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New scenarios for neuronal structural plasticity in non-neurogenic brain parenchyma: The case of cortical layer II immature neurons

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Abstract

The mammalian central nervous system, due to its interaction with the environment, must be endowed with plasticity. Conversely, the nervous tissue must be substantially static to ensure connectional invariability. Structural plasticity can be viewed as a compromise between these requirements. In adult mammals, brain structural plasticity is strongly reduced with respect to other animal groups in the phylogenetic tree. It persists under different forms, which mainly consist of remodeling of neuronal shape and connectivity, and, to a lesser extent, the production of new neurons. Adult neurogenesis is mainly restricted within two neurogenic niches, yet some gliogenic and neurogenic processes also occur in the so-called non-neurogenic tissue, starting from parenchymal progenitors. In this review we focus on a population of immature, non-newly generated neurons in layer II of the cerebral cortex, which were previously thought to be newly generated since they heavily express the polysialylated form of the neural cell adhesion molecule and doublecortin. These unusual neurons exhibit characteristics defining an additional type of structural plasticity, different from either synaptic plasticity or adult neurogenesis. Evidences concerning their morphology, antigenic features, ultrastructure, phenotype, origin, fate, and reaction to different kind of stimulations are gathered and analyzed. Their possible role is discussed in the context of an enriched complexity and heterogeneity of mammalian brain structural plasticity.

Abbreviations

BrdU, 5-bromo-2'-deoxyuridine; CNS, central nervous system; CAMKII, Ca(2+)/CaM-dependentproteinkinase II; CNGA-3, cyclic nucleotide-gated ion channel-3; DCX, doublecortin; DLL, pan distalless; GABA, γ-aminobutyric acid; GAD, glutamic acid decarboxylase; GFAP, glial fibrillar acidic protein; GFP, green fluorescent protein; MAP-2, microtubuleassociated protein-2; NeuN, neuronal nuclear antigen; Ng2, nerve/glial antigen 2 proteoglycan; NMDA, N-methyl-d-aspartate; NR1, subunit 1 of the NMDA receptor; OPCs, oligodendrocyte progenitor cells; p-CREB, phosphorylated cAMP response element-binding protein; PSA-NCAM, polysialylated form of the neural cell adhesion molecule; SGZ, subgranular zone; SVZ, subventricular zone; ST8SiAII, ST8 alpha-N-acetyl-neuraminide alpha-2,8-sialyltransferase 2; ST8SiAIV, ST8 alpha-N-acetyl-neuraminide alpha-2,8-sialyltransferase 4; Tbr1, T-box brain-1; TUC4, TOAD/Ulip/CRMP-4; TuJ1, class III beta-tubulin

1. Introduction

Plasticity is the ability to make adaptive changes related to the structure and function of a system. Such capability is of paramount importance in the nervous system, which is devoted to dynamically interact with the internal and external environment. Further knowledge of neural plasticity physiological role(s) also draws interest for regenerative medicine, in the perspective of modulating plastic changes to foster repair within the damaged nervous tissue.

Due to its heterogeneity, plasticity is one of the most often used, yet most poorly defined terms in Neuroscience. In this review we will restrict our interest to structural plasticity, by referring to all types of changes, which modify the shape and structure of the central nervous system (CNS; Bonfanti, 2006 and Theodosis et al., 2008) and then focusing on a population of immature neurons in the layer II of certain regions of the adult cerebral cortex.

Structural plasticity can occur in different forms and for this reason it has become a very wide field of investigation. Although a highly conserved feature in evolution, structural plasticity shows striking quantitative/qualitative differences among animal species. The situation of substantial 'general plasticity' and cell renewal existing in the oldest living metazoans is strongly reduced in vertebrates (Koizumi and Bode, 1991), although some fish, amphibians and reptiles still exhibit a great neurogenic potential and good CNS regenerative capability (Sirbulescu and Zupanc, 2010, Endo et al., 2007 and Lopez Garcia et al., 2002). In birds and mammals a transition between regeneration permissive and non-permissive stages occurs soon after birth (Whalley et al., 2009). Hence, in the large-sized/architecturally-complex brain of mammals, structural plasticity is a compromise established between a need for neural circuit invariability and the requests for its adaptive modification, which suggests that most of such plasticity deals with pre-existing neural elements (reviewed in Bonfanti, 2011). This is reasonable, since a fundamental feature of mature CNS parenchyma 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 neural networks are initially sculpted by experience during the sensitive periods and then they are stabilized at different postnatal developmental stages (reviewed in Spolidoro et al., 2009). The architectural specificity is 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 and Bonfanti, 2006).

On these bases, the discovery of neural stem cells (Reynolds and Weiss, 1992) and adult neurogenesis in the mammalian brain (Lois and Alvarez-Buylla, 1994, Gould, 2007 and Kempermann et al., 2004) were viewed as a breakthrough in neurobiology, leading to hypothesize a regenerative medicine able to heal traumatic, vascular and neurodegenerative pathologies in our nervous system (reviewed in Arenas, 2010 and Lindvall and Kokaia, 2010). Yet, no substantial, efficacious therapies based on cell replacement are at present available in the CNS. Adult mammalian neurogenesis is confined within two small brain regions – the forebrain subventricular

zone (SVZ) and the hippocampal subgranular zone (SGZ) – which are germinal layer-derived sites under the control of a highly regulated microenvironment (Gage, 2000 and Kriegstein and Alvarez-Buylla, 2009). As a consequence, outside the two privileged areas harbouring neural stem cells, the mammalian nervous system is largely made up of non-renewable, non-regenerative tissue (Sohur et al., 2006, Gould, 2007, Ponti et al., 2010, Bonfanti, 2011 and Bonfanti and Peretto, 2011). Yet, recent reports of progenitor cell populations capable of proliferation in many brain, cerebellum, and spinal cord regions, suggest that a slow glial cell renewal (and also genesis of young neurons in some mammalian species; see below) can also occur physiologically (Horner et al., 2002, Dayer et al., 2005, Luzzati et al., 2006 and Ponti et al., 2008; reviewed in Nishiyama et al., 2009 and Bonfanti and Peretto, 2011) and/or after injury (Ohira, 2010) in the so-called non-neurogenic parenchyma.

All these forms and 'levels' of plasticity, which have been progressively revealed during the last decades, have increased the complexity in the landscape of mammalian brain structural plasticity.

1.1. Heterogeneity of plasticity in the so-called non-neurogenic tissue

The prevalent view in modern neurobiology considers the non-neurogenic mammalian tissue as intrinsically plastic under the profile of synaptic connections (Holtmaat and Svoboda, 2009, Bavelier et al., 2010, Chen and Nedivi, 2010 and Fu and Zuo, 2011; see Table 1), which can structurally change connectivity without changing the number and type of neurons. On the other hand, evidences for adult parenchymal gliogenesis and neurogenesis can increase the heterogeneity of such plasticity by introducing new structural modifications through the addition of new cellular elements (Bonfanti and Peretto, 2011).

Table 1

Different types of structural plasticity in the mammalian CNS.

Structure	Plasticity	Phys	Path	PE	NB	References
	Synapse formation and elimination	U	U	U		Holtmaat and Svoboda (2009),
	Changes in synaptic connectivity	U	U	U		Bavelier et al. (2010), Chen and Nedivi (2010), Fu and Zuo (2011)
Dendrites	Protrusions from dendritic shafts (filopodia)a	U		U		
	Spine formation and elimination	U	U	U		
	Dynamic branches of cortical interneurons	U	U	U		
	Dendritic sprouting	U	U	U		
	Dendritic pruning	U	U	U		
	Spine loss and shaft atrophy		U	U		
Axons	Axonal sprouting	U	U	U		
	Terminaux and en passant boutons changes	U	U	U		
	Axonal regeneration		U	U		
Neurons	Whole cell shape modificationsb	U			U	Theodosis et al. (2008)
	Adult neurogenesis (neurogenic sites)	U			U	Gage (2000)
	Adult neurogenesis (parenchyma)	U			U	Bonfanti and Peretto (2011)
	Differentiation of preexisting immature neurons (cerebral cortex layer II)	U	U	U		Gomez-Climent et al. (2008, 2011b)

	Reactive neurogenesis from neurogenic sites		U		U	Kokaia and Lindvall (2003)
	Reactive neurogenesis from parenchyma		U		U	Ohira (2010)
Glial cells	Whole cell shape modificationsb	U		U		Theodosis et al. (2008)
	Structural modifications at the synapses	U	U	U		Perea et al. (2009)
	Trophic/instructive role at the synapses	U	U	U		Dityatev and Rusakov (2011)
	Reactive astrogliosis (swelling)		U	U		Sofroniew (2009), Boda and Buffo (2010)
	Reactive astrogliosis (astrogliogenesis)		U	U	U	
	Proliferation of other glial progenitors		U		U	
Networks	Rewiring of neuronal circuits	U	U	U	Uc	Chen and Nedivi (2010)

Phys, Physiological (homeostatic) plasticity; Path, Reactive (induced) plasticity after pathological conditions/injury; PE, pre-existing cells; NB, newly born cells.

a Mostly considered as restricted to development.

b Neuronal-glial plasticity.

c Integration of new neurons demonstrated in neurogenic sites, not yet in the parenchyma.

