estrogen also promotes newborn neuron survival is still unknown. Finally, because prairie voles are a highly social species that form enduring selective pair bond between mates after mating, it would be interesting to examine whether this estrogen-mediated neurogenesis may play a role in the trace memory acquisition of the identity of the sexual partner. In a separate study, neither increase in proliferation nor in survival of the newborn neurons has been observed in female prairie voles exposed to a male for 48 h with mating compared to isolated or female-exposed female prairie voles [36]. The discrepancy between these two studies needs clarification. In contrast, the later study revealed a higher density of newborn cells that proliferate in the amygdala and the hypothalamus of female prairie voles exposed to a male compared to females housed in isolation. However, estradiol administration alone does not exert any specific effect on cell proliferation in these areas of the brain in female prairie voles despite the presence of estrogen receptors in these regions [35,52]. This indicates that other factors including social interaction, chemosensory cues and other hormones may be necessary for an increase in cell proliferation increase in these brain areas of this species. These findings require supporting evidence of the origin, maturation, integration, functional properties and functional significance of these newborn neurons in the amygdala and hypothalamus.

A functional approach of olfactory neurogenesis was carried out by Huang and Bittman in male hamsters following mating [53]. Immunohistochemical staining revealed that 3 and 7 weeks after BrdU injection, some BrdU-positive cells were also c-Fos-positive in the olfactory bulb. Although no exact quantification has been reported in this first experiment, the overlap between BrdU-labeled and Fos-labeled cells indicate that some adult-generated neurons are functionally incorporated into sexual circuits in male hamsters. In a subsequent experiment, the authors showed that newborn cells in the main and accessory olfactory bulbs of male hamsters were also activated following exposure to an oestrus female, female hamster vaginal secretions or an aggressive male. Among these stimuli, an oestrus female appeared to be the most effective one. The fact that the exposure to an oestrus female elicits a greater percentage of activated newborn neurons within the main and accessory olfactory bulbs than female vaginal secretions indicates that multisensory cues are required for inducing the activation of some bulbar newborn neurons within the olfactory bulb of male hamsters during sexual encounters. Interestingly, although BrdU-positive cells were also detected in the medial nucleus of the amygdala, the bed nucleus of the stria terminalis and the medial preoptic area of male hamsters exposed to these different stimuli, none of them was activated by socio-sexual stimuli. These results suggest that newly-generated neurons within the adult olfactory bulb might partly integrate and functionally sustain the socio-sexual brain circuits in male hamsters. Further studies should shed light on how long this morpho-functional plasticity will last in the adult circuits.

4. Social behavior decreases the rate of neuronal production

As mentioned above, the effects of socio-sexual stimuli on adult neurogenesis are largely mediated by stress and gonadal hormones. This has been assessed in pharmacological studies involving hormone administration as well as physiological studies aimed to investigate the contribution of endogenous hormones on adult neurogenesis in specific socio-sexual contexts. The interested readers can consult several comprehensive reviews on this topic [38,40].

The consequences of gonadal hormone treatment on adult neurogenesis have been the subject of many researches during recent years, and most of the literature to date has focused on the hippocampus of rodents [8,9,80,81,86,93,94]. The effects of gonadal steroid administration on hippocampal neurogenesis in the adult brain is far from being clear and differ greatly according to the sex and the species used, the mode and the timing of administration, the length of exposure as well as the age of the newborn neurons [40].

