# The Neural and Molecular Basis of Learning and Memory

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# Adult Hippocampal Neurogenesis and Memory

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## 1. Introduction

Adult neurogenesis, a concept emergent in the late 1990s, is the generation of new neurons in the adult brain. This process occurs thank to cells who have this proliferative feature, named as Neural Stem Cells (NSCs). Neural Stem Cells (NSCs) are primary progenitors who can generate the two neural types (neurons and glia). Classically it was assumed that NSCs are only present in the embryo, but today it is extensively known that are also present in the postnatal and adult brain, although the majority were found in embryo stage.

According with Merkle et al. 2006, these cells are characterized by the following features: 1. They come from glial cells, 2. They are related linearly between adult and embryonic cells (since they are transformed from neuroepithelial cells to radial glia, and then they show astroglial cells characteristics), and 3. These cells are divided essentially asymmetrically leading to another intermediate progenitor (IPC) as a parent, and sometimes divided symmetrically, to increase the progeny (Ortega Martinez and Trejo, 2015). Meanwhile, intermediate progenitors (IPCs) are always divided symmetrically to amplify the number of progeny dividing (Merket et al., 2006). These symmetric divisions are an important determinant of the brain size, so those species with larger brains have a larger pool of intermediate progenitors (Marshall et al., 2005).

These cells, in adults, are mainly found at the subventricular zone (SVZ), adjacent to the lateral ventricles and at the dentate gyrus (DG) of the hippocampus, known like subgranular zone (SGZ) the *'imaginary line'* below granular zone of DG where these cells are found (see Fig. 1). However, there are evidences of the existence of these cells elsewhere in the adult brain, including the cortex (Feliciano et al., 2012) or the hypothalamus (Lee et al., 2012). These precursor cells are quiescent (usually non-dividing) that can be divided into different stimuli. When this happens, there are two possibilities; A) their division generates intermediate progenitor cells (IPC), which then gives rise to neurons; B) whereas if they come from astroglial progenitors, the result will be the generation of glial. The process of formation of neurons through intermediate progenitors is a longer process, as there are different types of intermediate progenitors known as 2a, 2ab, 2b and type 3 according to their stage of development and expressing markers, whereas astroglial progenitors have comparatively a lower proliferative capacity. However, intermediate progenitors send numerous processes before being symmetrically divided, motivated by local sensing factors (Noctor et al., 2004).

The NSCs don't only come from the nervous system but can be derived from embryonic stem cells (ES cells) or reprogrammed fibroblasts (Wernig et al., 2008). Different kinds of neural progenitor/stem cells basis have been established on their characteristics. There are two different populations known like: neural stem cells which show glial characteristics (Radial Glia Cells, RGLs), and intermediate progenitors (IPC). The latter are also divided into other types (2a, 2ab, 2b, 3). The classification of these cells and the markers used to identify them has created much controversy among scientists. However, there is a large consensus that the astrocytic NSC have many features, such as the expression of glial fibrilar acidic protein (GFAP), which has made us change our perception of glia (Merkle et al., 2006). Other studies (Kempermann et al., 2003) support the interpretation that radial astrocytes have a role as primary progenitors.

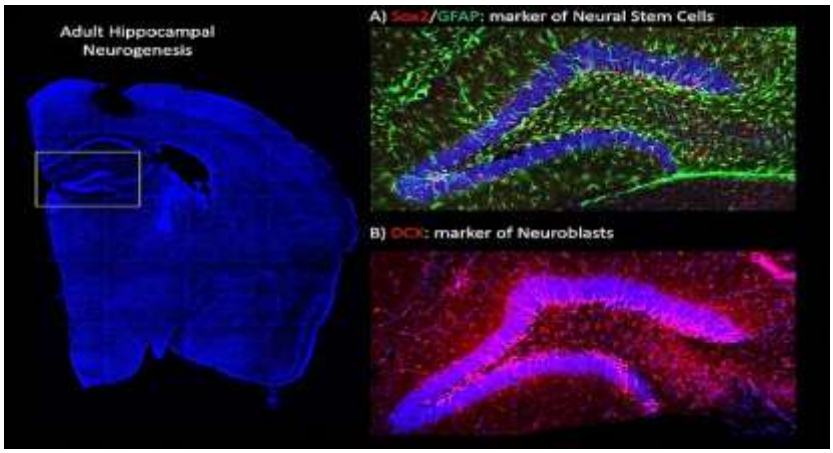


**Fig. 1.** Adult hippocampal neurogenesis within the brain. A) Dorsal dentate gyrus showing by immunofluorescences the NSCs (Sox2/GFAP), while in the B) it is possible to observe the new neuroblasts generatedlabelled with DCX (immunofluorescence), (Ortega-Martinez).

Despite the neurogenesis importance acquired nowadays, this emergent concept remained obscure until neurogenesis was found to occur in the brain of adult humans (Eriksson et al., 1998; Ortega-Martinez, 2015). Neurogenesis, or the new neurons generation, was traditionally understood to be mainly an embryogenetic phenomenon, but during last 50 years since its discovery, research in the field has shown the existence ofneural cells generation in several areas of the adult brain, including the Dentate Gyrus (DG) in the hippocampus, subventricular zone (SVZ), olfactory bulb (OB), and other areas where it was recently observed such as the cortex, amygdala and hypothalamus, where its function remain unclear (Gould, 2007; Ortega-Martinez, 2015).