1.1.1. Structural plasticity affecting pre-existing elements

In addition to the striking plasticity existing in early life, some experience-dependent structural changes also persist during adulthood (Sale et al., 2008 and Holtmaat and Svoboda, 2009). Although the large-scale organization of axons and dendrites is remarkably stable for most of the animal lifespan, a subset of synaptic structures can display cell type-specific, experience-dependent structural plasticity in terms of formation/elimination of synapses (Holtmaat and Svoboda, 2009, Chen and Nedivi, 2010 and Fu and Zuo, 2011; see Table 1). Axonal sprouting occurs during spatial learning (Ramirez-Amaya et al., 2001), and in response to environmental enrichment (Galimberti et al., 2006). Structural plasticity involving pre-existing cells and circuits can also occur after a lesion in the form of compensatory events, i.e. synaptic formation/elimination and axonal sprouting/pruning (see Table 1). For example in mice, after stroke, dendrites become plastic in the vicinity of a cerebral infarct and these structural changes might provide a substrate for the long-term functional changes in the representational cortical maps (Brown et al., 2009). Due to the extreme heterogeneity of CNS neural tissue and circuitries, the outcomes of lesion-induced compensatory plasticity would be highly variable, exiting into a wide range of events depending on the specific site and type of injury (Darian-Smith and Gilbert, 1994, Chen et al., 2002 and Dancause et al., 2005).

A further level of structural plasticity consists of changes involving the entire cell morphology (Table 1). This can be observed in certain areas of the mature CNS wherein specific cell populations retain molecules usually expressed during development. The polysialylated form of the neural cell adhesion molecule (PSA-NCAM) is a prototypical example (Bonfanti, 2006 and Rutishauser, 2008; see Box 1). This 'repulsive' adhesion molecule is involved in the overall neuro-glial structural remodeling affecting astrocytes and magnocellular neurons of some hypothalamic nuclei under physiological stimulation linked to parturition, lactation, and osmotic regulation (Theodosis et al., 2008).

Box 1.

PSA-NCAM and DCX as players in different forms of plasticity

Molecules with multiple roles

The neural cell adhesion molecule (NCAM) is a member of the immunoglobulin superfamily of adhesion molecules. In the CNS, it exists in three forms of different size (NCAM 180, 140, 120), all of which can host 8–100 monomers of polysialic acid (PSA). The carbohydrate is added posttranslationally to the protein extracellular domain through two Golgi-associated polysialyltransferases, thus influencing its adhesive and other functional properties through a steric impediment for homophilic and heterophilic interactions (see Sandi, 2004, Bonfanti, 2006 and Rutishauser, 2008; for review). Doublecortin (DCX) is a microtubule-associated protein expressed by migrating neuroblasts in both developing and adult mammals (Francis et al., 1999, Gleeson et al., 1999 and Brown et al., 2003). First detected in mice at embryonic day 10.5, DCX plays a crucial role for microtubule stabilization (Gleeson et al., 1999), nuclear translocation during neuronal migration (Koizumi et al., 2006), and growth cone dynamics (Burgess and Reiner, 2000).

PSA-NCAM and DCX became widely used markers in neurobiology in coincidence with the starting of intense investigations on adult neurogenesis (Bonfanti and Theodosis, 1994 and Nacher et al., 2001a). Indeed, both molecules are heavily expressed in newly generated neuronal precursors, in neurogenic (Bonfanti and Theodosis, 1994, Rousselot et al., 1995 and Brown et al., 2003) and non-neurogenic regions (Luzzati et al., 2006 and Ponti et al., 2008). PSA-NCAM is expressed soon after the genesis of neuroblasts, then being maintained during their migration and first phases of differentiation (Bonfanti and Theodosis, 1994 and Rousselot et al., 1995). Similarly, DCX expression is induced in fast-dividing neuronal precursors, persists for about 30 days, and is terminated as a consequence of neuronal maturation (Brown et al., 2003), frequently associated with PSA-NCAM (Nacher et al., 2001a, Brown et al., 2003, Bonfanti, 2006, Luzzati et al., 2006 and Ponti et al., 2008). These characteristics led sometimes to the misunderstanding that PSA-NCAM and DCX can be specific markers for newly generated cells, although in the CNS they are not restricted to these cell populations (Bonfanti, 2006 and Gomez-Climent et al., 2011a). Indeed, PSA-NCAM persists in the adult in a spatially restricted way, even in the neuropil of many regions, contributing to synaptic plasticity, neuronal–glial structural remodeling, cell migration, cell differentiation (Bonfanti, 2006, Theodosis et al., 2008, Bonfanti and Theodosis, 2009 and El Maarouf and Rutishauser, 2010). In addition, abundant PSA-NCAM is present on neurons that are not newly generated, e.g., in layer II immature neurons that are the main topic of this review, and in mature interneurons of the cerebral cortex (Gomez-Climent et al., 2008, 2011). Similarly, DCX expression has been described in a wide number of cells of the cerebral cortex that have not been shown to be newly generated (Verwer et al., 2007, Xiong et al., 2008, Luzzati et al., 2008, Cai et al., 2009 and Bloch et al., 2011), among which are the neurons in layer II (Gomez-Climent et al., 2008).

In conclusion, PSA-NCAM and DCX can be frequently co-expressed in cells that take part in structural plasticity occurring in non-neurogenic contexts. PSA-NCAM/DCX co-expression is frequently found in non newly generated neurons of the mammalian cerebral cortex, which are a sterotypical example of the heterogeneous roles these molecule might play in different biological processes: from neurogenesis and the maintenance of undifferentiated states to intriguing, atypical differentiated states, with possible overlapping of these aspects.

Association of cellular markers with biological processes: heterogeneous relationships.

Another reason, which could explain some misunderstandings in developmental neurobiology, resides in the indistinct links existing sometimes between cells and markers. Cell markers are used to identify specific cell types/lineages and/or differentiation stages. In the past, the main neural cell types (neurons, astrocytes, oligodendrocytes) were defined on the basis of their morphology and expression of a restricted set of cellular markers (e.g., β-tubulins, GFAP, MBP). With the advent of the studies on adult neurogenesis (and on stem cells in general) further elements of complexity emerged, since different types of neural progenitor cells and the various differentiation stages of their progeny do coexist within the mature tissue (Kimelberg, 2004 and Gritti and Bonfanti, 2008). In other words, when considering stem/progenitor cells the concept of cell-specific marker falls into a relatively undefined domain, in which the transient expression of a given transcript or protein (at both the temporal and spatial levels) might hamper an unequivocal definition. In addition, glial and neuronal lineages can be intriguingly overlapping. Two examples for all: the asymmetric division of radial glia cells giving rise to neurons (Noctor et al., 2001), and the possible genesis of neurons in the piriform cortex starting from Ng2+ cells (Guo et al., 2010). Thus, in brain structural plasticity, the changes in cell morphology occur in parallel to 'phenotypic' plasticity, as a product of different developmental stages that affect the 'identity' of the cells. The subsequent steps that a newly generated cell undergoes from its birth to its final fate are a sequence (actually, a gradient) of biological changes involving its genetic transcription, molecular composition, and morphology. Theoretically, the visualization of such stages should be accomplished by cell markers associated with each one of them, yet, in the reality, most of them are not so specific since they are partially overlapping in time windows and/or neuronal/glial cell types, CNS regions, animal species. Examples are given by the microtubule-associated protein 5 (MAP5), which can be expressed in both neurons and glia (Ponti et al., 2010), or DCX, which in humans is present in both neurons and astrocytes (Verwer et al., 2007 and Bloch et al., 2011).

A possible explanation for the ambiguity and heterogeneity of markers with respect to biological processes resides in the fact that many molecules are involved in multiple tasks and can be expressed in multiple, different contexts since they subserve multiple, different functions. Hence, only the knowledge of the transcriptome and even proteome of single cells will be able eventually to characterize the type of cell and to give hints on functions.