Social interactions are subserved by a host of neuro-hormonal processes which can induce deep changes in the rate of cell proliferation and/or cell survival in the adult brain. Social stress is common in many animal species and results from competition for space, shelter, food, water or access to a potential mate. Some experiments have used different animal models based on dominance formation to examine the effects of social stress on adult neurogenesis. In rodents, the social defeat procedure is based on the initial occupation and establishing of a territory by a resident male such that the male subsequently and rigorously defends the territory against unfamiliar male intruders [72]. Following its transfer into the resident's cage, where it is generally attacked within the first 1–2 min, the intruder is separated from the resident by a wire mesh for the remaining social defeat period. The procedure is repeated for several consecutive days. However, because in such a situation the intruder cannot escape from the threat of the resident, one should consider this procedure as far from reflecting natural living conditions. Nevertheless, it has been shown that this paradigm induces a robust adreno-cortical response in intruder males. Multiple lines of evidence indicate that chronic social stress dramatically decreases the rate of cell proliferation in the adult dentate gyrus of a variety of species, including rats, mice, tree shrews and primates [25,43,44,74,96] and that glucocorticoid-mediated mechanisms account for this social stress-induced inhibition of cell proliferation. These results are clearly supported by the numerous studies which have reported the suppressive effects of glucocorticoids on cell proliferation in the adult dentate gyrus [2,20,22,42,75,95]. Interestingly, Mitra et al. [74] reported that individual differences in

hippocampal cell proliferation in intruder mice were related to the frequency of defensive behavior evoked by each test subject. In line with this result, defensive behavior displayed in the social defeat paradigm has been linked to an increase in secretion of glucocorticoids in male rats [34]. A detailed understanding of the effects of glucocorticoids on hippocampal neurogenesis is still unknown. Direct action of glucocorticoids may be mediated by glucocorticoid receptors expressed by a subpopulation of progenitor cells in the dentate gyrus [23]. Glucocorticoids can also indirectly exert their effects via the release of glutamate [21,76] or via neighboring cells releasing factors which control the cell cycle [100].

Contrasting results have been obtained using the visible burrow system (VBS) model of social hierarchy as a paradigm to investigate the effect of social stress on hippocampal neurogenesis in adult male rats [62]. Briefly, the VBS model involves housing mixed-sex groups of rats in a semi-naturalistic burrow environment containing the provision of a number of tunnels and chambers. Within 3 to 4 days after colony formation, a dominance hierarchy resulting in 1 dominant male and subordinate males can be observed [16]. In this model, dominance hierarchy remains stable over time. Behavioral differences of subordinates compared to dominants include decreased social, sexual and aggressive behaviors, reduced eating and drinking and a reduction of movements. Using the VBS model, Kozorovitsky and Gould showed that the dominance hierarchy did not affect cell proliferation in the dentate gyrus of dominant nor subordinate males, but that the dominant status was associated with enhanced new neuron survival. Furthermore, neither stress experience as assessed by similar plasma corticosterone levels between dominants and subordinates nor environmental complexity could be responsible for the difference in hippocampal neurogenesis between dominant and subordinate male rats.

5. Social behavior enhances the rate of neuronal production

Although chronic subordination is associated with a lower rate of cell production within the adult dentate gyrus, social interactions can also provide protective effects against negative consequences of experience-induced glucocorticoids on adult neurogenesis. First, social isolation decreases hippocampal cell proliferation in individually-housed rats. This isolation-induced decrease in cell proliferation can be reversed by subsequently housing the animals in groups [69], thus indicating that social housing represents a key regulator of hippocampal neurogenesis. Second, it has been previously shown that running stimulates hippocampal neurogenesis in the adult brain [33,97,98]. Physical activity and exercise are known to have beneficial effects on brain health despite the fact that running has also been associated with elevated expression of glucocorticoids which, as mentioned above, decrease hippocampal cell proliferation. Stranahan et al. have recently shown that social isolation prevents the running-induced increase of neurogenesis normally observed in adult rats living in groups [92]. Furthermore, exposure to stressful experience induced a decrease of hippocampal cell proliferation in individually-housed runners compared to sedentary controls. Lowering glucocorticoids by adrenalectomy reverses the suppression of neurogenesis in isolated runners, thus pointing at the adrenal steroids as reliable candidates underlying these effects. Altogether, these results indicate that social housing has a positive influence on the physiological regulation of adult neurogenesis. The benefits of social housing on hippocampal cell proliferation can be compared to the phenomenon termed 'social buffering' which refers to the ability of social individuals to inhibit psychophysiological stress responses, or to show a better recovery from negative experiences in the presence of specific social partners (for a review see [57]). There are multiple lines of evidence which demonstrated that social interaction exerts its effects on stress-endocrine activity, especially on the HPA axis [65,66].