Adult neurogenesis is not the process referred to new neurons generation, becausethis process involves cell proliferation, survival, migration, and cell differentiation. Adult hippocampal neurogenesis (AHN), or these new neurons generation in the adult hippocampus, occurs for specific brain functions (mainly related with cognitive and emotional function. See below), and involves not only new neuron formation but also integration of these new-born neurons into functional networks, making the process as a functional one. From this perspective, AHN facilitates memory consolidation via formation of networks (Deng et al., 2010; Weisz and Argibay, 2012; Ortega-Martinez, 2015). Furthermore, AHN provides plasticity required in memory processes and allows for ‘‘pattern separation mechanisms’’ which is crucial for memory consolidation (Bruel-Jungerman et al., 2007; Sahay et al., 2011; Bekinschtein et al., 2013; Yassa and Reagh, 2013; Ortega-Martinez, 2015).

**2. Points of view of neurogenesis through time**

Until the 1990s the neuroscience field was under the dogma established in the late 19th to early 20th centuries by the most famous Spanish scientist, Santiago Ramon y Cajal (1852-1934). Cajal is considered the father of modern Neuroscience, due to the fact that he established the individuality of neurons through the ‘neuron theory’, which radically opposed to the previous ‘reticular theory’ maintained by Golgi, among others. However, Cajal’s observations made think that the nervous system was a non-variable system, and he supported this dogma by stating: “Once the development was ended, the founts of growth and regeneration of the axons and dendrites dried up irrevocably. In the adult centers, the nerve paths are something fixed, ended, and immutable. Everything may die, nothing may be regenerated. It is for the science of the future to change, if possible, this harsh decree.” (Reviewed by Colucci-D’Amato et al., 2006). This doctrine was also approved by other scientists such as GiulioBizzozero, who classified the tissues of the human body into “labile, stable and perennial”, and other works (His, 1904) supporting the idea that the architecture of the brain appears to be fixed soon after birth.

For several years, there were occasional reports showing mitotic cells in the brain of adult mammals but these investigations did not convince the scientific community (Bryans, 1959), probably because the methods used to prove that these new cells, which could differentiate into neurons and be functionally integrated, were not good enough.

The first author that changed this point of view was Joseph Altman, who published a series of works in the nineteen sixties showing evidence for adult neurogenesis in adult rats and cats (for review see Gross, 2000), using autoradiography to track H3 Thymidine, incorporated by proliferating cells during mitosis. At the same time, an additional evidence for neurogenesis in songbirds was presented (Nottebohm, 1989), playing down the importance of adult brain neurogenesis. The central dogma, previously mentioned, didn’t disappear until the 1990s, when new techniques emerged. It was the use of a tritiated Thymidine analogue, Bromodeoxyuridine (BrdU), which was used as a proliferation marker. BrdU can easily be labeled with immunohistochemical methods and investigated with a bright filter and fluorescence microscopy. In addition, specific antibodies against neuronal or glial markers were developed, providing easy methods to distinguish neurons from glia. With the help of these methods adult neurogenesis has been demonstrated to exist until senescence in numerous mammalian species including humans (Eriksson, 1998). Finally, the neuronal behavior of these new cells and their integration into the network was confirmed by experiments testing long term potentiation (LTP), synapse formation and expression of immediate early genes after stimulation of the hippocampal network (Kempermann et al., 2003; Song et al., 2002; Van Praag et al., 1999).

Probably one of the most exciting scientific findings of the last 50 years is the discovery that discrete brain regions make new neurons throughout life. Classically it is accepted the presence of two main neurogenic areas in the adult brain of mammals, which are the subventricular zone adjacent to lateral ventricles, which provides the olfactory bulb (OB) constantly with a stream of progenitor cells through a path called the rostral migratory stream,

and the subgranular zone of hippocampal dentate gyrus. It has also been reported the presence of newborn cells in other brain places, like the hypothalamus or the cortex, but in fact, a consensus has not been reached yet.

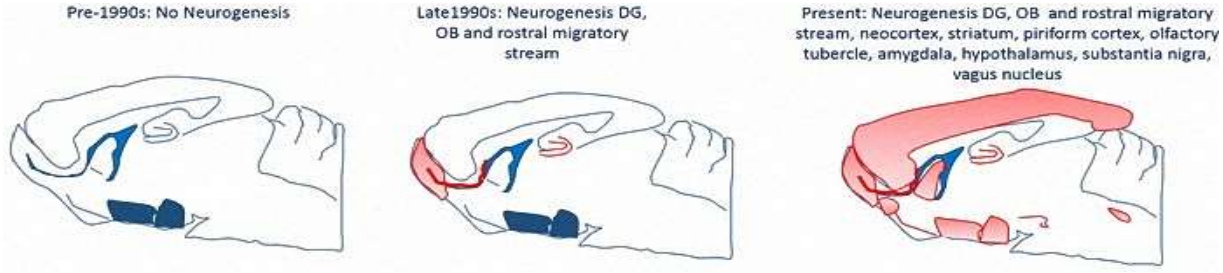


**Fig. 2.** Representation of the vision of adult neurogenesis through the time, in the last 16 years using a diagram-representation of an adult rat's brain. In the early 1990s due to the central dogma of the neuroscience, all brain regions were considered as 'non-neurogenic' (blue). This point of view, change thanks to Altman work, 50 years ago. In fact, in the late 1990s, first neurogenic areas where stablished. They were the dentate gyrus and the subventricular zone (which gives rise to the rostral migratory stream) and the olfactory bulb (red). Nowadays, these three known neurogenic regions are being increased with new research, considering right now also as neurogenic niches the neocortex, amygdala, striatum, among others. It should be noted that not all of these brain regions are present on the same sagittal plane, and their location is approximated on this diagram. Adapted from Gould, 2007 by Ortega-Martinez.

