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Chapter I

The Rabbit Brain As a Model of Structural Neuroplasticity

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Abstract

Plasticity is the ability to make adaptive changes related to the structure and function of a system. The central nervous system of mammals is endowed with structural plasticity, although prevalently composed of genetically-determined neural circuits which confer it a substantially static structure. Since two decades we know that such plasticity also involves the genesis of new neurons in the postnatal period and during adulthood (adult neurogenesis). Adult neurogenesis in mammals has been investigated mainly in laboratory rodents (mice and rats), and to a lesser extent in other species. Beside some differences concerning the amount of neurogenesis and its possible functional role, the genesis of new neurons in mammals is generally restricted to the same brain regions (neurogenic zones). Unexpectedly, some additional neurogenic processes have been found to occur in different brain regions of postnatal and adult rabbits. Despite the Orders Lagomorpha and Rodentia being quite similar, such difference is quite astonishing. In addition, some features of rabbit neurogenesis are more similar to humans than to rodents. Taking into account that adult neurogenesis is a phylogenetically highly conserved feature, yet with strong adaptation to the ecological niche of each animal groups, the rabbit could be an excellent model for studying the logic of neuroplasticity in mammals and its possible role in brain repair.

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Introduction

Plasticity, namely the ability to make adaptive changes related to the structure and function of the system, is an essential attribute of biological tissues and organs allowing adaptation to challenging environment and compensatory adaptation after traumatic injury or pathology. In addition, at least in some tissues, plasticity can also produce repair and regeneration (Ferguson and O'Kane, 2004). Nevertheless, such reparative capacity remarkably vary in different tissues/organs. Those undergoing continuous cell renewal (e.g., skin, blood, cornea, many epithelia) do contain multiple and disperse units of stem cell niches (e.g., intestinal crypts, hair follicle bulge in the skin, endosteal and perivascular hematopoietic niches in bone marrow; Nystul and Spradling, 2006; Morrison and Spradling, 2008). After injury, regeneration in these 'labile' tissues is favored by the persistence of undamaged stem cell niches. On the other hand, the adult central nervous system (CNS) of mammals can be considered as substantially static, both under the profile of cell renewal and of tissue repair (Bonfanti, 2011, 2013). The CNS reparative capacity is higher in invertebrates and non-mammalian vertebrates, whereas it has been largely lost in some animal groups, such as birds and mammals (Masaki and Ide, 2007; Bonfanti, 2011). A fundamental feature of CNS structure is its connectional, neurochemical and functional specificity which allows specific cell types to be connected and to act in a relatively invariant way (Frotscher, 1992). The mammalian CNS is a highly complex structure made up of a huge number of neurons (10^{11}), an even higher number of glial cells (10^{12}) and around 10^9 synapses per cubic millimetre ($10^{15}/mm^3$ in humans; Chklovskii et al., 2004). Its architectural specificity is attained during development and maintained in the adult through a vast cohort of membrane-bound and extracellular matrix molecules, mainly involving adhesion molecules and their receptors with permissive and/or instructive functions (Gumbiner, 1996). Most of these molecules, as well as different types of inhibitory factors, are also responsible for CNS stabilization thus leading to the well known incapability of mammals to undergo neuronal regeneration and repair (Caroni, 1997). In addition, with respect to other organs, the CNS shows structural peculiarities since neurons and glial cells possess ramified, intermingled processes, some of which projecting very far from the cell body. This fact makes the CNS not simply a 'mass' of organized cells but a complex set of circuits in which a remarkable portion is composed of 'cables' and synaptic contacts. For this reason, along with the old allocation of nerve cells as 'perennial' (non-renewable), the word «regeneration» in neuroscience was originally restricted to the re-growth/re-elongation of cell processes by surviving cell bodies after injury (e.g., axonal regeneration (Davies et al., 1997).

Besides this feature of substantially static architecture, *structural plasticity* is another attribute of the CNS, complementary to specificity (Zilles, 1992).

CNS Structural Plasticity

In addition to molecular changes (functional adaptive plasticity), which theoretically does not affect the shape of cells, structural plasticity involves changes which modify the shape and structure of the CNS at the cellular level (Bonfanti, 2006; Theodosis et al., 2008). An important distinction should be made between developmental and adult structural plasticity,

the former, being at the basis of CNS formation. Developmental plasticity is fundamental for building up the specificity of the mature CNS, allowing the occurrence of morphogenetic processes which involve massive structural changes (e.g., cell proliferation, cell migration, axonal/dendritic growth), undergoing a progressive downregulation during the postnatal period (Bonfanti and Peretto, 2011). The transition from developing to mature CNS leads to a stabilization of connections and ultimately to a substantially unrenewable tissue. The time-course of such a transition depends on the species, usually being linked to the complexity of the brain and its functions (Kornack, 2000). What remains after the downregulation of developmental plasticity is adult plasticity, which can be considered as an exception to the rule, restricted to specific locations, at the anatomical and/or the cellular level (Bonfanti, 2006,2011,2013).

In the extraordinary heterogeneity of CNS cellular composition different aspects of plasticity frequently overlap. Hence, the concept of structural plasticity can be further dissected by considering different types of cells (glial, neuronal) and different parts of the cell involved, as well as their relationships with the surrounding elements. Progressive degrees of morphological changes can be found: from synaptic plasticity, to axonal/dendritic growth and neuron-glial plasticity. A profound change in the concept of structural plasticity occurred in the 1990s, starting from two striking findings: the occurrence of a adult neurogenesis and cell migration within the forebrain sub ventricular zone (SVZ; Lois and Alvarez-Buylla, 1994), and the first isolation of adult neural stem cells (Reynolds and Weiss, 1992). These studies strengthened the idea that most typical developmental processes, ultimately converging to the genesis of new neurons, actually exist in the adult mammalian CNS (Gage, 2000; Alvarez-Buylla and Garcia-Verdugo, 2002; Kempermann, 2002; Carleton et al., 2003). Yet, neural stem cells of the mammalian CNS are restricted to two stem cell niches (neurogenic zones; see below). In many renewable tissues, the ability to dynamically redistribute and activate new niches is an important strategy for regenerative capacity (Wright et al., 2001; Morrison and Spradling, 2008). By contrast, in some stable organs showing low cell renewal rates, but retaining remarkable potentialities for compensatory hyperplasia upon functional demands, e.g., kidney and liver, stem cells and their niches appear to be less active (Kung and Forbes, 2009; Little and Bertram, 2009). As to the CNS, although we know that it is remarkably plastic under the profile of neural connection reorganization, e.g., experience-dependent (structural) synaptic plasticity (Holtmaat and Svoboda, 2009), the high topographical restriction of the only two stem cell niches do not allow regeneration in most of the neural parenchyma (Bonfanti, 2011,2013).

Neurogenesis

The word 'neurogenesis' indicates all those processes leading to building up the CNS through embryonic and fetal phases. Final CNS architecture is the result of cell divisions and precise cell-cell and cell-substrate interactions starting from a few undifferentiated cells in the neural tube (Bayer and Airman, 2004). The primitive neural tube is organized around the ventricular cavities which partially will persist in the adult filled with cerebrospinal fluid. In the neurogenic process, peri-ventricular germinative layers provide the source for most neuronal and glial cell precursors. These precursors subsequently populate the CNS

parenchyma mainly by centrifugal, radial migration from the neuraxis toward the pial surface, following a precise spatial and temporal pattern which allows undifferentiated cells to differentiate in their final destination and to establish appropriate connections (Rakic, 1990; Misson et al., 1991; Marin and Rubenstein, 2003). The primitive germinal layers consist of a ventricular zone (VZ) containing direct descendants of the primitive neuroectoderm (neuroepithelium), and a subventricular zone (SVZ), which later emerges from the VZ. The SVZ contains rapidly proliferating cells and expands at early postnatal development, eventually giving rise to subsets of neurons and glial cells (Levison, 2006).

Hence, the embryonic CNS is a highly dynamic environment undergoing dramatic changes in cell number and position, paralleled and followed by refinement of cell relationships at single projection and synapse level. After birth, through a brief postnatal period whose length depends both on species and brain complexity/size (Kornack, 2000), the CNS parenchyma undergoes stabilization, thus making plasticity an exception to the rule.