1.1.2. Structural plasticity involving newly-added cellular elements

Unlike adult neurogenesis in the SVZ and SGZ, which is well characterized and rather constant through different mammals, different 'types' of neurogenic processes may occur in the adult CNS parenchyma, depending on the animal species, age, and physiological/pathological states (Bonfanti and Peretto, 2011). In rabbits, newly generated neurons are spontaneously produced in specific regions of the adult brain starting from local, parenchymal progenitors. In the rabbit caudate nucleus, newly formed neuroblasts form longitudinally arranged, doublecortin (DCX) and PSA-NCAM immunoreactive striatal chains similar to the SVZ chains (Luzzati et al., 2006). These neuroblasts are generated from clusters of proliferating cells which express the astroglial marker brain lipid binding protein (BLBP; Anthony et al., 2004), and about 1/6 of them differentiate into calretinin striatal interneurons. Always in rabbits, in sharp contrast with our common knowledge concerning the CNS of other mammals, a remarkable genesis of cells is detectable in the peripubertal, and to a lesser extent, adult cerebellar cortex (Ponti et al., 2008). Systemically-

administered BrdU detected at different post-injection survival times (up to two months) reveals newly generated PSA-NCAM+/DCX+/Pax2+ interneurons of neuroepithelial origin homogeneously distributed in the cerebellar cortex. Thus, in the rabbit striatal and cerebellar parenchyma new neurons are generated independently from persisting germinal layers, although their role in the adult neural circuits remains obscure (reviewed in Bonfanti and Peretto, 2011). Various types and degrees of parenchymal neurogenesis have also been described in rodents, although with different outcomes (Dayer et al., 2005 and Kokoeva et al., 2005).

In addition to the parenchymal genesis of neurons, local, glia-like progenitors retaining some proliferative capacity are also present in wide areas of the mature CNS (Horner et al., 2002, Butt et al., 2005, Ponti et al., 2008, Nishiyama et al., 2009 and Trotter et al., 2010). The largest class of these cells were described in the adult mouse and express the nerve/glial antigen 2 proteoglycan (Ng2, Horner et al., 2002 and Dawson et al., 2003). They are also called synantocytes (Butt et al., 2005) or polydendrocytes (Nishiyama et al., 2009), and are morphologically, antigenically, and functionally distinct from mature astrocytes, oligodendrocytes, and microglia. Some of these cells are oligodendrocyte progenitor cells (OPCs) that can generate oligodendrocytes in the mature CNS, thus potentially serving as the primary source of remyelinating cells in demyelinated lesions (Dubois-Dalcq et al., 2008). Yet, in spite of their proliferative capacity and potentialities in vitro, the Ng2+ cells usually do not contribute to neurogenesis in vivo (reviewed in Boda and Buffo, 2010 and Trotter et al., 2010). On the whole, adult neurogenesis in terms of genesis of new neurons is restricted to neurogenic sites (with some exceptions, e.g., rabbits), whereas gliogenesis is prevalent in non-neurogenic areas. If neurogenic activity is conceived in a more extensive way, including the genesis of neurons and glial cells (that is the notion of embryonic neurogenesis), then the concept of non-neurogenic tissue is even more questionable, since a low rate of widespread gliogenesis involving a slow renewal of oligodendrocytes and astrocytes has been substantially proven (Horner et al., 2002, Dawson et al., 2003, Nishiyama et al., 2009, Boda and Buffo, 2010 and Trotter et al., 2010).

As for plasticity of pre-existing structures, various examples of 'reactive' neurogenesis can occur after different types of CNS injury. Beside reactive neuro/gliogenesis from adjacent neurogenic sites (Arvidsson et al., 2002, Kokaia and Lindvall, 2003 and Thored et al., 2006), some neurogenic/gliogenic processes can also start from local, parenchymal progenitors after different lesion paradigms/pathological states (Komitova et al., 2006, Ohira et al., 2009 and Vessal and Darian-Smith, 2010). 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). The occurrence of lesion-induced neurogenic/gliogenic responses indicates that the brain has an endogenous regenerative potential (Nakatomi et al., 2002, Nishiyama et al., 2009 and Ohira et al., 2009), which in most cases cannot manifest in a successful way, since the mobilization of neural progenitors is insufficient and inefficient to grant CNS healing, due to non-permissive aspects linked to anatomical, molecular and evolutionary constraints (Bonfanti, 2011). In this context, it is worth mentioning that while neurons born in adult SVZ-SGZ neurogenic sites actually integrate in some brain regions (complete neurogenesis), those generated within the parenchyma have not been shown to definitively enter the neuronal

circuitries (incomplete neurogenesis), their ultimate fate and function remaining obscure (Bonfanti and Peretto, 2011).

1.1.3. Further elements of heterogeneity

The concepts summarized above indicate that many types of plasticity involving remodelling of pre-existing structures (synapses, axons, dendrites, whole cell shape) and newly formed elements (parenchymal neurogenesis) do coexist and overlap in the so-called non-neurogenic mammalian CNS parenchyma. Such an overlapping makes more and more complex the heterogeneity of brain structural plasticity, whose mechanisms remain largely unexplored. In particular, with respect to classic SVZ and SGZ neurogenesis, the parenchymal genesis of new cells has different outcomes, apparently being not directed to the replacement of neurons (Bonfanti and Peretto, 2011). Thus, difficulties encountered in analyzing parenchymal plasticity are not only technical (many claims of neurogenic processes were subsequently refuted because not sustained by experimental evidence), but linked to processes differing from well characterized types of plasticity, such as synaptic plasticity or complete adult neurogenesis (see Box 1).

The piriform cortex is one of those regions, in which results reported by different researchers are quite controversial (see for example, Bernier et al., 2002, Pekcec et al., 2006, Shapiro et al., 2007a, Shapiro et al., 2007b and Gomez-Climent et al., 2008). Since long time, this cortical region is known to harbor a population of neurons immunoreactive for PSA-NCAM and DCX (Bonfanti et al., 1992, Seki and Arai, 1991, Luzzati et al., 2008, Gomez-Climent et al., 2008, Nacher et al., 2001a and Nacher et al., 2002a), which are two universally recognized markers for neuronal structural remodeling and also highly expressed in newly generated neuronal elements. Yet, PSA-NCAM and DCX cannot be considered as specific markers for neurogenesis (see Box 1), and deeper investigations have mostly denied the existence of adult neurogenesis in the piriform cortex of several species (Luzzati et al., 2003, Luzzati et al., 2008 and Gomez-Climent et al., 2008; see below). In alternative, recent studies have shown that this brain region contains a population of immature, non-newly generated neurons (Gomez-Climent et al., 2008), which represents a new element of structural plasticity to be discussed herein.

2. Immature, non-newly generated neurons in the adult rodent brain

Both in embryonic and adult neurogenesis, after being generated by progenitor cells, immature neurons express various molecules related to developmental events such as neuronal migration, neurite extension and synaptogenesis. These molecules belong to different protein families, such as transcription factors, cytoskeletal or cytoskeletal-associated proteins or cell adhesion molecules, among others. Their expression is in most cases transitory and ceases after the neurons have reached their position in the neural parenchyma, establishing and receiving appropriate connections. Consequently, during prenatal and early postnatal development, many neurons in

the CNS express these "neurodevelopmental" molecules, among which the most common are PSA-NCAM and DCX (see Box 1). Such an expression can also be detected in certain cell populations of the adult CNS (reviewed in Bonfanti, 2006). As expected, they are expressed transiently by immature, newly generated neurons in the dentate gyrus and the olfactory bulb, where new neurons are continually incorporated. Similarly, PSA-NCAM and DCX are present in newly generated neurons of the adult rabbit striatum and cerebellum.

The simultaneous expression of many "neurodevelopmental" molecules can also be found in a population of immature neurons in the layer II of certain regions of the adult cerebral cortex. Here we will focus on recent evidence obtained regarding the distribution, structure, phenotype and origin of these cells, then discussing their putative fate and function.