## 3. Adult neurogenesis in mammals

### 3.1. Introduction

As mentioned above, in mammals there are two main areas of own neurogenesis: The subventricular zone (SVZ), and the subgranular zone (SGZ) in the hippocampus. Indeed, the olfactory bulb was assumed like that recently, but we will discuss this process in the classical areas described. Neural stem cells from other brain areas like the neocortex or the hypothalamus have been isolated in vitro by dissecting these areas and growing the precursors in a medium growth factor rich, but their role in vivo is still very controversial, as previously mentioned.

In both cases, the newborn cells are generated from neural stem cells or precursor cells, and after maturation these cells will be integrated in the network. There is a big difference between the two main neurogenic areas related to the distance in which cells will be finally located. In the case of the subventricular zone, these new cells migrate through the rostral migratory stream (RMS) to the olfactory bulb (OB). Then, the migratory neuroblasts are divided until they are integrated as granular cells in the OB. Only very few mature new neurons originating from the SVZ invade the rest of the cortex. This was only found after distinct lesions and the cell numbers found were not significantly enough to replace the cell loss of the incident.

Meanwhile, in the dentate gyrus of the hippocampus, NSCs are mainly located in the subgranularcell layer, under the granular cell layer, formingcell clusters that will form progenitor cells. The difference between precursor (also named Neural Stem Cells, NSCs) and progenitor cells is the rate of divisions. In this case, precursors cells are mainly quiescent cells and they can enter into cell cycle after different stimuli. However, progenitor cells are characterized for its high rate of division, mainly symmetrical divisions, constituting the primordial source of new neurons in the brain. In addition, when new cells are generated they start their development (see B3), and asneuroblasts/ immature neurons migrate towards the granule cell layer (GCL) where they extend first dendrites into the molecular layer (ML) and send mossy fibers to the CA3 region. Many more cells are generated than the final number of them that ultimately survives. This survival ratio depends on a number of factors, but mainly it is due to the fact of how sufficiently the new cells are activated by incoming neural signals (a principle known as ‘use it or lose it’). Cells have to go through defined steps of division, differentiation, migration and maturation from the neural stem cell to the mature neuron, a process that takes between 4-6 weeks of age (see B3). In neurogenesis field, it is important to identify all these different stages along the route to neurogenesis. For that reason, neuroscientist have to use specificimmunohistological markers which are very useful to investigate the different phases of development separately (see Fig. 5).

### 3.2. Adult hippocampal neurogenesis

#### 3.2.1. The hippocampal formation: Anatomy and connectivity

The hippocampus, or hippocampal formation, is an archicortical region located in humans inside the medial temporal lobe, beneath the cortical surface. This structure is long known, and it was studied by Cajal (see Fig. 3). Basically it includes the Ammon's horn (or cornuammonis, CA), which is formed by CA1, CA2, CA3 and CA4, the dentate gyrus which contains the dentata fascia and the hilus, and the subiculum. However, the region known as CA4 is in fact the 'deep, polymorphic layer of the dentate gyrus' (as clarified by Theodor Blackstad, 1956; David Amaral, 1978). The hippocampal formation has been largely suggested to encode and consolidate memory (Scoville et al., 2000; Squire, 1992). Therefore it is known that these structure plays a role in memory retrieval (Maguire et al., 2000; Pastalkova et al., 2008), and code information about space (Ekstrom et al., 2003; Moser et al., 2008).

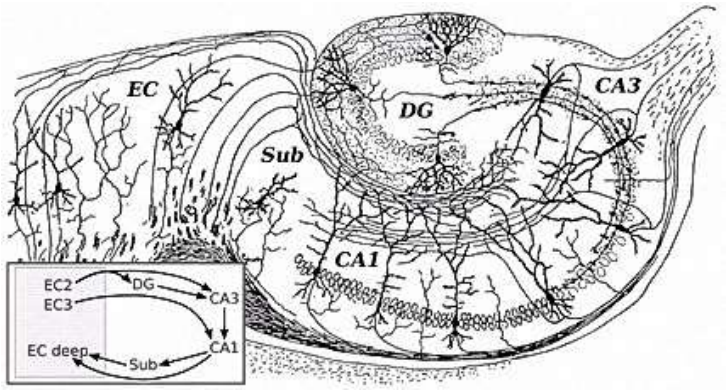


**Fig. 3.** Picture of hippocampus by Santiago Ramón y Cajal (1911).

Pyramidal cells in the hippocampal formation are majorly glutamic cells, containing AMPA and NMDA receptors which control sodium and calcium ion gradients. In relation to their connectivity, this complex structure receives the majority of its inputs from the superficial layers II and III of the entorhinal cortex, and connects with granule cells of dentate gyrus through the perforant pathway (reviewed by Witter et al., 1993). On the other hand, granule cells are connected with CA3 excitatory pyramidal cells via mossy fibers (Amaral et al., 1990), provide a powerful input into CA3, and they are also interconnected through hilar excitatory interneurons and receive recurrent inhibition through hilar inhibitory interneurons. The projections from the DG to CA3, CA3 to CA1, and CA1 to deep layers V and VI of the entorhinal cortex through the subiculum (for review see Rolls et al., 2006) are known like the majortrysinaptic loop (see Fig. 4).