Overall, it is clear from these studies that social environments can induce various and contrasting effects on the regulation of adult neurogenesis via the production of glucocorticoids. Social interactions are undeniably the source of complex experiences that impart a wide range of physiological and psychological variables, well beyond the changes of the blood levels of glucocorticoids. Finally, other variables, such as genotype, early experience and copying style may also contribute to individual differences in stress effects on adult neurogenesis.

6. Male pheromone-stimulated adult neurogenesis and mate selection in female mice

Mak et al. investigated the pheromone-stimulated neurogenesis in the adult brain of female mice and its functional consequences in mating behavior [70]. Exposure of female mice to the urine of a dominant male induced an increase in the rate of proliferation of adult-born cells in the SVZ and the dentate gyrus. Since non-social odorants as well as female urine did not induce any increased proliferation in the SVZ or dentate gyrus, it has been hypothesized that male pheromones constitute the chemosensory stimuli responsible for the increase in female SVZ and hippocampus proliferation. Indeed, exposure to castrated-male odors blocked the increased mitotic activity in both germinative zones of the adult female mice. Furthermore, dominant-, but not subordinate-, male pheromones provided specific sensory stimuli that stimulate proliferation in the adult female SVZ and dentate gyrus. Finally, the authors showed that the timing of exposure to the male pheromones is important for its effectiveness: a two-day period of exposure is ineffective while a seven-day period of male odor stimulation is sufficient to stimulate neurogenesis in the adult female brain. The same results have been confirmed in a separate study [63]. Destruction of the olfactory epithelium with intranasal $ZnSO_4$ abolished the male pheromone-stimulated neurogenesis both in the SVZ and dentate gyrus suggesting that the main olfactory system constitutes a critical pathway which conveys the sensory stimuli responsible for the increased female SVZ and dentate gyrus proliferation. As the contribution of the accessory olfactory system has not been specifically addressed in this study, one cannot exclude a synergistic functioning of the main and accessory olfactory systems in the male pheromone-stimulated neurogenesis in the adult female brain [11,12,17,19,51,71,88,99]. Finally it should be noted that exposure to dominant-male pheromones not only promotes the proliferation of new neurons from their respective niches, but also leads to a higher rate of integration of adult-born neurons in the olfactory bulb and the hippocampus.

Mak et al. investigated the underlying mechanisms and the functional contribution of male pheromone-stimulated neurogenesis in the adult brain of female mice [70]. On the one hand prolactin (PRL) receptors are expressed in the dorsolateral corner of the SVZ but not in the dentate gyrus of the hippocampus, while luteinizing hormone (LH) receptors are expressed in both neurogenic zones. Following male pheromone exposure, PRL and LH independently stimulate cell proliferation in the SVZ and dentate gyrus. Prolactin receptors mediate the increased production of neuroblasts in the SVZ of female mice, whereas LH receptors mediate the pheromone-induced cell proliferation in the dentate gyrus.

In mice, mate selection is largely influenced by sex pheromones and female mice prefer to mate with dominant males [31]. Processing pheromonal signature in female mice has been shown to be mediated by the main olfactory epithelium [56]. In their study, Mak et al. showed that a 7-day period of dominant-male odor stimulation (that stimulates neurogenesis in the female mouse brain), induced a preference for a dominant male over a subordinate male in a choice test [70]. No preference was observed when female mice were pre-exposed to subordinate-male pheromones. At this