2.1. Distribution and morphology of immature neurons in cortical layer II

The analysis of PSA-NCAM and DCX expression in the adult rat cerebral cortex has revealed that they are found in a large population of cells in the layer II of the piriform and lateral entorhinal cortices. Scattered cells were also found in the layer II of the perirhinal cortex and the most ventral region of the agranular insular and ectorhinal cortices (Bonfanti et al., 1992, Gomez-Climent et al., 2008, Nacher et al., 2001a, Nacher et al., 2002a and Seki and Arai, 1991; Fig. 1). A similar distribution was found in mice (Phillips et al., 2006, Shapiro et al., 2007b and Nacher et al., 2010). In mammals with larger cerebral cortices these cells show a wider distribution, being also found in various neocortical areas, preferentially in associative regions (Fig. 1). In rabbits and guinea pigs DCX+/PSA-NCAM+ cells can be found in layers II and upper III of the piriform, perirhinal and entorhinal cortices, as well as in the amygdaloid-piriform transitional region. In the neocortex of these animals these cells can be found in the somatosensory cortex and different regions of the insula, among others (Bonfanti, 2006, Luzzati et al., 2008 and Xiong et al., 2008). In adult cats, DCX and PSA-NCAM expressing cells in layers II and upper III, can be found more widely dispersed in the cerebral cortex, being especially abundant in the entorhinal cortex and in ventral portions of the frontal and temporoparietal lobes, but relatively scarce in dorsal regions, such as the primary visual areas (Cai et al., 2009 and Varea et al., 2011). A similar widespread distribution has been described in non-human primates, where these cells are also more common in associative rather than in primary cortical regions (Cai et al., 2009 and Zhang et al., 2009). The presence of a band of PSA-NCAM expressing cells similar to that found in layer II in rodents can be observed at least in the entorhinal cortex of human infants (Ni Dhuill et al., 1999) and a recent report has described the presence of DCX expressing cells in the upper border of cortical layer II of humans of different ages (Cai et al., 2009).
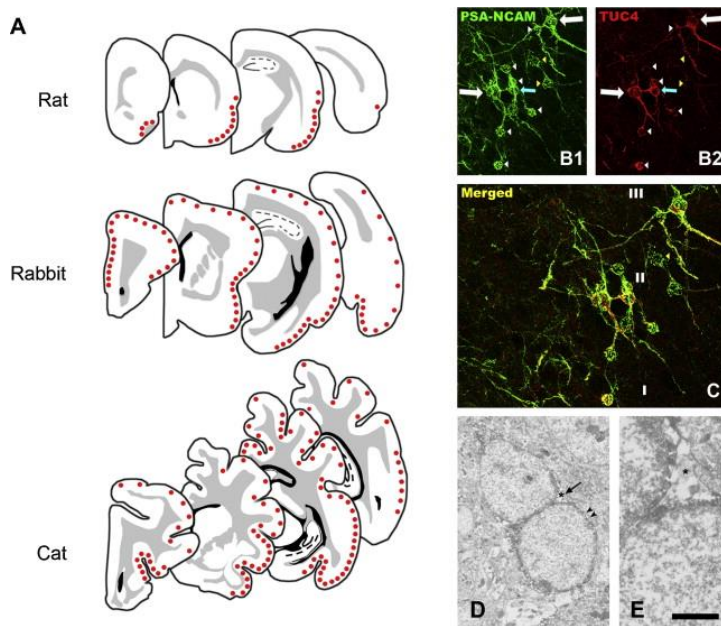
Fig. 1.

Distribution and morphology of immature neurons in cortical layer II. (A) Distribution of PSA-NCAM immunoreactive cells in cortical layer II of adult mammals. The dots represent their density. Note the wider distribution of these cells in the cerebral cortex of rabbits and cats, not restricted to paleocortical regions. (B and C) Confocal microscopic images of PSA-NCAM (B1) and TUC4 (B2) immunoreactive cells in the rat paleocortex layer II. White arrows indicate double-labeled semilunar-pyramidal transitional neurons. White arrowheads indicate double-labeled tangled cells. The blue arrow indicates a cell with intermediate characteristics. Yellow arrowheads indicate PSA-NCAM expressing tangled cells lacking TUC4 expression. (D and E) Electron micrographs of CNGA-3 immunolabeled cells in the rat piriform cortex layer II. The couple of somata in panel E are intimately associated and show a scarce but intensely labeled cytoplasm. Panel E offers a higher magnification of the region indicated by an arrow in D. Note the extracellular space swelling (asterisk) and an astroglial lamella located closely to the plasma membrane (arrowheads). Scale bar: 37.5 μm for B1 and B2, 50 μm for C, 5 μm for D and 2,5 μm for E.

Despite these differences in the overall distribution of PSA-NCAM/DCX expressing cells between species, the piriform or, more generally, the olfactory cortex are the cortical regions where these cells are consistently more abundant. These areas are three-layered cortical structures which receive major inputs from the olfactory bulb via the lateral olfactory tract. The axons branch and terminate on dendrites of superficial layer I, superficial somata in layer II and deep somata in layer III (see Wilson, 2001 for review, and Fig. 2). Direct reciprocal connections exist between the anterior and posterior parts of the piriform cortex and some prefrontal areas (Datiche and Cattarelli, 1996), as well as projections to the amygdala and entorhinal and perirhinal cortices (Johnson et al., 2000).
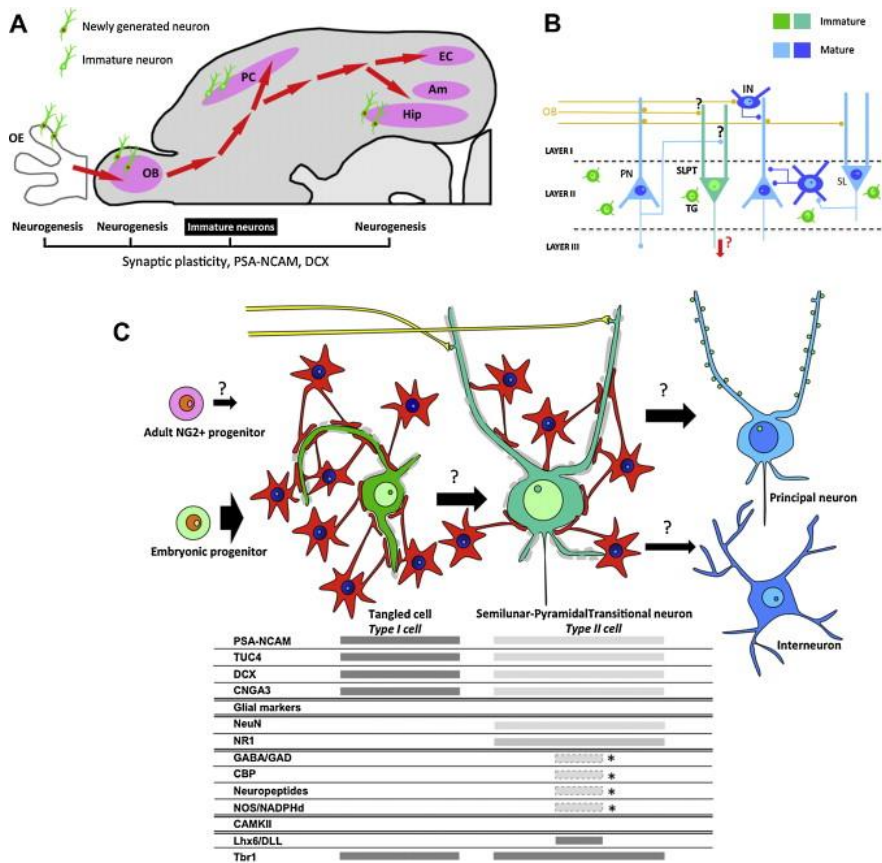
Fig. 2.

(A) Neural plasticity that allows dynamic processing of odors is present nearly ubiquitously in the olfactory pathway, from olfactory receptor neurons to the higher-order cortex, ranging from changes in synaptic efficacy to neurogenesis (Wilson et al., 2004). In the brain, several structures are involved in these widely interconnected pathways: the olfactory bulb and the primary olfactory cortex (piriform cortex, PC) consisting of three layered cortical structures (allocortical areas and transitional allo/iso-cortical areas), and the medial temporal lobe (hippocampal formation -Hip-perirhinal and postrhinal cortices). Most of these circuits represent multiple levels (primary sensory, projection and associative) of the same pathway (Wilson et al., 2004 and Wilson and Sullivan, 2011). Am, amygdala; OE, olfactory epithelium; OB, olfactory bulb; EC, entorhinal cortex. (B) Diagram depicting the major neuronal cell types and connectivity in the rodent piriform cortex: tangled cells (TG, light green), semilunar-pyramidal transitional neurons (SLPT, emerald green), pyramidal neurons (PN, light blue), semilunar neurons (SL, light blue), interneurons (IN, dark blue). Projections from the olfactory bulb are represented in yellow. Black question marks on SLPT cells indicate that we still do not know the origin of their scarce synaptic contacts in apical dendrites. Red arrow and question mark indicate that also the target of their axon remains obscure. (C) Phenotype and putative origin/fate of immature neurons in cortical layer II. Two types of cells are found in layer II expressing markers of immature neurons (PSA-NCAM, TUC4, DCX and CNGA3): tangled cells (light green) and semilunar-pyramidal transitional neurons (emerald green). The expression of these markers is usually more intense in the former cell type. Both cell types are covered by astroglial processes (red) and PSA-NCAM molecule (grey). Tangled cells and semilunar-pyramidal transitional neurons do not express markers of glial cells and they express NeuN and NR1, suggesting a neuronal fate. Although some studies have found the expression of molecules normally found in interneurons (GABA/GAD, calcium binding proteins, neuropeptides and nitrinergic markers) in semilunar-pyramidal transitional neurons (dashed bars and asterisks), some others have failed to find substantial numbers of these cells expressing these inhibitory markers. CAMKII a marker of mature principal neurons is also absent from these immature neurons in cortical layer II. The transcription factor Tbr1, expressed by principal neurons of pallial origin is

expressed in most immature neurons of cortical layer II, but a few of them express Lhx6 and DLL, transcription factors exclusively found in interneurons. Tangled cells appear to be in a more immature stage than semilunar-pyramidal transitional neurons and, consequently, the former may differentiate into the latter. Our studies mainly suggest that semilunar-pyramidal transitional neurons may differentiate into principal neurons (light blue), but the differentiation of some of these cells towards interneurons (dark blue) cannot be excluded. Most immature neurons in cortical layer II have been generated from progenitor cells (red) during embryonic development. However, recent studies indicate that some principal neurons in the piriform cortex layer II may arise from NG2 expressing progenitors (pink). Since some tangled cells also express NG2, it is possible that these progenitors may differentiate into tangled cells.