The trysinaptic loop is the most important connection of hippocampus, but not the unique one. In fact, the hippocampal formation is connected to locus coeruleus through noradrenergic input from this nucleus. Also, it receives dopaminergic stimulation from the ventral tegmental area (VTA), acetycholinergic stimuli from the medial septum and serotonergic input from the raphe nucleus. The connections which seem to be 'information' related are from the mammilary bodies, through the fornix. The structure also receives information from the amygdala regarding odors and emotions.

#### 3.2.2. Hippocampal dentate gyrus: The subgranular zone

The subgranular zone (SGZ) is located within the dentate gyrus, which is part of the hippocampus in the mammalian brain. It is a place not-structurally bounded, but defined by the presence of the neural stem cells, under the granule cell layer, where the presence of these kinds of cells, NSCs, as well as their divisions has been reported. This new generation of cells can lead to neurons aimed at becoming hippocampal granular cells.

The neural stem cells of this zone have been named as type 1 cells or radial glial cells. They have many similarities to adult astrocytes like the marking with glial fibrillar acidic protein (GFAP), but they are different because they are not positive to S100β, which is often used as a marker for astrocytes100. These cells have a triangular shape, with their soma located below the granular cell layer, and which possess an apical process that

reaches into the molecular layer of the dentate gyrus (reviewed in Ming and Song, 2011). They are identified by their expression of nestin, an intermediate filament found in progenitors in association with astrocytic features.

When type 1 cells have an asymmetric division, they give rise to type 2 cells, which are considered the highly proliferative intermediate precursor cells. These intermediate precursors allow a sufficient number of new cells to be formed with the minimum necessary divisions from the original stem cells84. Morphologically, type 1 and type 2 cells are different. In this case, type 2 cells lack long processes, have a smaller soma, and possess oval nuclei. Therefore, these cells can be arranged into two sub-categories based upon molecules expressed, type 2a and 2b. While the first ones (type 2a) still maintain glial markers (however they no longer have the morphology of a glial cell), type 2b cells begin to express some specific transcription factors, and they will be marked using NeuroD1 (neuronal differentiation 1) and Prox1 (prosperohomeobox 1). Type 3 cells are derived from type 2 cells, which are neuroblasts and immature neurons.

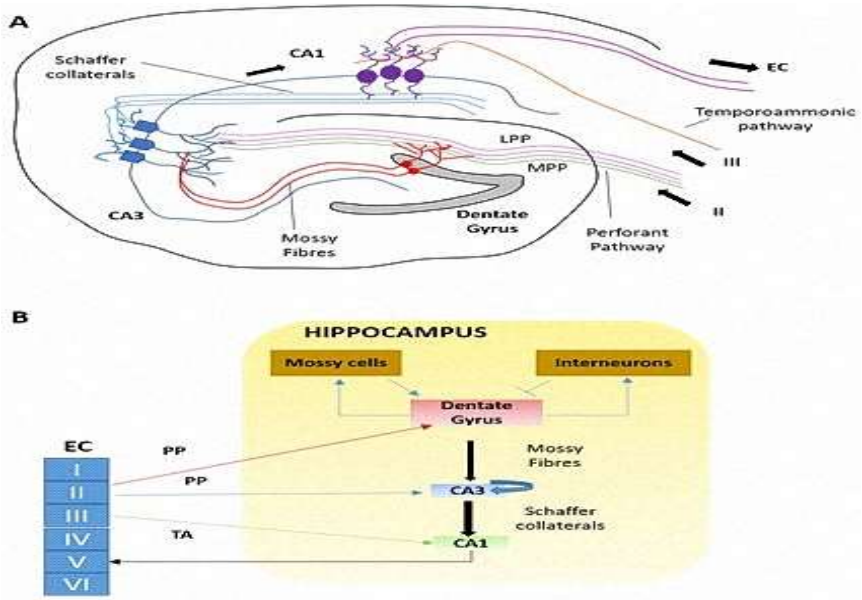


**Fig. 4.** The neural network in the hippocampus a) Scheme of the hippocampal circuitry showing the excitatory trisynaptic pathway (entorhinal cortex (EC)–dentate gyrus–CA3–CA1–EC) b) Diagram of the hippocampal neuronal network. The axons of layer II neurons in the entorhinal cortex project to the dentate gyrus through the perforant pathway (PP), including the lateral perforant pathway (LPP) and medial perforant pathway (MPP). The dentate gyrus sends projections to the pyramidal cells in CA3 through mossy fibres. CA3 pyramidal neurons relay the information to CA1 pyramidal neurons through Schaffer collaterals. CA1 pyramidal neurons send backprojections into deep-layer neurons of the EC. CA3 also receives direct projections from EC layer II neurons through the PP. CA1 receives a direct input from EC layer III neurons through the temporoammonic pathway (TA). The dentate granule cells (DGCs) (DGC) also project to the mossy cells in the hilus and hilar interneurons, which send excitatory and inhibitory projections, respectively, back to the granule cells. Adapted from Deng et al. 2010 by Ortega-Martinez.