point, this redefines the question 'is dominant male pheromone-stimulated neurogenesis required for mate selection in adult female mice?' To address this question, the authors treated female mice pre-exposed to dominant-pheromones with cytosine-β-D-arabinofuranoside (AraC), a common antimitotic agent known to suppress neurogenesis [27,28,47]. Blocking bulbar and hippocampal neurogenesis by AraC suppressed dominant preference in female mice pre-exposed to dominant-male pheromones. These results offer an ethological relevant function to adult female neurogenesis in the context of mate selection. They also raise a number of additional questions: among the different compounds present in the urine of dominant males, is there a specific molecule or a mixture of compounds that attracts female mice and increases SVZ and dentate gyrus neurogenesis of adult females? What is the relative contribution of the increased neuronal production within the olfactory bulb and the hippocampus of female mice in mate selection? What is the exact role of the increase in neurogenesis following male odor exposure in mating preference behavior? Clearly, additional approaches are needed to specifically address the functional contribution of the pheromone-enhanced neurogenesis in the adult female brain. It should be kept in mind that AraC-treatment not only inhibits the increase but also the production of newborn cells within the two neurogenic zones. Consequently, it is rather the role of the proliferation and the survival of newborn neurons than the enhancement of the rate of neurogenesis following dominant-odor exposure that has been addressed using AraC treatment. Additional strategies are needed to precisely assess the contribution of the male-pheromone enhancement of neurogenesis in the adult female brain. Further evidence of a functional integration of the new neurons induced by dominant-pheromone stimulation into the brain circuits activated during mate choice would come from quantifying the overlap between BrdU-labeled and Fos-labeled neurons. This will further elucidate whether adult-generated neurons in the SVZ and dentate gyrus following male-pheromone exposure have a functional contribution in mate preference in adult female mice.

7. Male pheromone-stimulated adult neurogenesis and maternal behavior in female mice

Recently, Larsen et al. investigated the effects of male pheromones on maternal behavior in female mice [63]. They showed that a prolonged exposure to a male or to its urine advanced maternal behavior in both virgin and postpartum female mice. Ovariectomy prevented this effect, suggesting that the presence of ovarian hormones is required. At least, 2 weeks of male pheromone exposure are necessary to advance maternal behavior in female mice. Females exposed to male pheromone exhibited an increase of serum prolactin levels during the first 3 days of exposure. Inhibition of pheromone-induced increase of prolactin by bromocriptine blocked the advance of maternal behavior in treated females. This strongly suggests that the prolactin increase observed during the early period of male exposure plays a key role in the advance of maternal behavior 2–3 weeks later. Furthermore, the authors showed that the production of neuronal progenitors is stimulated in the SVZ of female mice after a week of male pheromone exposure. Here again, this male pheromone-stimulated neurogenesis is dependent both on ovarian hormones and prolactin. Further work is needed to assess whether the pheromone-induced stimulation of new neurons into the olfactory bulb may contribute to the facilitation of the expression of maternal behavior observed in females exposed to male mouse pheromones.

Interestingly, in mice the production of neuroblasts within the SVZ, but not the SGZ, is also stimulated during normal pregnancy and lactation by the hormone prolactin [90]. The increase of the SVZ neurogenesis occurs by the first week postcoitum and the first week of lactation. In rats, cell proliferation has only been investigated during pregnancy. The examination of the SVZ revealed a significant increase of neuroblast production during the last week of gestation in this species [39]. The two waves of increased proliferation during the early period of pregnancy and lactation observed in mice lead to the integration of a greater number of newly generated interneurons in both the periglomerular and granule cell layers of the olfactory bulb. These results raise the untested possibility that the enhanced addition of new olfactory interneurons play a role in some functional aspects of maternal behavior, e.g. the onset and/or maintenance of maternal behavior, pup recognition, maternal aggression, etc. Regarding hippocampal neurogenesis, Leuner et al. reported a decrease in cell proliferation in the dentate gyrus during the early postpartum period of rats [64]. Since this inhibition of cell production is eliminated by adrenalectomy, it has been suggested that changes in corticosterone levels may affect hippocampal neurogenesis during the first few days following birth delivery. This particular decrease in cell production in the dentate gyrus during the first days following parturition has been confirmed in a more recent study, showing also that survival of cells born during the early postpartum period varies according to the reproductive experience of female rats [83]. Primiparous females showed a decreased survival rate of neurogenesis compared to multiparous females. Pup-exposure has been shown to exert a positive effect on hippocampal neurogenesis in nulliparous rats [83]. Meanwhile, the specific contribution of pup-exposure on the rate of proliferation and survival of newborn cells in the hippocampus of lactating rats remains to be determined.