Two main cell populations, which co-express DCX and PSA-NCAM, can be distinguished in the rat cerebral cortex layer II by the size of their somata: small cells (with a soma diameter around 9 μm) and large cells (diameter around 15 μm) (Fig. 1). This classification has been used in rats, guinea pigs and rabbits. Similar cells have been described in cats and non-human primates, although in these species a more heterogeneous morphology appears to exist (Cai et al., 2009, Varea et al., 2011 and Zhang et al., 2009). The morphological characteristics and the terminology of these cells are summarized in Fig. 2B and C.

In rats, the majority of PSA-NCAM+/DCX+ cells are small and show processes with highly irregular trajectories, usually restricted to layer II, although some of these processes with vertical trajectories are also found in layer I. Most of these cells appear frequently associated in clusters (2–5 cells). Initial studies classified these small cells as neurogliaform neurons, although we have revised this terminology recently and have denominated them tangled cells due to their intricate dendritic arborizations, which are always devoid of spines or excrescences (Gomez-Climent et al., 2008). Neurogliaform neurons are mature interneurons, which usually express GABA, GAD and α-actinin (Price et al., 2005), and none of these proteins is expressed by tangled cells (Gomez-Climent et al., 2008).

Large cells usually display one or two long dendrites expanding into layer I, which show occasional bead-like swellings, protrusions resembling thin dendritic spines, or typical spines, and some thin basal processes (Gomez-Climent et al., 2008), which resemble the transient basal dendrites of newly generated granule neurons in the adult hippocampus (Nacher et al., 2001a and Ribak et al., 2004). In certain cases, a thin long basal process resembling an axon can also be observed. These cells show the morphology of an old conserved cell type called "extraverted neurons" (Luzzati et al., 2008). Such a morphology involves a clear predominance of subpial dendrites over basal dendrites, whereas that of a classic pyramidal cell shows a well-developed basal skirt. Using PSA-NCAM immunohistochemistry, some of the larger cells were identified initially as semilunar or pyramidal neurons (O'Connell et al., 1997 and Seki and Arai, 1991). More recent studies have demonstrated that most of these large DCX+/PSA-NCAM+ cells correspond to those described by Haberly as pyramidal-semilunar transitional neurons (Haberly, 1983), although some cells with the morphology of semilunar, pyramidal and fusiform neurons can also be found (Gomez-Climent et al., 2008 and Nacher et al., 2002a).

In a report by Luzzati et al. (2008), a different denomination for PSA-NCAM/DCX cells in layer II has been used: tangled cells correspond to type I and the larger subtypes (e.g., pyramidal-semilunar transitional neurons) correspond to type II. It is, however, important to mention that some cells with characteristics of both tangled/type I cells and semilunar-pyramidal transition/type II neurons can also be found in layer II.

A discrete population of small monopolar and bipolar PSA-NCAM/DCX expressing cells, with short processes oriented vertically, can also be observed in the piriform cortex layer III, the endopiriform nucleus and deep layers of the entorhinal cortex of adult rodents. Some of them can also be found forming aggregates at the ventral end of the external capsule of the corpus callosum. Frequently, these small cells in deep paleocortical layers are located adjacent to long PSA-NCAM immunoreactive vertical processes (Nacher et al., 2001a, Nacher et al., 2002a and Nacher et al., 2010).

2.2. Phenotypic characterization of immature neurons in cortical layer II

Evidence conducting to the classification of a population of cells in the cerebral cortex layer II as immature neurons is based on 3 groups of experimental findings: (1) expression of markers of immature neurons, (2) lack of expression of mature neuronal and glial markers (the expression of markers indicated in points 1 and 2 is summarized in Fig. 2C), (3) ultrastructural characteristics.

2.2.1. Immature neuronal markers

During their development, neurons express a complex set of genes involved in their migration, neurite extension and synaptogenesis. Some of these molecules are exclusively expressed by immature neurons, but most of them can also be found in mature neurons, in which they are probably involved in different plastic events. For this reason, in order to be considered a "bona fide" immature neuron, a cell has to co-express several of these neurodevelopmental molecules.

One of the most widely used marker for immature neurons is PSA-NCAM, because of its involvement in neurodevelopmental processes such as migration, neurite extension and synaptogenesis (Bonfanti, 2006, Gascon et al., 2007 and Rutishauser, 2008). Because of the polysialylation, cells expressing PSA-NCAM show reduced interaction with the surrounding neuropil elements (see Box 1). In the early nineties, Seki and Arai (1991) using an antibody against PSA, described for the first time the presence of a population of cells expressing this molecule in layer II of the cerebral cortex of adult rats. One year later, this population was also described by Dr. Theodosis laboratory (Bonfanti et al., 1992). In the subsequent years, several reports

confirmed the presence of these PSA-NCAM expressing cells in rats (Hayashi et al., 2001, Knafo et al., 2005, Nacher et al., 2002a, Nacher et al., 2004 and Sairanen et al., 2007), mice (van der and Brundin, 2007), guinea pigs (Luzzati et al., 2008 and Xiong et al., 2008), rabbits (Bonfanti, 2006 and Xiong et al., 2008), cats (Varea et al., 2011), non-human primates (Zhang et al., 2009) and infant humans (Ni Dhuill et al., 1999) (Fig. 1).

TUC4, a protein expressed transiently in recently generated neurons (Minturn et al., 1995), was also found in a similar cell population in the piriform, perirhinal and lateral entorhinal cortices layer II of adult rats (Nacher et al., 2000). This molecule belongs to the TOAD/Ulip/CRMP family of proteins, which putatively functions as intracellular signalling mediators that transduce signals related to axonal guidance (Kolodkin, 1998 and Luo et al., 1993).

Cells in the layer II of the cerebral cortex also express DCX, a microtubule associated protein, heavily present in immature neurons (Francis et al., 1999, Friocourt et al., 2003 and Gleeson et al., 1999; see Box 1). These DCX+ cells were initially described in the paleocortex of adult rats (Nacher et al., 2001a). Their presence was later confirmed by other studies in rats (Gomez-Climent et al., 2008, Nacher et al., 2002a, Nacher et al., 2004, Pekcec et al., 2006 and Shapiro et al., 2007a) and mice (Lazic et al., 2007, Phillips et al., 2006, Shapiro et al., 2007a and Shapiro et al., 2007b), and, with a wider distribution, in rabbits (Bonfanti, 2006), guinea pigs (Luzzati et al., 2008 and Xiong et al., 2008), cats (Cai et al., 2009 and Varea et al., 2011), non-human primates (Cai et al., 2009, Zhang et al., 2009 and Bloch et al., 2011) and humans (Cai et al., 2009).

Recent reports have revealed that most, if not all, PSA-NCAM expressing cells in the cerebral cortex layer II of adult rats (Gomez-Climent et al., 2008) and cats (Varea et al., 2011) co-express the cyclic nucleotide-gated ion channel (CNGA-3), which is intensely expressed by migrating neuroblasts of the rostral migratory stream (Gutierrez-Mecinas et al., 2007). These PSA-NCAM+ cells in adult rats also co-express the phosphorylated cAMP response element-binding protein (p-CREB; Gomez-Climent et al., 2008), a molecule expressed transiently in differentiating granule neurons of the adult hippocampus (Nakagawa et al., 2002). However, although in adult mice immature neurons in the dentate gyrus and olfactory bulb express calretinin (Brandt et al., 2003 and Dominguez et al., 2003), this calcium binding protein is not found in PSA-NCAM expressing cells in the paleocortex layer II (Gomez-Climent et al., 2008). DCX+ cells in the layer II of the guinea pig cerebral cortex also express the immature neuronal marker class III beta-tubulin (TuJ1; Xiong et al., 2008). Cells expressing DCX, PSA-NCAM, TuJ1, TUC-4, and the antiapoptotic protein Bcl-2 have also been found in the layer II of the temporal cortex of adult primates (Bernier and Parent, 1998, Bernier et al., 2002 and Zhang et al., 2009).