Zhao et al. 2006, used retrovirus mediated gene transduction in the hippocampus of adult mice to track the developing neurons. They described in their work four different morphological stages: Stage A that occurs during migration. In this stage developing neurons begin to polarize and grow axons and dendrites. Then in stage B, considered as the stage of development, dendrites grow to reach into the molecular layer, and the axon of each immature neuron reaches into the CA3 area of the hippocampus. Stage C is where the spines are initially developed, which will only begin after the axon is integrated into the CA3. Finally, stage D is the longest one, as it occurs in several months, where spines are continually modified (See Fig. 5).

During these stages, most of new neurons will be eliminated before they form connections with their targets in the CA3. This is the reason by which it is usually accompanied by an increase in apoptosis when there is a neurogenic increase, because not all cells can survive. The neurons that survive are integrated into the current

circuitry, and share many of the same properties as the preexisting neurons. For example, they have similar threshold and resting potentials, and input resistances (Van Praag et al., 2002). Beyond the similar functional properties, newly generated cells are morphologically indistinguishable from the older cells surrounding them, and in order to label them it is necessary the use of mitotic markers (Ming and Song, 2011).

Researchers have inferred that these granule cells are not created to replace old cells and, in addition, the current circuitry is indicative of a specific functional role for adult neurogenesis (reviewed in Appleby et al., 2011).

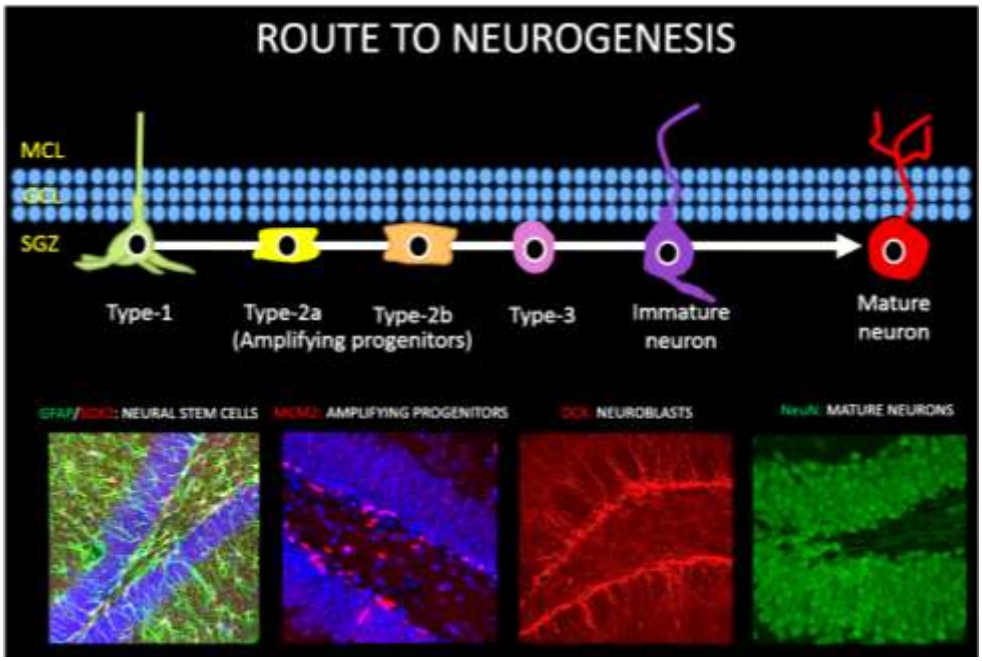


**Fig. 5.** Summary of the route of adult neurogenesis in the dentate gyrus of the hippocampus. The expression of stage-specific markers is also represented. In this regard, Neural Stem Cells are characterized by the expression of GFAP+/Sox2+; the amplifying progenitors by the expression of MCM2+; Neuroblasts are labelled with DCX+, and finally the mature neurons are marked with NeuN. In this route to neurogenesis occurs this different processes 1) activation of quiescent radial glia-like cell, also named NSCs in the subgranular zone (SGZ); 2) proliferation of non-radial precursor and intermediate progenitors; 3) generation of neuroblast; 4) Integration of immature neurons; 5)maturation of adult-born dentate granule cells (DGCs) (DGC). Abbreviations: MCL: molecular cell layer; GCL: granule cell layer; SGZ: subgranular zone; GFAP: glial fibrillar acidic protein; Sox2: sex determining region Y-box 2 MCM2: minichromosome maintenance complex component 2 DCX:doublecortin; NeuN: neuronal nuclei. From Ortega-Martinez.

### 3.2.3. Development of newborn neurons in the adult hippocampus (Adapted from Deng et al., 2010)

The neurons formed during the adult neurogenesis process, come from neural stem cells or progenitor stem cells in the SGZ, as mentioned above. When the new cells are generated, then they need to go through the process of maturation and migration, until they reach the granular cell layer of the dentate gyrus becoming new mature neurons, named as dentate granule cells (DGCs). However, in the process of proliferation from NSCs there is also a few cell population which becomes glia. Once new cells are formed they must change their morphology and physiology. It is a long process that is species-dependent, but we analyses the process in mice (Reviewed by Deng et al., 2010).

For their first week after birth, when these new born cells, now in the stage of intermediate progenitors (see Fig. 5) are differentiating and migrating a short distance to reach the granule cell layer, these cells then extended limited cellular processes in this layer. At this point, cells are not synaptically integrated yet into the network. However, they are capable to respond to γ-aminobutyric acid (GABA). This specific GABA- mediated activity was postulated to be crucial for both, survival and maturation of new granular cells (Deng et al., 2010).