Adult Neurogenesis

Twenty years ago, the discovery was made that neural stem cells do exist even in the adult CNS (Reynolds and Weiss, 1992) accounting for adult neurogenesis throughout life within restricted brain regions of many mammals (Lois and Alvarez-Buylla, 1994; Gage, 2000; Kornack and Rakic, 2001a; Bernier et al., 2002; Luzzati et al., 2003; Rodriguez-Perez et al., 2003; Amrein et al., 2007), including humans (Eriksson et al., 1998; Sanai et al., 2004; Curtis et al., 2007). New neurons are continuously produced within two neurogenic sites harbouring neural stem cell niches, the forebrain subventricular zone (SVZ) and the hippocampal subgranular zone (SGZ) (reviewed in Bonfanti and Ponti, 2008). Since then, a lot of detail has been made available about the cell composition, structure, organization, function and modulation of these neurogenic regions (Luskin, 1993; Lois and Alvarez-Buylla, 1994; Bonfanti and Theodosis, 1994; Doetsch et al., 1997; Gage, 2000; Alvarez-Buylla and Garcia-Verdugo, 2002; Carleton et al., 2003; Kempermann et al., 2004; Seri et al., 2004; Zhao et al., 2006; Ihrie et al., 2011).

Forebrain SVZ

In laboratory rodents, an anterior extension of the SVZ forms a solid chord of migrating cells through the olfactory peduncle and bulb axes called *rostral migratory stream* (RMS; Lois and Alvarez-Buylla, 1994; Bonfanti and Theodosis, 1994; Figure 1). Both SVZ and RMS contain two main cell compartments: i) newly generated, migrating neuroblasts, in the form of tangentially-oriented *chains* (Doetsch and Alvarez-Buylla, 1996; Lois et al., 1996), and ii) protoplasmic astrocytes organized to form a dense meshwork throughout the SVZ area, giving rise to longitudinally-oriented channels called *glial tubes* (Lois et al., 1996; Peretto et al., 1997; Figure 1).

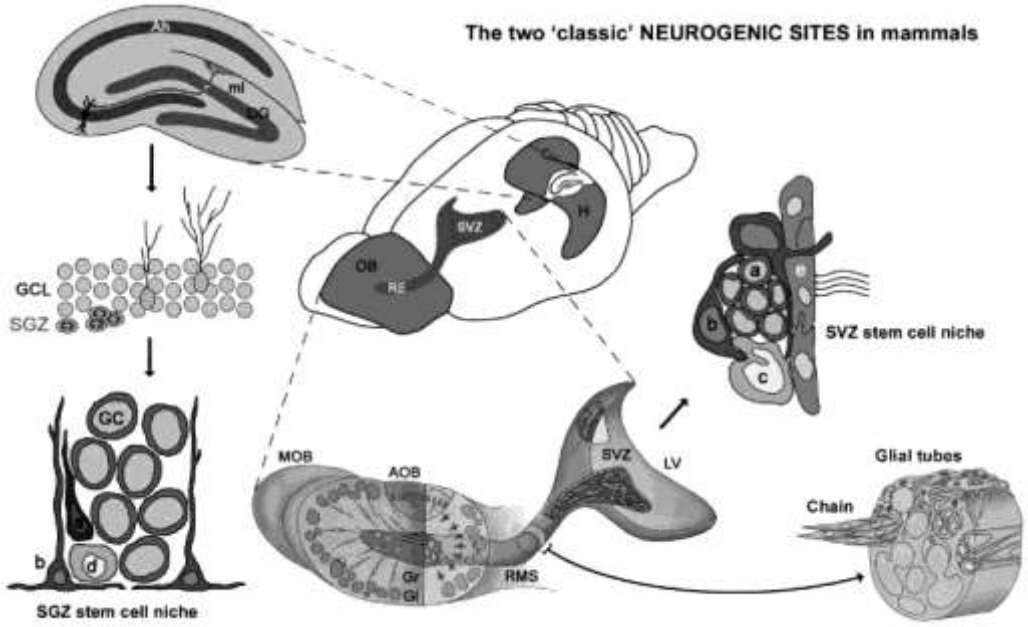

Figure 1. Schematic representation of the two main neurogenic sites in the adult rodent brain (adapted from Bonfanti and Ponti, 2008). Genesis of new neurons occurs in two main brain areas (in the middle): the olfactory bulb (OB) and the hippocampus (H). Their germinative layers are respectively the SVZ (bottom and right) and the subgranular zone (SGZ, left). The SVZ is composed of two main compartments: astrocytic *glial tubes*, and tangential *chains* of neuronal precursors, the latter sliding within the glial ensheathment (adapted from Peretto et al., 1997). In electron microscopy they correspond to type A cells (a) and type B cells (b). A third cell type (C cell, c) is present in the stem cell niche (left, top; adapted from Doetsch et al., 1997); e, ependyma. The SVZ chains dissolve in the olfactory bulb, whereby single neuroblasts move radially through the main (MOB) and accessory (AOB) olfactory bulb layers (Gr, granular layer; GL, glomerular layer). RE, rostral extension (rostral migratory stream). The hippocampal SGZ is located in the inner layer of the dentate gyrus (DG, left top) and gives rise to granule cells (GC) with dendrite arborisation in the molecular layer (ml) and an axon projecting to the Amnion's horn (Ah). Even in the absence of glial tubes and chains, cell types similar to those described in the SVZ form a stem cell niche in the SGZ (left, bottom; adapted from Seri et al., 2004). For details on the functional relationships among different cell types, see text.

The SVZ was the first site in which neural stem cells were isolated (Reynolds and Weiss, 1992) and identified as astrocytes (Doetsch et al., 1999), being considered as the major stem cell reservoir of the mature brain (Gage, 2000). Neuroblasts (also referred to as type A cells; Lois et al., 1996) have a leading and trailing process, a large nucleus and a thin rim of electrondense cytoplasm, with abundant free ribosomes. Astrocytes (type B cells) are stellate-shaped cells detectable by immunocytochemical staining for GFAP and deriving from postnatal transformation of embryonic radial glia (Merkle et al., 2004). In addition to A and B cell types, a third element with intermediate ultrastructural features and high proliferative capacity has been identified as type C cells, considered as 'transit amplifying' cells forming a bridge between slow proliferating stem cells and their progeny (Doetsch et al., 1997; Ponti et al., 2013). After a few cell divisions occurring within 4 days, each astrocytic neural stem cell is estimated to give rise to 16 young neurons (neuroblasts; Ponti et al., 2013). Neuroblasts generated in the rodent SVZ migrate within the glial tubes, performing a particular type of

PSA-NCAM-dependent tangential 'chain migration' which allows a long distance displacement (about 5 mm in mice) towards the olfactory bulb (Bonfanti and Theodosis, 1994; Lois and Alvarez-Buylla, 1994; Hu et al., 1996). Chain migration is proper to adult neurogenesis, the first SVZ chains being detectable during the second/third postnatal week in rodents (Peretto et al., 2005). Once in the olfactory bulb, the migrating neuronal precursors leave the glial tubes and pursue their migration radially as isolated neuroblasts through parenchymal layers of the main (Lois and Alvarez-Buylla, 1994) accessory olfactory bulb (Bonfanti et al., 1997; Figure 1). Most of these cells differentiate within the granular layer as GABA-containing granule cells, whereas a smaller subpopulation reaches the glomerular layer becoming dopaminergic periglomerular cells (Betarbet et al., 1996; De Marchis et al., 2004). By marking newly born granule cells with GFP-encoding retrovirus injected in the SVZ, it has been shown that both granule (Carleton et al., 2003) and periglomerular neurons (Belluzzi et al., 2003) grow dendritic spines, display spontaneous synaptic currents, and form synapses with other bulbar neurons, although they have distinct electrophysiological properties from old neurons. Thus, the SVZ provides new local inhibitory interneurons that synaptically integrate into olfactory bulb circuitry likely regulating the spatial and temporal coding of mitral and tufted cells at the first sensory relay of olfaction. It has been estimated that about 1% of total olfactory bulb interneurons are added each day in the adult, one-half of them dying between 15 and 45 days after their birth (Petreanu and Alvarez-Buylla, 2002; Doetsch and Hen, 2005).