The individual presence of PSA-NCAM, TUC-4, CNGA-3 or p-CREB is not exclusive of immature neurons in the cerebral cortex: some mature interneurons show PSA-NCAM in regions such as the neocortex and the hippocampus (Gomez-Climent et al., 2011a, Nacher et al., 2002b and Varea et al., 2005); TUC-4 is also found in a subset of cortical oligodendrocytes (Nacher et al., 2000); CNGA3

is also expressed by some mature principal and inhibitory neurons, at least in the olfactory bulb (Gutierrez-Mecinas et al., 2007). p-CREB is intensely expressed by recently generated granule neurons in the adult hippocampus (Nakagawa et al., 2002), but several mature neuronal types also display this transcription factor in the adult cerebral cortex (Thome et al., 2000). Although DCX was thought to be exclusively present in neuronal progenitors and cells committed to the neuronal lineage (Brown et al., 2003, Dayer et al., 2005 and Walker et al., 2007), recent reports described its expression in subpopulations of human cortical astrocytes (Verwer et al., 2007 and Bloch et al., 2011; see Box 1). However, the co-existence of PSA-NCAM, DCX, TUC-4, CNGA-3 and p-CREB in the adult CNS has only been found in immature neurons of the neurogenic regions and in the cerebral cortex layer II.

2.2.2. Mature neuronal and glial markers

The existence of immature neuronal phenotypes in cortical layer II was further confirmed by studies demonstrating the lack of expression of mature neuronal and glial markers. The majority of these cells do not express NeuN (Gomez-Climent et al., 2008 and Nacher et al., 2002a), a nuclear protein found in most mature neurons (Mullen et al., 1992) and a similar pattern has been found for MAP-2, a microtubule associated protein intensely expressed in mature neurons (Gomez-Climent et al., 2008). Interestingly, NeuN is almost completely absent from tangled cells, but it is displayed at low levels in some of the nuclei of the larger cell types (semilunar-pyramidal transitional, semilunar, pyramidal and fusiform neurons; Gomez-Climent et al., 2008, Nacher et al., 2002a and Xiong et al., 2008). This gives support to the hypothesis that larger cells in layer II are more mature than tangled cells, because similar increases in NeuN expression have been found during neuronal differentiation in the adult dentate gyrus (Kempermann et al., 2004 and Marques-Mari et al., 2007). The fact that these larger cells, but not tangled cells, expressed the NR1 subunit of the NMDA receptor (Gomez-Climent et al., 2008) also supports this view, because this receptor is not present in early differentiating granule neurons of the adult dentate gyrus (Nacher et al., 2007).

Immature neurons in cortical layer II also lack oligodendroglial, astroglial and microglial markers in rats, guinea pigs and cats (Cai et al., 2009, Gomez-Climent et al., 2008 and Xiong et al., 2008).

2.2.3. Ultrastructure

The immature neuronal phenotype of the cell population in cerebral cortex layer II has been confirmed by ultrastructural studies in the adult rat (Gomez-Climent et al., 2008 and Shapiro et al., 2007a) (Fig. 1D and E). Both tangled cells and semilunar-pyramidal neurons had only a small rim of cytoplasm surrounding the nucleus. Many astroglial lamellae appear in close apposition to the plasma membrane of both the somata and processes. In addition, swellings of the extracellular space can be observed adjacent to the portions of the plasma membrane, which are not covered

by these glial processes. The immature nature of these cells is further supported by the chromatin organization in their nuclei, which frequently display heterochromatin clumps, and by the absence of synapses on their somata or proximal processes in layer II. Some very scarce asymmetric synapses with round clear vesicles can be found making contact on the dendrites of semilunar-pyramidal transitional cells in layer I. Future studies using electron microscopy should expand our current knowledge of these cells by evaluating other ultrastructural features, such as the presence of glycogen granules, basal bodies, primary cilia or filopodial expansions.

2.3. Developmental stage of immature neurons in layer II

Six different cell types representing successive neurodevelopmental milestones can be identified in the adult dentate gyrus (Kempermann et al., 2004). There is a multipotential precursor cell (type-1), which expresses nestin and GFAP. This precursor gives rise to three putative transiently amplifying progenitor cells, all of them lacking GFAP expression: type-2a cells express nestin alone, type-2b express nestin and DCX and type-3 cells express DCX alone. These progenitors generate immature neurons (neuroblasts), which retain DCX expression and start to express NeuN. The neuroblasts progressively differentiate into mature neurons, which express NeuN and lack DCX. These differentiation steps in the hippocampus have been further simplified in order to generalize them to any newly born neuron of the adult CNS (Bonfanti and Peretto, 2011). If we consider these neurodevelopmental milestones, the PSA-NCAM/DCX expressing cells in the adult cortical layer II can only correspond to type-3 cells or to immature neurons, because they do not express GFAP or nestin, they express DCX and PSA-NCAM and only a minor portion express NeuN. These cells cannot, however, be considered true type-3 progenitors. We suggest that the PSA-NCAM+/DCX+ cells in the adult paleocortex layer II are in an intermediate stage between type-3 cells and differentiating neurons, namely they have accomplished neuronal specification but not complete differentiation (Fig. 2C).

A recent report using transgenic mice expressing GFP under the promoter of DCX has given support to the idea that many DCX expressing cells in the piriform cortex layer II are in an immature stage (Klempin et al., 2011). Using electrophysiological recordings, the authors have found that tangled cells showed similar features to those of newly generated neurons in the dentate gyrus and subventricular zone, such as low Na+ currents, although many of them were able to fire single action potentials under current clamp. By contrast, semilunar-pyramidal transitional neurons show large Na+ currents and current clamp elicited both single and multiple action potentials. However, these results should be considered cautiously because it was described that only a fraction of GFP expressing cells also express DCX protein.

3. Origin and fate of immature neurons in cerebral cortex layer II

3.1. Origin

After finding that mammalian cortical layer II cells express immature neuronal markers in the adult, different laboratories undertook BrdU pulse-chase experiments to test whether these cells were recently generated. We did not find evidence of newly generated neurons in this region in adult rats (Nacher et al., 2002a). Moreover, we have recently demonstrated that the majority of immature neurons in layer II of the rat paleocortex are generated during embryonic development. Most of these cells are born in E15.5 (Gomez-Climent et al., 2008), namely, a stage that appears to coincide with, or to occur slightly before, that of most layer II neurons in this region (Bayer, 1986). This result gives support to the idea that adult neurogenesis in the paleocortex of adult rodents either does not exist, or must occur at very low levels.

Some other reports have failed to find evidence that DCX, TUC4 or PSA-NCAM expressing neurons in this region of adult mice (Fontana et al., 2005), rabbits (Luzzati et al., 2003), cats (Varea et al., 2011) or primates (Kornack et al., 2005) were recently generated.

However, previous studies in rats, mice and primates have described that some of the cells in the paleocortex layer II have been generated during adulthood (Bernier et al., 2002, Pekcec et al., 2006, Shapiro et al., 2007a and Shapiro et al., 2007b). Bernier et al. (2002) found labeled cells expressing NeuN, MAP2 and TuJ1 in the piriform cortex of adult Old world and New world primates 28 days after BrdU injection. Pekcec et al. (2006) described the presence of low numbers of recently generated neurons in the piriform cortex layer II of adult mice using NeuN/BrdU labeling, 4 days after BrdU administration. However, these authors did not find these labeled cells when observing animals sacrificed 12 weeks after BrdU administration, which lead them to suggest that the vast majority of these recently generated neurons degenerate. Two reports from Charles Ribak's laboratory have described BrdU/DCX and BrdU/NeuN labeled cells in the piriform cortex of adult mice and rats, 21 days (only in mice; Shapiro et al., 2007b) and 7 days after BrdU administration (Shapiro et al., 2007a). However, in none of the studies mentioned above the precise layer location of these double-labeled cells was indicated. Despite the elevated number of DCX or PSA-NCAM expressing cells in the lateral entorhinal cortex layer II of adult rodents, no evidence of recently generated immature or mature neurons has been described.

A possible intrinsic origin for some of the immature neurons in the adult cerebral cortex layer II should not be discarded. In fact, Heather Cameron's laboratory has described the presence of recently generated interneurons in the adult rat cerebral cortex and has suggested that these cells may arise from precursors located in this region, based on the expression of Ng2 (Dayer et al., 2005). Some of the Ng2+ cells in the adult cerebral cortex are actively dividing cells that have been found to generate oligodendrocytes, but also cells with a neuronal phenotype (Belachew et al., 2003). Moreover, the presence of DCX+/Ng2+ cells has been described in the layer II of the piriform and entorhinal cortices of adult rats (Tamura et al., 2007) and we have observed that a very small subpopulation of tangled cells co-expresses Ng2 and PSA-NCAM (Gomez-Climent et al., 2008). Tamura et al. (2007) have also shown that, in the cerebral cortex, some of these DCX/Ng2 expressing cells may be proliferating or may have been recently generated. Two recent reports have also demonstrated that a, most likely local, population of Ng2+ precursors is able to

differentiate into projection neurons in the adult murine piriform cortex (Guo et al., 2010); however, BrdU analyses suggest that these principal neurons have been generated from precursors that ceased to proliferate at least since the first postnatal month (Guo et al., 2010 and Rivers et al., 2008). Our laboratory has also failed to find evidence of such dividing or recently generated cells in the adult rat paleocortex layer II, studying BrdU labeling and the expression of proteins commonly found in neuronal precursor cells of the adult CNS, such as nestin (Doetsch et al., 1997 and Nacher et al., 2001b) or Pax6 (Hack et al., 2005, Maekawa et al., 2005 and Nacher et al., 2005). It is possible that some of these Ng2+ cells that differentiate into mature pyramidal neurons were the ones that we have described to co-express PSA-NCAM. A recent report has suggested layer I as a putative niche for newly generated cells in the cortical layer II of young adult guinea pigs, although, in consonance with previous studies, the number of recently generated neurons observed was very low (Xiong et al., 2010).