Later, in the second week, they acquire neuron-like characteristics. For example, they reach polarization process, with dendrites extending towards the molecular layer and axons (mossy fibres) growing through the hilus towards CA3. Even do, at this stage, they are still as immature DGCs, and are notable different from mature neurons. Some of this different features are: 1) their higher membrane resistance, 2) firing properties different, 2) they receive GABAergic inputs from local interneurons but lacking their glutamatergic ones, concluding with slow rising responses and decay kinetics (Deng et al., 2010).

It is in the third week after birth, when these new adult-born DGCs start to form afferent and efferent connections with the local neuronal network (see Fig. 6). Spines on the dendrites of these new born cells appear approximately day 16, giving rise to first synapses connecting with the afferent axon fibres in the perforant pathway (from the entorhinal cortex). All this network integration, is enhanced by local synaptic activity. In fact, efferent synapse formation of adult-born DGCs can also be affected by existing synapses. Thus, the connection of both afferent and efferent synapses from newly generated DGCs is believed to involve targeting to pre-existing synaptic partners, suggesting a key role for circuit activity in the integration of adult-born DGCs (Deng et al., 2010). The synaptic integration coincides in time with the transition of GABAergic input changing from excitatory to inhibitory inputs, and also with the activation of glutamatergic synaptic inputs (Deng et al., 2010).

Between the second and the third week of age, the survival of adult born DGCs depend on N-methyl-D-aspartate (NMDA)-receptor mediated cell-autonomous activity. In fact, this kind of glutamate receptor is involved in neuronal development and plasticity (Deng et al., 2010). According to the growth of these new DGCs (between the forth and the sixth week of age), they also exhibit higher maturation of their physiology and connectivity, with stronger synaptic plasticity than mature DGC. It is observed due to their lower threshold for the induction of long-term potentiation (LTP) and their higher LTP amplitude. Continuing their maturation, these new DGC present structural modification of dendritic spines and axonal buttons becoming older. At the eight week of age, these physiological and synaptic features from new DGCs and mature granular cells are indistinguishable (Deng et al., 2010).

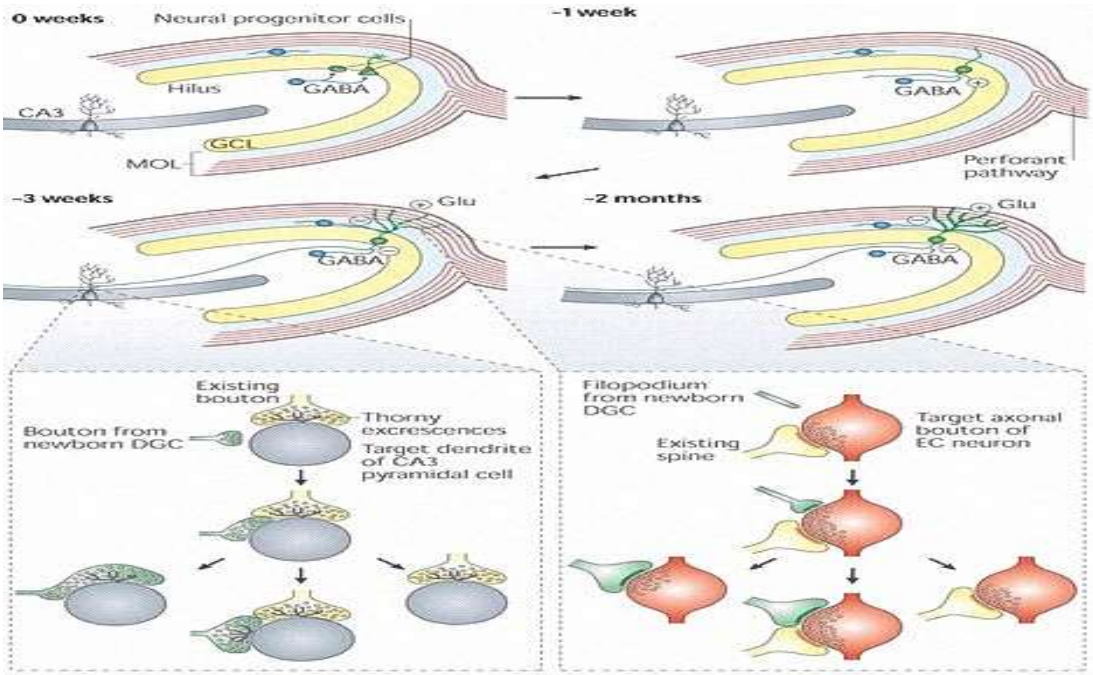


**Fig. 6.** Maturation of new-born dentate granule cells (DGCs) (DGC) (DGC) in mice (Deng et al., 2010).

Several works showed that newborn neurons in adult hippocampus are functionaland are integrated into hippocampal circuitry (Kempermann et al., 2003). CA3 pyramidal neurons do respond differently to the granule cell activity, given the different electrophysiological properties of immature neurons. On the other hand newborn neurons may have the ability of contributing only to the encoding within the hippocampus.