In the same vein, Barkan et al. addressed the possibility that in adult zebra finches there is an upregulation of new neuron recruitment in the nidopallium caudale (NC), a structure receiving auditory inputs which may play a role in storing auditory information, that coincides with the ability of the zebra finch parents to memorize the vocalizations of their nestlings before they fledge [7]. The authors provided evidence that the recruitment of new NC neurons increased from hatching to fledging, suggesting that this increase in neuronal addition may facilitate young recognition in zebra finch parents. In addition, the data suggested that the rate of increase of new NC neurons in the parents' brain is influenced by the number of fledglings, a result in line with the idea that adult neurogenesis is experience-dependent. However, we should confess that to date we have only circumstantial evidence showing that changes in parental behavior are paralleled by changes in the regulation of newborn cell production in parents. We need more than correlational evidence to guarantee a role of new neurons in regulating complex social behavior. Obviously, knowledge of functional significance of adult neurogenesis in the field of parental behavior will grow from studies that selectively suppress the changes of adult neurogenesis that may occur during a breeding cycle.

8. Concluding remarks

The selected findings that we have reviewed in this article illustrate a part of the range of social contexts that can be captured regarding the functional significance of neurogenesis in the adult brain. This review aims to underscore the importance of actively pursuing research on the links between adult neurogenesis and social behavior. Although this enterprise is still in infancy, consequential progress has been recently made in connecting the production of adult born neurons with specific aspects of social behavior in some species. Undoubtedly, there is now compelling evidence that addressing questions in this specific domain will be of great importance in improving our knowledge of the mechanisms and significance of functional integration of newly-generated neurons in the adult brain. Many studies suggest that, in addition to contributing to endogenous repair, newly generated neurons may contribute to the learning and memory functions of the hip-

pocampus and the perceptual and memory functions of the bulb. The studies cited above also suggest that the olfactory and hippocampal neurogenesis might specifically support several aspects of the perceptual and memory demands associated with reproduction. Although we do not know yet whether newborn neurons can accomplish these tasks, they deserve more extensive exploration to understand their potential functions associated with reproductive behaviors such as mate selection, individual recognition, parental behavior, territorial maintenance and defense.

A comparative approach using species, including wild-living species, living in social environments which differ according to their degree of organization and complexity should also be promoted [4,5,6]. This would help to extract some basic principles that could underlie the interplay between adult neurogenesis and social behavior. For instance, one would expect to find different levels of production and regulation of adult newborn neurons in species with differential constraints in their social organization and abilities in the domain of social cognition. These expectations still await investigation. While we are accumulating detailed knowledge of the different steps governing the production, regulation and integration of newborn neurons in the adult brain due to a great expansion in studies of adult neurogenesis, ethologists provide a high level of expertise in the description, causation and function of social behavior. Both approaches have developed sophisticated methods that allow a promising and comprehensive understanding of the relations between the integration of newborn neurons in the adult brain and social behavior.

Adult neurogenesis has been reported in other brain regions different from the hippocampus and the olfactory bulb. Some of these regions are fully integrated in neural circuits through which specific social behavior and their components are expressed. To date most research on the regulation and function of adult neurogenesis has largely neglected the examination of the neurogenic potential of these brain areas in relation to some specific social information that these brain regions process. For instance, new granule and periglomerular neurons have been shown to be added in the accessory olfactory bulb [18,85]. Unfortunately the possible contribution to, and functional properties of, newly-generated interneurons of the accessory olfactory bulb in some specific social behavior (e.g. mating, mate recognition, aggressive behavior) are still awaiting investigation. Obviously, identifying the regulatory pathways and consequences linking the production of newborn cells in the adult brain to social behavior constitutes an enormous challenge for the future. Each of them represent dynamic systems with their own temporal patterns and scale times that are still waiting to find a niche within adult neurogenesis areas.

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