3.2. Fate

The cells expressing immature neuronal markers in cortical layer II become undetectable as aging progresses. The number of PSA-NCAM expressing cells in the rat paleocortex layer II dramatically declines during aging (Abrous et al., 1997, Murphy et al., 2001 and Varea et al., 2009) and this reduction is also observed when analyzing DCX or TUC4 expression (Nacher et al., unpublished observations). This decrease is already found in 6 month old rats and persists in 1 and 2 year old animals (Varea et al., 2009). Similar results have been observed when studying DCX expression in the cerebral cortex of guinea pigs (Xiong et al., 2008), cats (Cai et al., 2009) and primates (Zhang et al., 2009).

The fate of these immature neurons is far from clear. Although these cells may have only a transient existence and progressively die during the progression from youth to adulthood, previous studies have failed to find evidence of elevated TUNEL activity in the cortical layer II during aging in guinea pigs (Xiong et al., 2008) or substantial numbers of pyknotic nuclei in aging rats (Gomez-Climent and Nacher, unpublished results). However, these studies do not rule out death as a possible fate for these immature neurons. Alternatively, these cells may be differentiating into mature neurons, which would lack these immature markers and thus would be no longer detectable. As mentioned above, tangled cells appear more immature than pyramidal-semilunar transitional neurons; since intermediate cell types are commonly found in layer II, it is possible that tangled cells mature into this larger cell type and then into mature neurons (Fig. 2C). However, the neurochemical nature of these mature neurons is still controversial. While some studies suggest a major interneuronal fate for immature neurons in cortical layer II (Cai et al., 2009, Xiong et al., 2008 and Zhang et al., 2009) other studies support the hypothesis of a differentiation mainly into excitatory neurons (Gomez-Climent et al., 2008 and Luzzati et al., 2008).

The evidence supporting an inhibitory fate for immature neurons in cortical layer II is based mainly on the analysis of DCX+ cells. These studies have reported that, in guinea pigs, cats and non-

human primates, GABA expression was absent from DCX expressing tangled cells, but that the larger cells (especially those expressing low levels of DCX) were faintly labeled with anti-GABA or anti GAD antibodies (Cai et al., 2009, Xiong et al., 2008 and Zhang et al., 2009). In guinea pigs, these DCX-low expressing cells lacked expression of calcium binding proteins, but they were labeled with nitrinergic interneuron markers (Xiong et al., 2008). In adult cats similar faint DCX labeled large cells co-expressed parvalbumin, calbindin, somatostatin and nitrinergic markers, but not calretinin (Cai et al., 2009). These DCX-low expressing cells with a putative interneuronal phenotype were not only found in layer II, but also in deep cortical layers.

In contrast with these results, other reports have never found similar large DCX expressing cells in these deep layers, neither in rats (Gomez-Climent et al., 2008 and Nacher et al., 2001a) nor in mice (Nacher et al., 2010), cats (Varea et al., 2011) or primates (Nacher et al. unpublished results). Although Cai et al. (2009) erroneously indicated that we had found DCX/somatostatin expressing cells in deep cortical layers, what we described was a population of cells expressing exclusively PSA-NCAM, but never DCX, which have been classified as mature interneurons (Varea et al., 2005 and Varea et al., 2007).

Several evidences support the hypothesis of an excitatory fate for most immature neurons in cortical layer II. Immature neurons in layer II, especially those belonging to the large subtype, do not show morphological characteristic of interneurons: most of these cells have been classified as semilunar-pyramidal transitional, semilunar or pyramidal neurons, which are common excitatory neuronal types in the cerebral cortex. Moreover, the morphology of inhibitory neurons commonly found in this region does not coincide with that of the immature neurons (Suzuki and Bekkers, 2007).

Immature neurons in cortical layer II of adult rats lack mature interneuronal markers, such as GABA, GAD67, calbindin, parvalbumin, calretinin, somatostatin, neuropeptide Y, cholecystokinin or VIP (Gomez-Climent et al., 2008). In contrast with the results reported by Cai et al. (2009), similar findings have been recently found in cats, where PSA-NCAM/DCX expressing cells in cortical layer II lack expression of GAD67, calcium binding proteins, neuropeptides or the neural isoform of the nitric oxide synthase (Varea et al., 2011). However, DCX/PSA-NCAM expressing cells in the cerebral cortex layer II of adult rats and cats also lack the expression of Ca(2+)/CaM-dependent protein kinase II (CAMKII), a marker of excitatory neurons (Gomez-Climent et al., 2008 and Varea et al., 2011). It is possible that the mature markers used until now start to be expressed once the neurons have already lost the expression of the immature markers. Consequently, new excitatory/inhibitory markers, expressed earlier in the neuronal development, should be assayed or new experimental approaches discovered to follow the progress of these immature neurons in real time.

The analysis of the expression of different transcription factors also supports the hypothesis of an excitatory fate. The majority of immature neurons in the cortical layer II of mice, rats, rabbits and

guinea pigs does not express Lhx6 or pan distalless (DLL), and, consequently, do not come from the subpallium (a region where most cortical interneurons originate) (Luzzati et al., 2008). By contrast, most of these immature neurons express Tbr1, a transcription factor specific for pallium-derived principal neurons, in the species described above (Luzzati et al., 2008) and in adult cats (Varea et al., 2011). However, it has to be noted that, although very rarely, some elements displaying faint DCX expression were found to express low levels of DLL and GABA expression in the cortex layer II of different mammals (Luzzati et al., 2008), which suggests that, although most immature neurons in layer II may differentiate into principal neurons, a small subpopulation may develop into interneurons.

Interestingly, a recent study (Gomez-Climent et al., 2011b) has described that after unilateral olfactory bulbectomy the number of PSA-NCAM and DCX expressing cells is significantly reduced in the piriform cortex layer II of adult rats. Moreover, this reduction in cells expressing immature neuronal markers is paralleled by an increase in the number of NeuN expressing cells, suggesting that some of the cells that stop expressing immature neuronal markers may differentiate into mature neurons. Apparently these new neurons are not inhibitory, because there is no parallel increase in the number of GAD expressing cells in the piriform cortex layer II after the bulbectomy.

Obviously, apart form their differentiation into mature neurons, these cells may undergo several types of structural plasticity described in Table 1. However, there are still no reports studying other forms of structural plasticity in these cells, such as synaptic, dendrite and spine remodeling. Future studies should be directed to unravel whether various types of plasticity occur in these cells under normal circumstances, after experimental manipulations or in animal models of CNS disorders.

4. Immature neurons in the cerebral cortex layer II respond to various extrinsic and intrinsic factors

Immature neurons in cortical layer II may constitute a "reservoir", which in different circumstances may complete its differentiation program. The number of these immature neurons is particularly high, in young adult rats a stereological estimation of the total number of PSA-NCAM expressing neurons in layer II revealed more than 55.000 cells, only considering the piriform cortex (Nacher et al., 2002a). The numbers of these immature neurons in young mammals with larger cerebral cortices, including humans, must be impressive because of their similar density and much wider distribution. Although the absence of definitive information on the fate of these immature neurons makes it difficult to decipher their final function, some studies have shown that they are affected by intrinsic or extrinsic factors.

Different paradigms, such as spatial and passive avoidance learning, significantly increase the number of PSA-NCAM expressing cells in the paleocortex layer II of rodents (Fox et al., 2000 and

O'Connell et al., 1997). By contrast, some other studies using piriform cortex-dependent olfactory learning paradigms did not find changes in the number of PSA-NCAM expressing cells in this cortical region (Knafo et al., 2005 and Gomez-Climent et al., 2011b). However, although the presence of newly generated neurons is scarce in the adult piriform cortex, olfactory enrichment seems to promote the differentiation of these new cells (Shapiro et al., 2007b). The fact that in mammals with larger cerebral cortices immature neurons in cortical layer II have a more widespread distribution, being present in many neocortical regions and not only in areas primarily related to olfaction (Bonfanti, 2006; Cai et al., 2008; Xiong et al., 2008 and Zhang et al., 2009), indicate that these cells may participate in some basic processes general to cerebral cortex and not only related to olfactory processing. However, at this point it is still difficult to speculate about the real nature of these processes.