## 4. Function of adult hippocampal neurogenesis

Adult neurogenesis is extensively studied nowadays due to its important brain functions. In this sense, it has been related with two main important ones: cognitive function, attributed to the dorsal dentate gyrus, and emotional function, attributed to the ventral dentate gyrus. It will be described in further detail the role of hippocampal neurogenesis in cognitive function:

### 4.1. Learning and memory, 'Cognitive functions

In recent years there are so many groups interested in the function of adult hippocampal neurogenesis. Thanks to their efforts today we can understand a little bit more about the process and we are sure of some of these functions. To study this complex process they had used different in vivo and in vitro approaches. Most of them had been focused on the ablation of adult neurogenesis through X-ray irradiation (several low-dose, typically 5Gy, treatments spaced several days apart), drugs administration (the most common is the systemic antimitotic agent methylazoxymethanol acetate (MAM) or transgenic mice. The following has been a common design used to evaluate the functionality of adult hippocampal neurogenesis: knock-down adult born neurons in the intact adult hippocampus in animals and then behaviorally challenge the animals in paradigms designed to test learning and memory.

The results obtained from neurogenesis ablation reports are contradictory, probably due to two main explanations: the first one, adult hippocampal neurogenesis contribution may be specific and thus commonly used behavioral paradigms do not adequately test functional deficits. A second explanation is that a compensate process could exist in animals which had lost mature granule cells within the DG or other hippocampal subregions. For that, the demand of techniques that selectively ablate adult neurogenesis within the DG without impacting the integrity of the mature DGC, the hippocampus, and surrounding cortex (and can be demonstrated to do so unequivocally) is high. At present, different experiments using non-overlapping techniques, and presumably non-overlapping patterns of off-target effects, provide the best support for the functional contribution of the adult hippocampus neurogenesis.

Currently, the idea of a different function of dorsal and ventral hippocampus, referred to dentate gyrus, gains importance. Fanselow et al. 2010, says 'The dorsal hippocampus, which corresponds to the posterior hippocampus in primates, performs primarily cognitive functions. The ventral (anterior in primates) relates to stress emotion and affect. Strikingly, gene expression in the dorsal hippocampus correlates with cortical regions involved in information processing, while genes expressed in the ventral hippocampus correlate with regions involved in emotion and stress (amygdala and hypothalamus).'

Referred to well-known functions, the adult hippocampal neurogenesis has been implicated in learning and memory (Van Praag et al., 2002), and it plays an important role in the normal function of the DG in spatial learning (Zhang et al., 2008; Zhao et al., 2003). It may be also necessary for the functional integrity of the circuits in which new cells are born. In fact, hippocampal lesions or disruptions of the function of the hippocampus impair spatial working memory (Cassel et al., 1998; Lee et al., 2002). Therefore, it is known that newborn neurons contribute to synaptic plasticity (LTP) in the DG (Saxe et al., 2006; Snyder et al., 2001; Zhao et al., 2003).

Today, it is known that different subregions of the hippocampus contribute differentially to learning and memory. In fact, CA1 subregions participate in temporal processing (Gilbert et al., 2006). On the other hand, CA3 appears to process spatiotemporal memory; and lesions or inactivation of CA3 lead to deficits in spatial working memory (Gilbert et al., 2006; Kesner et al., 2001). Therefore, CA3 and the trisynaptic pathway (DG-CA3-CA1) are thought to be important for rapid and one-trial spatial and contextual learning (novelty detection) and to tune CA1 place fields. CA3 is also thought to mediate the pattern completion and learning of associations where space or sequence is a component. In contrast, CA1 participates in consolidating memory through establishing associations between the hippocampus and neocortex as well as processing temporal information (Rolls et al., 2006).

Lesion and inactivation studies of the DG subregion result in impaired spatial working memory. Therefore, a recent work demonstrates that adult neurogenesis contributes to cognitive flexibility when it requires changing a learned response to a stimulus-evoked memory (Burghardt et al., 2012). Several studies in rodents and humans have shown that the DG has specific functions in the formation of different similar representations or interfering inputs (be it spatial, object-related, or episodic), a process known as pattern separation (Rolls et al., 2006; Hunsaker et al., 2008).

The recurrent connectivity (mainly of CA3), has been hypothesized to participate in episodic and working memory (Granger et al., 1996; Kesner et al., 2011; Wiebe et al., 1997). CA3 and CA1 pyramidal neurons and DG granule cells are suggested to participate in formation of a cognitive map, remapping to novel stimuli/environments, and memory consolidation (Ainge et al., 2007; Ekstrom et al., 2003; Foster et al., 2006; Ninkovic et al., 2007). It appears that with repeated trials and additional training, mice with lesions to or inactivation of the DG and/or CA3 can still learn spatial information incrementally, presumably mediated by CA1 (Lee et al., 2003; Young et al., 2008).

**4.2. Pattern separation**

The DG has been accepted to be responsible for pattern separation through sparse coding (Yung et al., 1993; Kesner et al., 2001; Kesner et al., 2004; O'Reilly, 1994; Rolls et al., 2006). Strictly, pattern separation is a process of encoding (Marr, 1971). The process happens by the fact that granule cells have small place fields (Mizumori et al., 1990), exhibit low, but highly reliable firing rates (Jung et al., 1993), and must overcome inhibitory interneuron input. For that reason, there is a low probability that a similar subset of DG cells will send input to the same CA3 neurons (O'Reilly, 1994; Rolls et al., 2006).