Hippocampal SGZ

The dentate gyrus is part of the hippocampal formation, located in the dorsal-caudal part of the telencephalon, beneath the corpus callosum (Witter and Amaral, 2004). It is a three-layered cortex (allocortex) made up of small neurons called granule cells which form a 4-10 cell thick layer comprised between two fiber layers (the hilus and the molecular layer). Progenitor cells divide in the inner part (SGZ), with the progeny giving rise to mature granule cells that extend an axon within the mossy fibre pathway during the first four days which reaches Ammon's horn during the first month (Hastings and Gould, 1999; van Praag et al., 2002; Zhao et al., 2006; Figure 1). Most newly generated cells die during the first two weeks (Kempermann et al., 2003). The surviving elements translocate their cell body through the outer layers for a few microns and successfully integrate into circuits in about six weeks (Hastings and Gould, 1999; Van Praag et al., 2002). It has been estimated that about 250.000 new neurons are added to the rodent dentate gyrus within one month, representing 6% of the total number in this area (Cameron and McKay, 2001). The generation of hippocampal cells in humans was recently analysed by measuring the concentration of nuclearbomb-test-derived ^{14}C in genomic DNA, estimating a rate of 700 new neurons per day (Spalding et al., 2013). The rate of adult hippocampal neurogenesis significantly decreases with age, more evidently than the forebrain SVZ (Kuhn et al., 1996). Since hippocampal newly born cells differentiate locally, no chain migration can be found in the dentate gyrus. Instead of SVZ glial tubes, radial and horizontal astrocytes are present, the former being a special type of SGZ radial glia-like astrocyte, similar to the type B cells described in the forebrain (Figure 1). These glial cells can divide and give rise to the granule cell precursors, probably representing the stem

cell compartment of the hippocampus (Seri et al., 2004). Hippocampal neurogenesis is modulated by many factors. It has been used as a model for quantitative studies aimed at unravelling how cell production and survival are regulated. For example, an enriched environment increases the survival of newly born cells (Kempermann et al., 1997; Gould et al., 1999a) whereas stress conditions exert the opposite effect (Mirescu and Gould, 2006). Hormonal levels (Tanapat et al., 1999), physical activity (Van Praag et al., 1999) and diverse experimental/lesion paradigms (Parent et al., 1997; Kokaia and Lindvall, 2003) also affect hippocampal neurogenesis, although the exact mechanisms are still obscure (Gould et al., 1999a; Mirescu and Gould, 2006).

Notwithstanding differences in the anatomical distribution and cy to architecture of the two neurogenic sites, a common pattern can be found in their cell composition under a morphological and functional profile. Both the SVZ and the SGZ are persistent, active germinative layers associated respectively with the anterior part of the lateral ventricles and the inner layer of the hippocampal dentate gyrus (Figure 1). Astrocytic stem cells in both neurogenic sites do derive from VZ radial glia cells (Kriegstein and Alvarez-Buylla, 2009). While the SVZ maintains direct contact with the ventricles, the SGZ loses such contact during development. The SVZ neuronal precursors undergo long-distance migration to reach their final site of destination in the olfactory bulb whereas those generated within the dentate gyrus differentiate locally. Once integrated, these cells prevalently replace dead neurons in the olfactory bulb or add to preexisting populations in the hippocampus (Imayoshi et al., 2008). In both systems, adult neurogenesis is modulated during learning of different tasks, thus it may play a role in learning and memory (Gould et al., 1999a; Leuner et al., 2006; Lledo et al., 2006). From the functional point of view, adult neurogenesis has been related to adaptation to ecological pressures (Barker et al., 2011). At present, this is one of the most satisfactory functional explanations in the entire phylogenetic tree, along with multiple, genetically determined variables spanning from the brain anatomy/developmental history to the animal lifespan (Amrein et al., 2011). This range of possibilities can also be increased by non-genetic variables, such as experience-dependent cues (Johnson et al., 2010; Barker et al., 2011; Kempermann, 2012). Benefits of adult neurogenesis appear to converge on increased neuronal and structural plasticity subserving coding of novel, complex, and fine-grained information, usually with contextual components that include spatial positioning (Konefal et al., 2013). Three main hypotheses for the functions and adaptive significance of adult neurogenesis, which are not mutually exclusive, involve pattern separation, memory consolidation, and olfactory spatial. Roles for neurogenic plasticity have also been suggested for a wide range of human physiological functions and pathological conditions (Sohur et al., 2006; Konefal etal., 2013).

A link between Adult Neurogenesis and Brain Repair Is not Granted

At the beginning of the nineties, the discovery of neural stem cells and adult neurogenesis led many people to consider definitively broken the dogma of the CNS as made up of non-renewable elements (Gage, 2000; Gross, 2000). This finding triggered new hopes for brain repair, yet, twenty years later, the dream of regenerative medicine applied to CNS injuries and

neurodegenerative diseases is still very far (Arenas, 2010; Lindvall and Kokaia, 2010). As a matter of fact, adult neurogenesis in mammals occurs mainly within the two restricted neurogenic sites (see above), and, as a direct consequence of such topographical localization, most of the CNS parenchyma out of the SVZ and SGZ remains substantially a non-renewable tissue (Bonfanti, 2013). An indirect proof of this statement resides in the fact that most of the traumatic/vascular injuries and neurodegenerative diseases, which actually occur in "non-neurogenic" regions, have still not found efficacious therapies capable of restoring CNS structure and functions through cell replacement (Arenas, 2010).

Nevertheless, during the last decade, new heterogeneity has been revealed by studies showing a substantial and widespread gliogenic (Horner et al., 2000; Dawson et al., 2003; Butt et al., 2005; Nishiyama et al., 2009), and to a lesser extent, neurogenic potential (Dayer et al., 2005; Luzzati et al., 2006; Ponti et al., 2008) within the CNS parenchyma, namely, in those areas previously considered as non-neurogenic (reviewed in Bonfanti and Peretto, 2011; Bonfanti, 2013). This new field of investigation revealed many unexpected potentialities for *de novo* cell genesis in the CNS, although most aspects of parenchymal neuro-glio-genesis remain quite obscure and ill-defined.

Parenchymal Neurogenesis

All neurogenic processes occurring outside the two germinal layers (SVZ and SGZ) are indicated as *parenchymal* neurogenesis, since located in the CNS parenchyma. Spontaneous parenchymal neurogenesis can be considered as a very rare phenomenon in mammals, and its regional location has been shown to be dependent on the animal species, age, and physiological/pathological states (Bonfanti and Peretto, 2011). Different examples have been described in rodents (Dayer et al., 2005; Kokoeva et al., 2005), rabbits (Luzzati et al., 2006; Ponti et al., 2008), and monkeys (Gould et al., 2001; Bernier et al., 2002), with remarkable interspecies differences. Most parenchymal neurogenesis described in adult rodents seems to occur spontaneously at very low levels, rather being elicited/enhanced after specific physiological or pathological conditions (Ohira et al., 2009; Pierce and Xu, 2010).

Among the unsolved issues of parenchymal neurogenesis are the numerous reports which have not been confirmed by further studies or by other laboratories (Gould et al., 1999b; Magavi et al., 2000; Nakatomi et al., 2002; Zhao et al., 2003; Rivers et al., 2008; Guo et al., 2010), along with a series of data which have been denied in studies trying to reproduce the same results (Kornack and Rakic, 2001b; Richardson et al., 2011; Frielingsdorf et al., 2004). Hence, it is evident that we still not grasp the real limits and/or opportunities of parenchymal neurogenesis and that further studies are required before finally accepting, or denying the existence of each 'unusual' neurogenic process. On the other hand, what appears clear is that some stem/progenitor cells in the parenchyma are able to give rise to new neurons in experimental and/or pathological conditions (Luzzati et al., 2011; Ohira et al., 2009; Pierce and Xu, 2010). Various examples of 'reactive' neurogenesis are known to occur after different types of CNS injury. Beside neurogenesis induced from adjacent neurogenic sites (Arvidsson et al., 2002; Thored et al., 2006), some neurogenic/gliogenic processes are also thought to start from local, parenchymal progenitors (Luzzati et al., 2011; Ohira et al., 2009; Komitova et al., 2006). For instance, local progenitors in layer I of the rat cerebral cortex, which in

normal conditions seem to be rather quiescent, are activated after ischemia giving rise to new cortical interneurons (Ohira et al., 2009). Also in a slow and progressive model of striatal neuronal degeneration, besides activation of SVZ progenitors, genesis of neuroblasts has been found to occur also from local progenitors in mice (Luzzati et al., 2011). This suggests that certain pathological states can stimulate either migration of progenitors from the adult SVZ or activation of local neuronal progenitors. Yet, one of the issues which remain poorly investigated is whether the adult brain parenchyma belonging to spontaneously non neurogenic areas could be endowed with quiescent progenitor cells which can be stimulated to awake under specific environmental conditions, independently from the contribution of germinal layers.