The immature neuronal population in cortical layer II also appears affected in some neurological/psychiatric disorders or in animal models of these disorders, suggesting a putative relationship. Transgenic murine models of Huntington disease had a large reduction in the number of DCX and PSA-NCAM immunoreactive cells in the piriform cortex (Lazic et al., 2007 and Phillips et al., 2006). On the contrary, rats submitted to transient cerebral ischemia (Hayashi et al., 2001) and humans with temporal lobe epilepsy (Mikkonen et al., 1998) had increased numbers of PSA-NCAM expressing neurons in this cortical region.

Adrenal steroids and stress also have an impact on this population of immature neurons, although not in the same direction: while stress increases the number of these cells, corticosterone decreases it (Nacher et al., 2004). The effects of corticosterone should be indirect, because these cells do not express glucocorticoid receptors (Gomez-Climent et al., 2008). Stress has also an important impact on excitatory aminoacid neurotransmission, specially affecting NMDA receptors (Popoli et al., 2011). Thus, it is possible that effects on immature neurons in cortical layer II were mediated by these receptors, since they are present in pyramidal-semilunar transitional neurons (Gomez-Climent et al., 2008) and the number of PSA-NCAM expressing cells in this region is increased after NMDA receptor antagonist treatment (Nacher et al., 2002a). Other pharmacological treatments are also known to affect these immature neurons, including the anti-epileptic valproic acid (Murphy et al., 2001) or the antidepressant imipramine (Sairanen et al., 2007). The exact effects of all these extrinsic and intrinsic factors on the immature neurons of cortical layer II still remain to be determined, but they strongly suggest an involvement of these cells in the response to cognitive stimuli and a role as direct or indirect targets of hormones, neurotransmitters and pharmacological treatments.

5. Concluding remarks

The CNS of mammals, in spite of having lost most of its regenerative/repair capacity with respect to other phyla, is endowed with remarkable plasticity. This property is heterogeneously distributed in different regions and can manifest in different ways. A better knowledge of the

various forms of spontaneous structural plasticity, of their mutual relationships and of the relative underlying mechanisms is fundamental in order to figure out new efficacious therapeutic perspectives for brain repair. During the last two decades, studies on adult neurogenesis have opened the intriguing perspective of cell replacement-aimed therapeutic strategies, yet this approach is still hampered by overwhelming problems concerning the final integration of both transplanted and endogenously-induced cells (Arenas, 2010 and Bonfanti, 2011). The reason of this failure might be mostly due to evolutionary constraints (Weil et al., 2008), and to the fact that cell renewal typical of adult constitutive neurogenesis is primarily involved in tissue homeostasis of highly restricted regions, being hardly useful in response to external injury and neurodegenerative brain damage (Kozorovitskiy and Gould, 2003 and Bonfanti, 2011). In addition, adult neurogenesis is a quantitatively small, topographically restricted phenomenon, whereas synaptic plasticity is more widespread and quantitatively consistent (Chen and Nedivi, 2010 and Fu and Zuo, 2011). Thus, due to difficulties in achieving cell replacement/regenerative approaches (cell therapy) in the nervous system, that of rehabilitation remains a feasible alternative. Rehabilitation approaches mostly reside on compensatory exploitation of undamaged, preexisting structures through enhancement/implementation of their plasticity. In this context, the presence of immature, non-newly generated neurons in the adult rodent cortex could be viewed as a form of plasticity placed in between the extremes of axonal/synaptic remodeling (modification of pre-existing structures) and adult neurogenesis (addition of new cells) (see Fig. 3). According to this hypothesis, the neurons remaining in an immature state for indeterminate time might be recruited into the preexisting neural circuits under specific stimuli. Thus, they could represent a 'reservoir' of neurons that are not generated ex novo, yet ultimately would act as 'new neurons'. If, as our studies suggest, these immature neurons will eventually differentiate into principal neurons, they may receive new connections coming from the olfactory bulb and will participate in the integration of these new signals into cortical networks. Whether these connections onto recently differentiated neurons come from circuits of the olfactory bulb in which adult generated neurons have been incorporated, still remains to be explored. Experimental approaches to study the fate of immature neurons in the cerebral cortex layer II and their integration into the circuitry, such as the use of inducible transgenic mice expressing fluorescent proteins under the promoter of DCX (Zhang et al., 2010), or the proteolipid protein (Plp; Guo et al., 2010), should be explored in the near future. Experiments to be developed in the future and addressed at the depletion or inactivation of these cells using genetic approaches will also be extremely interesting. Although we know that some extrinsic and intrinsic factors can affect the immature, non-newly generated neurons, the specific aspects of such a modulation are still obscure and should be the focus of further investigations. The widespread occurrence of PSA-NCAM+/DCX+ neurons in the cortex of non-rodent mammalian species such as rabbit, cat and monkeys (Luzzati et al., 2008, Cai et al., 2009, Varea et al., 2011 and Zhang et al., 2009) and that of DCX+ cells in the human cortex (Verwer et al., 2007, Cai et al., 2009 and Bloch et al., 2011) do support interest in exploring such a possibility. In particular, evidence that immature neurons are not restricted to the paleocortex, being also found in associative neocortical areas of some mammalian species, widely expands their possible role in physiological as well as reactive plasticity.
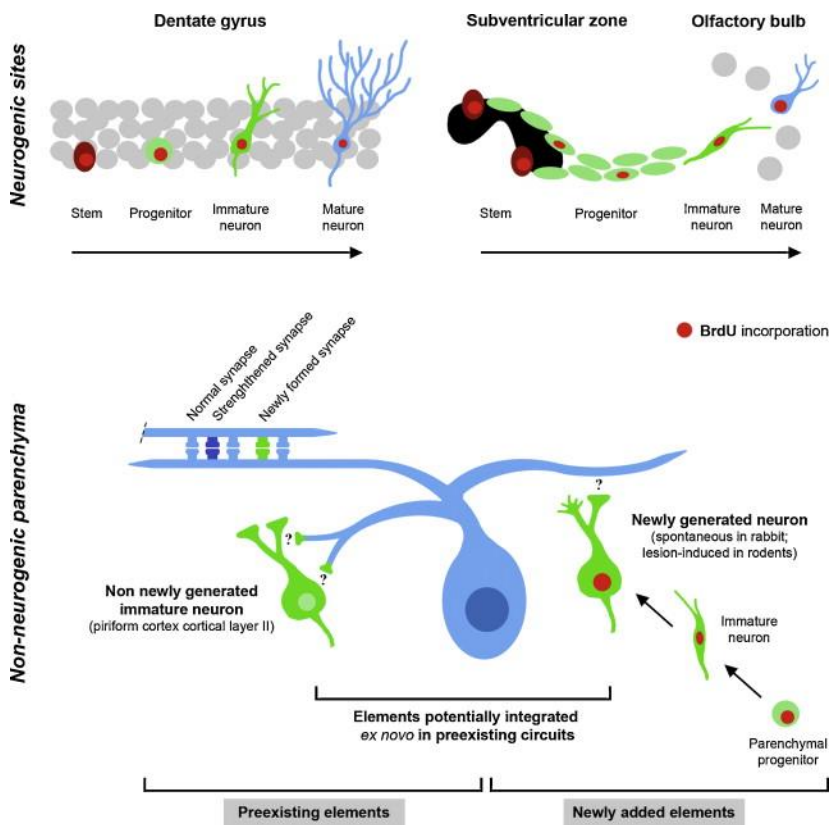
Fig. 3.

Different forms of plasticity in constitutively neurogenic (top) and so-called non-neurogenic (bottom) areas. In classic neurogenic sites the genesis of new neurons during adulthood ultimately allows mature neurons (light blue) to integrate into the preexisting circuits, by transiting through a stage of immature neurons (green). Among the well known events of structural plasticity in non-neurogenic areas, synaptic plasticity allows mature neurons to establish new connections. Recent findings indicate that some neurons can also be generated within some non-neurogenic regions, both of the intact and damaged mammalian brain (bottom, right). Non-newly generated, immature neurons in piriform cortex layer II (bottom, left) might be in between these extreme degrees of structural plasticity, functionally representing new elements to be recruited in the preexisting circuits, yet structurally not corresponding to newly born elements. The question marks highlight the hypothesis that both newly generated parenchymal neurons and non-newly generated immature neurons might be integrated in the circuits, what has not yet been demonstrated.

In conclusion, alternative and multiple forms of plasticity described in the present review can overlap within the so-called non-neurogenic tissue, affecting preexisting cells/circuits and increasing the complexity of the whole picture of brain structural remodeling. Further knowledge in this direction could lead to uncover new perspectives for interventions aimed at recovery in neurological diseases. In particular, this emerging, heterogeneous scenario of structural plasticity could be possibly less attractive in terms of neuronal replacement or 'cell therapy', yet more promising in terms of rehabilitation relying on pre-existing, plastic neuronal structures.

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