A case placed in between the spontaneous and experimentally-induced neurogenesis is that of the hypothalamus. Several publications based on experiments carried out on rodents have been reporting data on this brain region as a new site for adult constitutive neurogenesis in mammals (for review see Cheng, 2013).

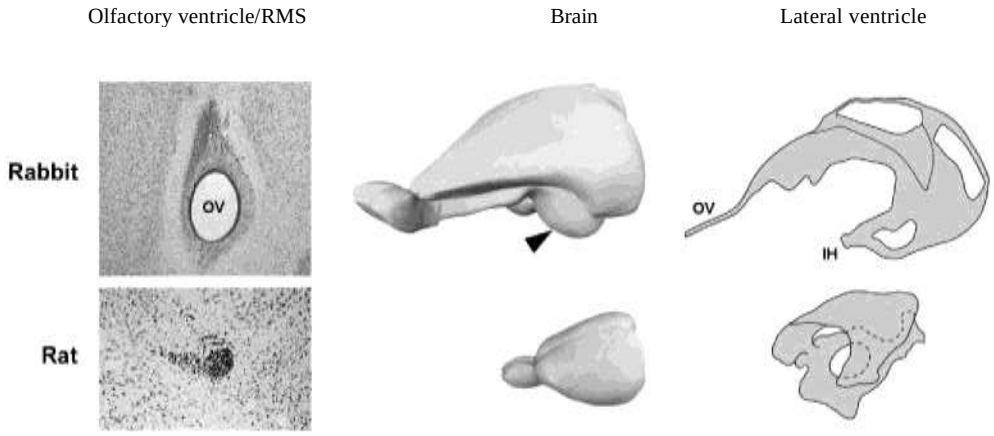

Figure 2. Differences in the overall organization of forebrain ventricular cavities in rabbit and rodents: an open olfactory ventricle (OV) remains associated with the SVZ rostral extension (rostral migratory stream, RMS) of rabbits; another extension of the lateral ventricle, the inferior horn (IH) is present in the well developed temporal lobe of lagomorphs (arrowhead). These ventricular extensions are absent in the smaller brain of rodents (adapted from McFarland et al., 1969; Leonhardt, 1972; Bonfanti and Ponti, 2008).

Several unresolved aspects make parenchymal neurogenesis a difficult territory to be explored: (i) the contrast between a wide range of potentialities displayed by parenchymal progenitors isolated *in vitro* and far more restricted potentialities which can be observed *in vivo* (Palmer et al., 1999; Belachew et al., 2003), (ii) the existence of studies reporting neurogenesis in parenchymal regions which have been denied or not confirmed by other researchers (Gould et al., 1999b; Magavi et al., 2000; Kornack and Rakic, 2001b), and (iii) the real origin of progenitors which are induced to proliferate/migrate in different lesion models (either mobilized from neurogenic sites or activated locally within the parenchyma (Arvidsson et al., 2002; Nakatomi et al., 2002; Thored et al., 2006; Luzzati et al., 2011).

In conclusion, alternative and multiple forms of plasticity involving neurons can overlap within the CNS parenchyma, affecting preexisting cells/circuits and increasing the complexity of the whole picture of brain structural remodeling. Notably, in recent years differences in

adult neurogenesis have been emerging among mammals, so that there are several reasons for further analysis of adult mammalian neurogenesis in a comparative perspective.

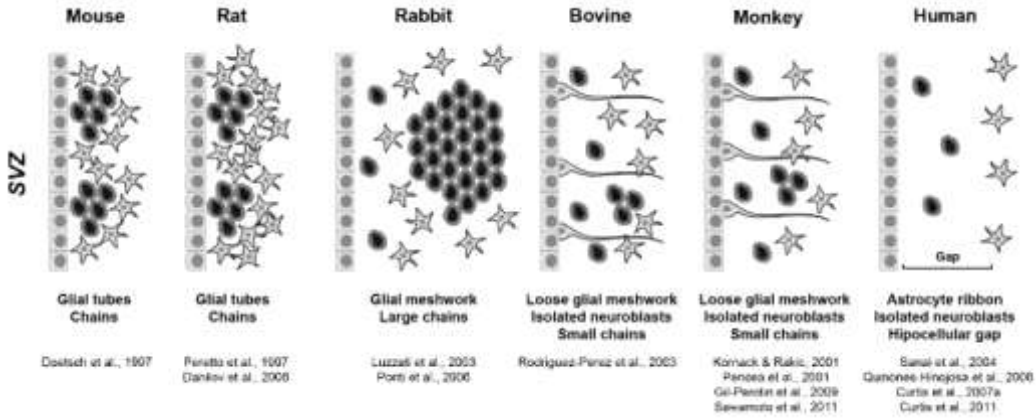

Figure 3. Organization of the subventricular zone (SVZ) neurogenic niche in different mammals. Most differences concern the astrocytic spatial organization and the neuroblast assembly into chains. Type C cells and displaced ependymal cells are not showed. Although still fragmentary, the data available suggest some general principles: (i) chain assembly could be linked to robust and fast cell migration; (ii) chain assembly and cell migration are not directly linked with persistence/closure of the olfactory ventricle; (iii) glial meshwork density is not directly linked with chain assembly nor cell migration. Note that rabbit SVZ architecture is different from both that of rodents and that of animals endowed with large brains (bovine, monkey, humans), yet more similar to that of humans in the part located close to the ventricle (adapted from Bonfanti and Peretto, 2011).

The Rabbit as a Model for Postnatal and Adult Neurogenesis

The New Zealand white rabbit *(Orictolagus cuniculus)* belongs to the lagomorphs (order Lagomorpha), forming a distinct order compared with rodents (order Rodentia), despite being grouped together in the past. Rabbits are both domestic and laboratory animals, yet from the neurological point of view they are mainly used as models in vision research (Manning et al., 1994).

As neuroanatomy is concerned, in contrast with a deep knowledge in rodents few detailed studies have been performed in lagomorphs, making it difficult to set up comparative considerations. Two evident features concerning rabbit brain anatomy can be relevant to adult neurogenesis: the occurrence of more prominent cerebral ventricular extensions and more expanded temporal lobes (Figure 2). Differences in the overall brain anatomy have been proposed as relating to a different shape and extension of the ventricles, since "cerebral ventricles are primordial hollows of the brain that reflect in changes of their configurations and size the development and growth of the neural tube" (McFarland et al., 1969). Besides a basic common plan, the ventricles of mammals vary in relation to the different degrees of expansion of different CNS parts (e.g. the neocortex can vary up to 10.000-fold range in surface in different species; Kornack, 2000).

The lateral Ventricles and SVZ of Rodents and Lagomorphs

In many domestic animals including dogs, cats, cows, sheep and rabbits the lateral ventricle is prolonged into a persistent *olfactory ventricle*, whose walls do not collapse after birth (McFarland et al., 1969; Leonhardt, 1972; Figure 2). This feature does not seem to be related to brain size since an open olfactory ventricle is absent and replaced by a solid chord of tissue both in rodents and primates, including humans (McFarland et al., 1969). The tissue forming the rostral migratory stream in rodents is replaced in rabbits by a SVZ rostral extension ensheathing the dorsal part of the olfactory ventricle (Figure 2). Another extension of the lateral ventricular system called *inferior horn* and protruding ventrally within the temporal lobe, is absent in rodents but present in rabbits and primates, and correlates well to the expanded temporal lobes of these species (McFarland et al., 1969; Leonhardt, 1972; Figure 2). This trend is confirmed by the occurrence of a *posterior horn* in species with massive development of the occipital lobes and high degree of visual specialization, maximally evident in primates and humans.

The rabbit SVZ, delineated as an area in which a high proliferation rate, chains of PSA-NCAM+/doublecortin+ cells, and an astrocytic meshwork do overlap (Luzzati et al., 2003; Ponti et al., 2006a), extends along the lateral wall of the lateral ventricle and the dorsal part of the olfactory ventricle (rostral extension). From the posterior part of the lateral ventricle, a ventral lateral extension (Luzzati et al., 2003) lines the lateral ventricle inferior horn, somehow adapting to a different ventricular conformation with structures which are absent in rodents.

Cytoarchitecture of the Rabbit SVZ

Concerning the rabbit SVZ internal arrangement, three main differences are found compared with rodents: (1) heterogeneous distribution of the chain and glia compartments; (2) simultaneous occurrence of isolated neuroblasts and very large chains; (3) existence of a looser astrocytic meshwork (Ponti et al., 2006a). Two distinct parts can be detected all along its extension: a 'ventricular' SVZ, adjacent to the ventricular wall and containing small aggregates of neuroblasts immersed within a relatively dense glial/ependymal sheath, and an 'abventricular' SVZ, detached from the ventricles and containing large chains of neuroblasts immersed in a loose network of astrocytic processes (Figure 3). This distinction is reinforced by a thick band of tissue, poor in cells and enriched in nerve fibres and glial processes, which could be reminiscent of the 'hypocellular gap' of the human SVZ (Quinones-Hinojosa et al., 2006; Figure 3). Another common feature is the absence of well organized glial tubes, replaced by an incomplete astrocyte row reminiscent of the human 'astrocyte ribbon' (Sanai et al., 2004). Something similar has also been described in the bovine SVZ (Rodriguez-Perez et al., 2003; Figure 3), suggesting that in non-rodent mammals the glial meshwork could be less tightly-packed and less compartmentalized than in rodents. On the other hand, a striking difference between rabbit and human SVZ consists of large chains in the rabbit abventricular SVZ in contrast with the absence of chains on both sides of the astrocyte ribbon in humans. About 10-20 medium-large chains are visible, some of which include up to 15-20 nucleated cells in transverse section (Ponti et al., 2006a; schematically represented in Figure 3). Thus, the SVZ appears structurally more heterogeneous in lagomorphs than in rodents, suggesting

that both chain and glia compartments can differ in their architecture and mutual relationship, in relatively close mammalian species. Studies carried out on rodents show SVZ chains are not present at birth but they assemble around the third postnatal week (Peretto et al., 2005). In rabbits the pattern of chain formation is observed very early, starting from postnatal day 10 (Ponti et al., 2006a). This difference is strengthened by the fact that postnatal development is temporally different in these species, being earlier in rodents (puberty occurs in the first or second postnatal months) than in rabbits (around the fourth month). On the other hand, the rabbit SVZ glial compartment will never attain the degree of organization typical of rodent glial tubes (Peretto et al., 1997, 2005), thus appearing to retain a certain degree of 'morphological immaturity' for quite a long period. After ultrastructural analysis of the SVZ associated with the lateral ventricle, in which most of the stem cell niche is expected to occur, the same cell types described in rodents were found, yet with a different spatial organization. The absence of glial tubes and chains in the rabbit ventricular SVZ, along with the occurrence of astrocytes forming a row parallel to the ependyma, makes this structure somehow more similar to the human stem cell niche than that of rodents (Doetsch et al., 1997; Sanai et al., 2004; Quinones-Hinojosa et al., 2006; summarized in Figure 3).

Extensions of the Rabbit SVZ within the Brain Parenchyma

In addition to its internal arrangement, another intriguing feature of the rabbit SVZ is the occurrence of numerous extensions entering the surrounding mature parenchyma (Figure 4). These *parenchymal chains* were identified after serial reconstruction of brain tissue sections immunostained for PSA-NCAM revealing two groups of chain-like aggregates: (1) anterior chains, leaving the rostral extension and immersed within the corpus callosum beneath the frontal cortex (Figure 4), and (2) posterior chains, apparently leaving the ventral-lateral extension, along the external capsule (Luzzati et al., 2003). The real nature of chains is confirmed by ultrastructural reconstruction and analysis of BrdU-treated animals at different post-injection survival times, showing no cell proliferation within the parenchymal chains yet revealing the occurrence of newly generated cells after 5-10 days (Luzzati et al., 2003; Ponti et al., 2006a). The immunoreactivity for PSA-NCAM and doublecortin on these tangentially-oriented bulks of cells as well as the ultrastructural features of bipolar neuroblasts displayed by their cellular components are both features of 'chain migration' (Lois et al., 1996; Luzzati et al., 2003; Ponti et al., 2006a). On the other hand they are relatively glia-independent, being directly in contact with axons (anterior chains) or at the interface between white and gray matter, including contact with mature neurons and oligodendrocytes (posterior chains). Similarly to abventricular SVZ chains, parenchymal chains are very large, abundantly trespassing the average number of cells found in rodents (usually 3-5). The 'compact' morphology of anterior chains (Figure 4) is consistently different from the more irregular, 'laminar' arrangement of the posterior ones, made up of clusters and rows of cells which partially disaggregate and re-aggregate as they progress through the tissue. Anterior chains show continuity with large chains of the abventricular SVZ, in some cases following blood vessels in their shift from SVZ to white matter (Ponti et al., 2006a). The affinity between chains of neuroblasts and blood vessels appears quite important since it has been demonstrated to occur in the mouse striatum following a stroke (Yamashita et al., 2006). Interestingly, the occurrence of rabbit anterior chains is limited to the postnatal/peripuberal

period (Ponti et al., 2006a). This is another feature similar to humans, in which a stream reaching the ventro-medial prefrontal cortex has been described during the first 18 months of life (Sanai et al., 2011; see also Bonfanti and Peretto, 2012).

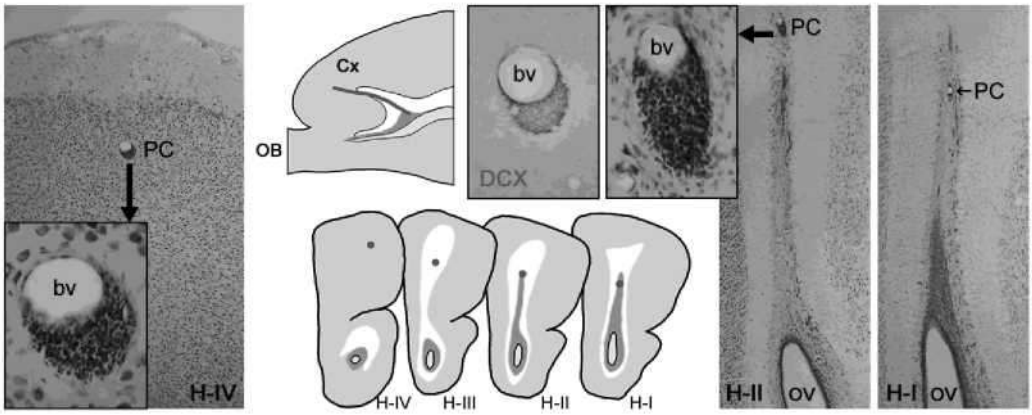

Figure 4. An anterior parenchymal chain of neuroblasts (PC) in a 6-month-old rabbit. After reconstruction, the chain is followed along a blood vessel (bv) through the white matter of the corpus callosum and in the frontal cortex (Cx). On the right another parenchymal chain viewed with electron microscopy within the corpus callosum. ov, Olfactory ventricle; DCX, doublecortin (from Bonfanti and Peretto, 2012).

On the other hand, the posterior parenchymal chains due to their fragmentary arrangement and distribution could be made up of locally generated elements characterized by inconstant relationships with the SVZ. Indeed, even appearing as a homologue of the 'temporal stream' described in monkeys (Bernier et al., 2002) they could hardly be considered as a true SVZ extension. The in vivo observations carried out on rabbits show that chains of neuroblasts can be found in various contexts but suggest that cell migration outside the SVZ and its glial meshwork, although possible, could turn out more difficult and inefficient by the occurrence of non-glial substrates. In other terms, if a glial substrate is not essential for the occurrence of chain migration, when it does occur in the form of sheaths (glial tubes) it could provide a favourable environment.

Notwithstanding the occurrence of many PSA-NCAM+ cells with typical bipolar-shaped morphology of migrating elements, radially-oriented in the cortical/subcortical areas adjacent to parenchymal chains, no newly generated cells are detectable in the cortex and a few newly born cells were occasionally observed in the amygdala one month after the BrdU treatment (Luzzati et al., 2003).

In conclusion, migration in parenchymal chains could be discontinuous and slow if compared to that directed to the olfactory bulb through the SVZ. Although it is very unlikely that such alternative routes could provide functional cell addition/renewal in the brain parenchyma (apart from the amygdaloid regions), their existence show the heterogeneity of SVZ arrangement in mammals leaving open possibilities for modulation of such endogenous sources of cell progenitors in the perspective of brain repair.

Protracted Neurogenesis in the Cerebellum

Mammalian neurogenesis has a species-specific timetable, with detectable differences at both embryonic and postnatal stages. This is related to differences in length of gestation and postnatal growth period prior to puberty (Bayer and Airman, 2004). In addition to species-specific variations, the temporal windows of onset and downregulation of neurogenetic processes can be heterogeneous throughout the neuraxis. For instance, most neocortical neurons are generated during mid-gestation whereas some neuronal cell populations continue to be added after birth in the cerebellum, hippocampus and olfactory bulb (reviewed in Rakic et al., 2004). Thus, although in most CNS regions germinative layers are exhausted at birth, in some locations they persist postnatally or throughout adulthood (Figure 5).

The mammalian cerebellum is a typical example of postnatal neurogenesis aimed at establishing a huge population of granule cells during the period in which the animal is interacting with the external environment. For such 'neurogenesis regionalization', the cerebellum is a remarkable model of *protractedneurogenesis* (Bonfanti and Peretto, 2011).

Although the genesis of most cerebellar cell types occurs very early from the periventricular neuroepithelium lining the 4th ventricle (Figure 6 A), intemeurons and some astrocytic glial cells complete their centrifugal migration through the white matter and their specification postnatally (Maricich and Herrup, 1999; Grimaldi et al., 2009). Cell proliferation of these progenitors still occurs in prospective white matter. In addition, the postnatal mammalian cerebellum undergoes a protracted genesis of granule cells through a transitory, secondary germinative layer localized on its surface: the external germinal layer (EGL; Figure 6 A-C).

The EGL is formed by tangential subpial displacement of cell precursors from the germinal trigone of the 4th ventricle, then leads to protracted genesis of the granule cell population by radial, centripetal migration of cell precursors. This transitory germinal zone progressively reduces its thickness as the granule cell precursors migrate deep into the cortex, then disappear at specific ages in different species (from 3 weeks in mice to 11 months in humans, which is very early compared with puberty; reviewed in Ponti et al., 2008, 2010; Figure 6 A-C).

In rodents, the delayed proliferation, specification and differentiation of glial cells and intemeurons coming from the prospective white matter is concluded before the end of granule cell genesis (Grimaldi et al., 2009; Leto et al., 2009). After this stage, no more cell genesis is detectable, as no germinal layers remain active, so that cerebellar plasticity throughout life is granted solely by synaptic changes in pre-existing circuits. Under the functional profile, this delayed genesis of granule cells and intemeurons shares a logic with the role of cerebellar circuits in learning / adapting motor skills to the environmental cues the animal is dealing with during postnatal / young stages of its life. This process does not involve simply the addition of new neurons, but also the choice between different types of cell specification (Grimaldi et al., 2009; Leto et al., 2009). The delayed cerebellar neurogenesis might be considered as part of the critical periods that allow formation of new synaptic contacts as well as involving the recruitment of new neurons.

Recent comparative work carried out by our laboratory on the cerebellum of New Zealand white rabbits revealed a far more complex situation, as in these lagomorphs protracted neurogenesis extends around and beyond puberty (Ponti et al., 2006b, 2008).

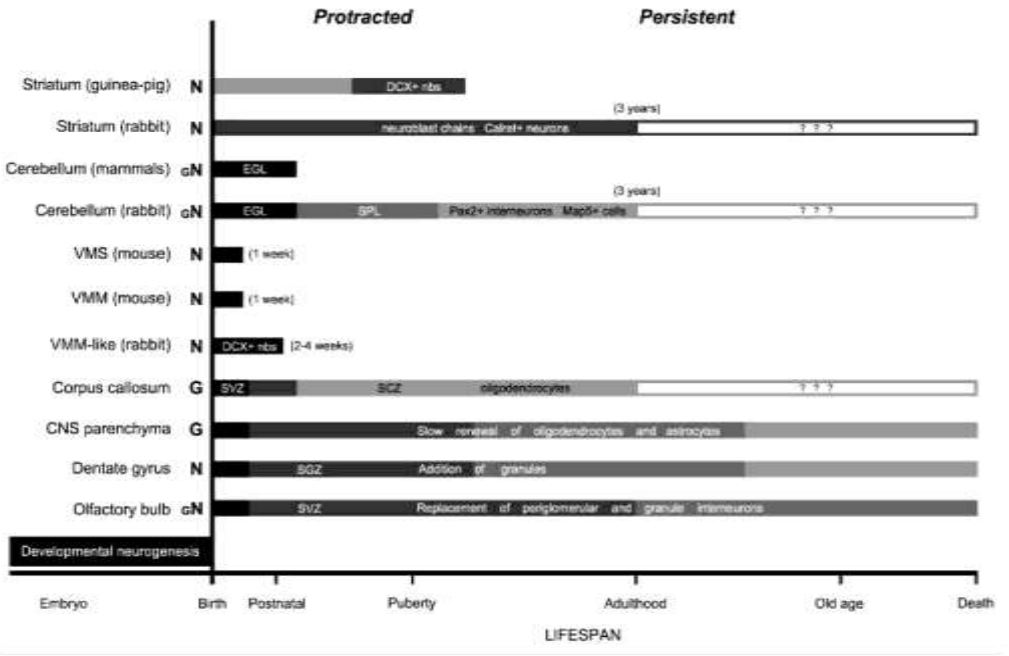

Figure 5. Different developmental extensions of protracted and persistent neurogenesis. Black, postnatal extensions of embryonic neurogenesis (delayed morphogenesis). Shades of grey indicate different rates of cell genesis, usually decreasing with increasing age (note the exception of the guinea pig). DCX, doublecortin; EGL, external granule layer; G, glial progeny; gN, glial and neuronal progeny (prevalently neuronal); Map5, microtubule-associated protein IB; N, neuronal progeny; nbs, Neuroblasts; SCZ, subcallosal zone; SGZ, subgranular zone; SPL, subpial layer; SVZ, subventricular zone; VMM, ventral migratory mass; VMS, ventral migratory stream (adapted from Bonfanti and Peretto, 2011).

The Rabbit Subpial Layer (SPL)

Unlike the forebrain, the mammalian cerebellum was considered incapable of any spontaneous cell production after the delayed genesis of granule cells occurring in the postnatal cerebellar cortex (see above). In rodents, after EGL exhaustion direct contact between pia mater/Bergmann glial endfeet and parallel fibres characterizes the cerebellar surface (Airman and Bayer, 1997) and no signs of cell proliferation can be detected in the cerebellar cortex (Bonfanti et al., 1992; Dusart et al., 1999; Ponti et al., 2006b). These facts match with the notion of the cerebellum as made up of non-renewable elements. Nevertheless, we reported in rabbits the existence of a secondary germinal matrix persisting beyond puberty in subpial position, called *subpial layer* (SPL, Ponti et al., 2006b), thus suggesting that this is not a general rule in mammals.

The SPL originates from structural modification of the EGL and is capable of generating PSA-NCAM+/doublecortin+ neuronal precursors oriented tangentially on the cerebellar surface and assembled into chains (Figure 6 C,D). Thousands of subpial chains are regularly arranged with a medial to lateral orientation and cover the whole cerebellum from the 2nd to the 5th month of life, then disappearing after puberty. We showed that subpial chains are made up of neuronal precursors and share features with forebrain SVZ chains (Ponti et al., 2006b). Cell proliferation occurs among chains, the newly born neuroblasts being incorporated within them in the subsequent days. By studying the shift from EGL to SPL in young rabbits we

found that SPL chains form through fragmentation of the EGL pre-migratory layer around the end of the first postnatal month, then increase their distance and progressively dilute on the cerebellar surface until they disappear (Figure 6 C,D,G). Although we do not have direct evidence of cell migration in rabbit SPL chains, they could be involved in the tangential displacement of neuronal precursors which has been shown to occur in the mouse EGL pre-migratory layer prior to engagement in radial migration (Komuro et al., 2001). The lengthy persistence of rabbit SPL chains do suggest that remarkable structural plasticity could persist in the relatively mature environment of the peripubertal rabbit cerebellar cortex. The newly generated cells of the SPL are detectable far beyond the estimated end of rabbit granule cell genesis (Smith, 1963) and show an absolutely different morphology and distribution compared with the 'ectopic' granule cells described in the molecular layer of the rabbit cerebellar cortex (Spacek et al., 1973).

Interestingly, in parallel with the persistence of the SPL, high amounts of PSA+/doublecortin+ newly born cells were also detectable within the cerebellar cortex, and some of them were still present at subsequent ages, after the disappearance of the SPL. An hypothesis explaining the occurrence of young cortical cerebellar neurons in the absence of an active germinative layer could be linked to a delayed arrival of immature interneuron precursors coming via radial migration from the underlying white matter, as classically described for cerebellar cortex interneurons of neuroepithelial origin (Maricich et al., 2001).

Genesis of Interneurons in the peripuberal and Adult Cerebellar Cortex

Until a few years ago, it was universally accepted that in the cerebellum all processes of delayed neuronal cell genesis were exhausted with the end of granule cell genesis and concurrent EGL (Airman, 1972) or SPL (Ponti et al., 2006b) disappearance. Yet, further studies carried out on rabbits revealed substantial genesis of cerebellar interneurons until peripubertal ages, and to a lesser extent, in adult animals (Ponti et al., 2008). These cells are PSA-NCAM+/doublecortin+/Pax2+ neurons that continue to proliferate within the cerebellar cortex parenchyma in the absence of any residual germinal layers (Ponti et al., 2008, 2010). The presence of the trancription factor Pax2 indicate that these cells are neuroepithelial-derived elements (Weisheit et al., 2006), thus originally coming from the periventricular germinative layer through withe matter radial migration (see Maricich et al., 2001). This neurogenic process occurs spontaneously in the intact rabbit CNS, even in fully adult animals (1-2 year old rabbits; summarized in Figure 6 G). The newly generated Pax2+ interneurons were followed by BrdU injection and long-term survival (2 months); they also express PSA-NCAM and doublecortin during the first 3 weeks of their life, thus revealing their morphology of bipolar, migratory cells, which is followed by a typical neuronal morphology, being GABA positive, and negative for Sox2 and Olig2 (Ponti et al., 2008; Figure 6 E). We know the cellular source, but it is not clear if cell divisions occur either within the white matter or the cerebellar cortical grey matter (the first BrdU+ / PSA-NCAM+ cells are detectable several days after injection; Ponti et al., 2008), although the occurrence of bipolar double-stained cells suggests they could come from the white matter.

At present, this is the only case of adult neurogenesis known in the mammalian cerebellum. Nevertheless, such a process has been documented in adult rabbits up to 3 years old, then progressively decreasing in intensity (10/1 in the first 6 months, and once again 10/ 1 from 6 months to 3 years; Ponti et al., 2008).

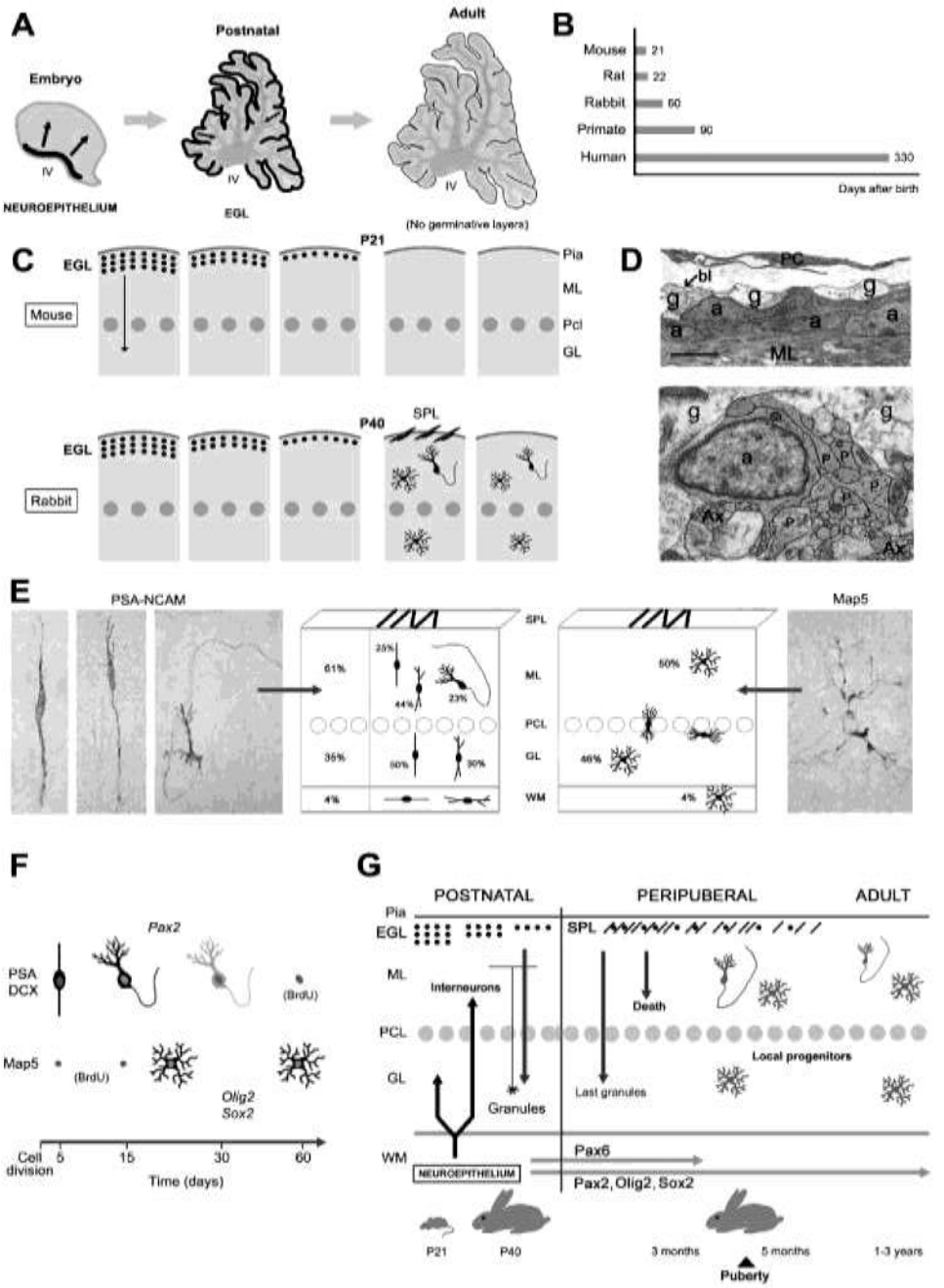

Figure 6. Protracted neurogenesis in the cerebellum of young/adult rabbits. A, Exhaustion of germinative layers in the pre- and post-natal cerebellum of rodents. B, Estimated end of granule cell genesis in different mammals. C, Persistence of subpial layer (SPL) and parenchymal genesis of neuronal and glial precursors in the rabbit cerebellar cortex, with respect to rodents. D, Ultrastrucural evidence for SPL chains of neuroblasts (top, longitudinal; bottom, transversal). E, Two populations of newly generated cells in the peri-puberal rabbit cerebellum (left, neuronal-shaped cells; right, multipolar cells). F, The two cell populations acquire and lose cellular markers at different stages of their postmitotic life. G, Time course of germinative layer-dependent and independent cell genesis in the rabbit cerebellum (adapted from Ponti et al, 2010).

Subsequent ages have not been investigated, yet the substantial decrease in newly generated cerebellar neurons suggests a further dilution/exhaustion of the process in older rabbits.

Under the comparative profile, the rabbit cerebellar neurogenesis appears as a unique example of protracted neurogenesis in mammals whose functional meaning remains obscure. Its decreasing rate suggests that the rabbit cerebellum pursue its growth (and structural plasticity) for extended peripuberal-young/adult periods.

These results obtained in lagomorphs show that remarkable differences may exist in mammals, perhaps requiring further comparative re-examination of postnatal cerebellar development by taking into account different functional aspects. Little is known about which factors determine the timing of the onset of walking, which represents a fundamental milestone in motor development of mammals (altricial vs. precocial mammals; Sanchez-Villagra and Sultan, 2001). Hoofed animals start walking within hours after birth, both rodents and small carnivores require days or weeks, and non-human primates take months (approximately 1 year in humans) to achieve this locomotor skill (Garwicz et al., 2009).

Striatal Adult Neurogenesis

Although different degrees of cell proliferation have been described in the adult striatum of some mammals (see above), full demonstration that the genesis of new neurons can occur spontaneously in this brain region has been provided in lagomorphs. Clusters of newly generated cells do exist in the nucleus caudatus of the rabbit (Luzzati et al., 2006). These cells co-express PSA-NCAM and doublecortin, and form small chain-like structures which have been shown to be independent from the adjacent SVZ by the use of intraventricular cell tracer injections and cultured explants (Luzzati et al., 2006). This spontaneous genesis is attributable to clusters of proliferating cells located within the striatal parenchyma. As in other adult neurogenic sites, PSA-NCAM is transiently expressed on striatal neuronal precursors, being detectable shortly after cell proliferation and disappearing in the late phases of neuronal differentiation into calretinin+ interneurons, herein occurring within 2 months (Luzzati et al., 2006).

Unlike other examples of structural plasticity in rabbit, whose existence is limited to a delayed postnatal period (e.g. anterior parenchymal chains and see below), the occurrence of spontaneous, local striatal neurogenesis has been consistently observed in fully adult animals. Nevertheless, the survival of newly born striatal neurons after 2 months is limited to 1% of the initial BrdU+ cell population, thus indicating the rabbit striatum as a favourable environment for genesis rather than for survival of newly born cells.

Gliogenesis

Another intriguing aspect of plasticity in the adult CNS tissue involves parenchymal glial progenitors which are still capable of cell division during adulthood (reviewed in Dawson et al., 2003; Nishiyama et al., 2009; Boda and Buffo, 2010; Bonfanti, 2013). Most of these progenitors display neural developmental markers of the glial lineage, express a chondroitin sulfate proteoglycan (Nerve/glial antigen 2, Ng2; referred to as Ng2+ cells; Stallcup, 1981),

and are committed to the oligodendrocyte lineage (Nishiyama et al., 2009). The Ng2+ cells are generally considered as synantocytes (Butt et al., 2005) or polydendrocytes (Nishiyama, 2007), endowed with multiple functions in physiology and pathology which are still far from being utterly elucidated. A proportion of these cells persist in the adult in a phenotypically immature form (Dawson et al., 2003; Nishiyama, 2007; Trotter et al., 2010), most of which do continue to proliferate throughout life, thus being considered the main cycling population of the mature mammalian CNS (Simon et al., 2011).

The widespread location of these progenitor cells within the white and grey matter of all brain and spinal cord regions makes them extremely promising as an endogenous source for repair. Yet, in spite of intense investigation carried out during the last decade, such progenitors remain largely obscure in their identity and physiology, due to a scarce availability of stage-specific markers. In particular, what appears difficult is the distinction between real cell populations and various differentiation stages of the same population. We recently focused on a subset of multipolar, polydendrocyte-like cells we found in the rabbit cerebellum (Ponti et al., 2008; Crociara et al., 2013; Figure 6 E). We called these elements mMap5 cells since they express the microtubule associated protein 5 (Map5), which is known to be present in most neurons (Schoenfeld et al., 1989; Riederer, 2007). These cells show a morphology (ramified, multipolar) and a molecular signature (e.g., Olig2 expression) reminiscent of synantocytes/polydendrocytes, and some of them are newly generated within the mature cerebellar parenchyma (Ponti et al., 2008). The Map5 molecule (Riederer et al., 1986; also referred to as Map-IB, MaplX, or Mapl.2), belongs to a family of large and fibrous microtubule associated proteins (Maps) and shows a very wide range of expression in the CNS. Map5 is the first Map detectable in neurons of the developing nervous system, expressed at high levels in growing axons/growth cones and usually downregulated after cessation of axonal growth (reviewed in Riederer, 2007). Nevertheless, the protein remains expressed in the whole CNS during adulthood, its phosphorylated form reaching high levels within some regions endowed with plasticity, or under conditions that elicit axonal/synaptic plasticity in relation to physiological conditions and in response to injury (Riederer, 2007). We characterized the morphology, phenotype, regional distribution, proliferative dynamics, and stage-specific marker expression of these cells in the rabbit and mouse CNS (Crociara et al., 2013).

We showed that mMap5 cells can be better visualized in rabbit than in mouse, what probably accounts for the fact they were not described in vivo for long time. In mice, mMap5 cells were never found to co-express the Ng2 antigen. They appear to be a population of glial cells sharing features but also differences with Ng2+ progenitor cells. We showed that mMap5 cells are newly generated, postmitotic parenchymal elements of the oligodendroglial lineage, thus being a stage-specific population of polydendrocytes (Crociara et al., 2013). Interestingly, the number of mMap5 cells is progressively reduced in the brain of adult/old animals, but can increase in neurodegenerative and traumatic conditions (Crociara et al., 2013).

The occurrence of mMap5 cells was also assessed in other mammalian species, including guinea pig, cat, sheep, monkey and human.

Conclusion

In this chapter, some intriguing processes of structural plasticity specifically existing in rabbits have been reported and compared with our knowledge in other mammals. On the whole, the rabbit brain is characterized by the following features: i) the existence of local, parenchymal neurogenesis within the striatum throughout life; ii) the persistence of streams of newly generated neuroblasts reaching the frontal cortex during the juvenile period; iii) the persistence of a transitory germinal layer (subpial layer, SPL) on the cerebellar surface, extending the post-natal EGL beyond puberty; iv) the occurrence of post-puberal and young/adult genesis of interneurons within the cerebellar cortex; v) the presence of an SVZ architecturally different from that of rodents and somehow similar to that of humans.

Most of these processes are examples of 'protracted' neurogenesis, thus extending postnatally embryonic neurogenesis (see Figure 5). Rather than a singular event that suddenly appears during adulthood, adult neurogenesis has long been recognized as the continuation of postnatal neurogenic activity. During the first postnatal weeks, significant cellular changes occur within the germinal layer-derived neurogenic sites: SVZ and dentate gyrus (see for example Tramontin et al., 2003; Peretto et al., 2005) and cerebellar granule cells are generated by the postnatal EGL. Yet, the dynamics of neurogenic processes in the peripuberal and adult rabbit cerebellum are strikingly different from those described in rodents and other mammalian species studied so far (Ponti et al., 2006a, 2008). The production of new cell progenitors, including neuronal precursors, does not cease after the end of granule cell genesis, but continues at remarkable rates up to and beyond puberty, although progressively decreasing with age. Thus, the rabbit cerebellar cortex could represent a permissive environment for widespread parenchymal neurogenesis, as the frontal cortex seems to represent for the anterior parenchymal chains. In mammals, the first postnatal weeks are critical as the brain growth rate is maximal, and changes during this period can have a great impact on overall brain function later in life. In parallel, clinically relevant dysregulations can occur during this postnatal period, and such changes can have an impact on cognitive function later in life (Kuhn and Blomgren, 2001). For its peculiar features in terms of protracted neurogenesi the rabbit could be a good experimental model for studying the neurodevelopmental aspects of adult neurogenesis.

In addition, local, parenchymal cell progenitors capable of generating neurons are present within the rabbit striatum througout life (Luzzati et al., 2006), indicating that in lagomorphs constitutive parenchymal neurogenesis can persist in different CNS regions. In that perspective, some regions of the rabbit CNS could be considered atypical in mammals. What it is not yet clear, at present, is whether an 'atypical' niche is required for the activation of resident (quiescent) parenchymal progenitors. Other than investigating the quality of stem/progenitor cells in the perspective of cell transplant or induced local activation, maybe should be also important to understand more about the local tissue environment in which they live.

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