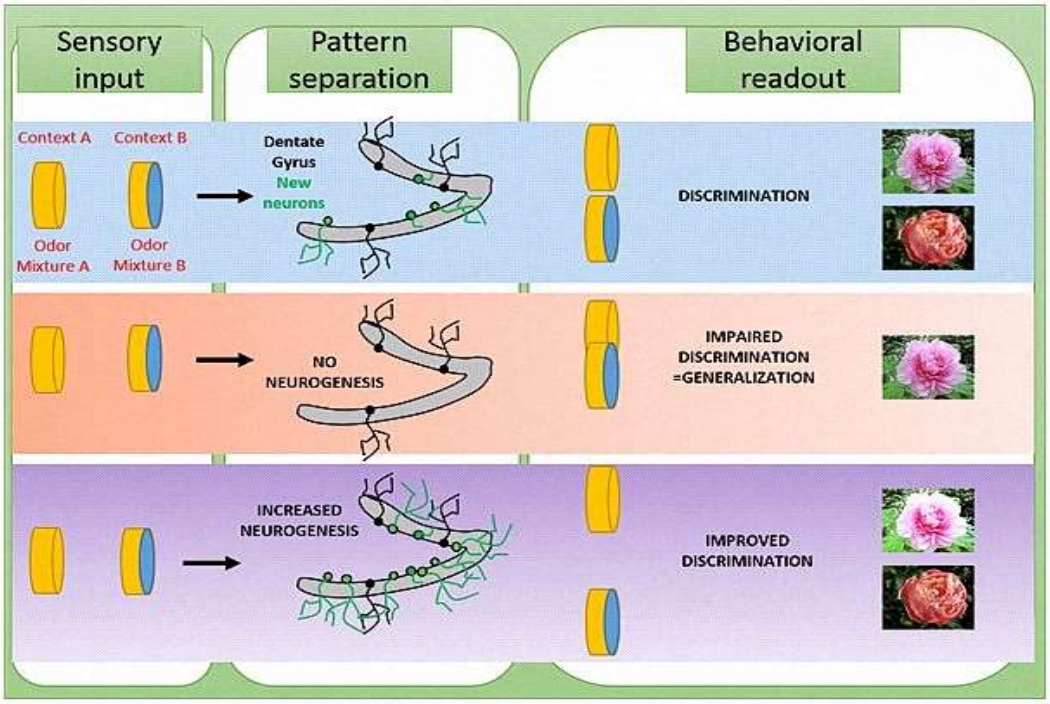


**Fig. 7.** Pattern separation in the dentate gyrus and the olfactory bulb. Both brain areas (DG and OB) are crucial for discrimination between similar contexts and odors (A and B), respectively, through the process named pattern separation. Pattern separation is modulated by adult neurogenesis. When adult neurogenesis is disrupted either by irradiation (X-ray) or by genetic ablation, discrimination is impaired leading to generalization and an inability to distinguish A from B. In contrast, when neurogenesis is enhanced by genetic manipulations (iBax for example) or exercise, discrimination is improved. Adapted from Sahay et al. 2011 by Ortega-Martinez.

The DG's role in pattern separation is certainly required for initial memory formation, but their role in reconsolidation memory is unclear. It has been suggested that memory retrieval may bypass the DG altogether (Kesner et al., 2004; Leutgeb et al., 2007). Once a spatial pattern separation has led to the encoding of distinct spatial representations, presumably CA3 place cells are able to maintain (for at least brief periods of time) these 'memories' and selectively reactive them depending on experience (Leutgeb et al., 2007; O'Reilly et al., 1994) (see Fig. 7).

While pattern separation refers to a process of encoding, pattern completion is the process of retrieval of a whole representation/memory from an incomplete part. Functionally, the hippocampus has been widely studied in

its role in memory and cognitive function, and as a result it is widely accepted that these brain region acts in two ways to subserve memory: By one hand, the hippocampus functions as a competitive learning network reducing the degree of overlapping among different activity patterns and in last term, this facilitatesthe information storage with minimal interference with other activity patterns. By the other hand, the hippocampus also acts as an auto association network allowing the recalling stored activity patterns from partial cues (Kesner et al., 2001; Marr, 1971; Rolls et al., 2006; Hunsaker et al., 2013). In order to make this hippocampal feature efficient and to prevent false, noisy, or erroneous recall; the idea is that representations in the hippocampus must be kept distinct, since very similar activity patterns need to be distinguished during retrieval (Hunsaker et al., 2013).

It is necessary to highlight that, by definition, pattern separation and pattern completion are separate and different processes that are dynamically at odds with each other (Hunsaker et al., 2013). During pattern separation, occurs that the system takes similar input patterns and separates them into orthogonal representations, allowing the formation of unique memories which cannot overlap with previous or subsequent memories. Nevertheless, this orthogonalization interferes with the pattern completion process. In this last process, it is required that a partial or overlapping input pattern trigger the recall of an existing memory instead of the creation of a distinct, new one. Due to this short balance between pattern separation and pattern completion processes in the hippocampus, it has been widely described that any inequality between both mechanisms could be responsible for a wide array of diseases (e.g., autism and schizophrenia), as well as neurocognitive aging (Hunsaker et al., 2013).

Pattern separation is typically tested by comparing behavioral or physiologic response to conditions in which inputs are more similar to those in which inputs are dissimilar. In behavioral studies, a goal-related object/space serves as the input that must be separated from a familiar object/space (Lee et al., 2003). Similarly, pattern separation is often tested by comparing cellular response to similarities/dissimilarities between environments in which an exploration task is performed (Lee et al., 2003; Leutgeb et al., 2007). Lesions of the DG, and non-lesions of CA3 or CA1, produce deficits when the similarities between spaces or objects to be discerned are maximal or testing environments are very similar, but DG lesioned rodents are not impaired when (spatial) interference is low (Hunsaker et al., 2008; Hunsaker and Kesner, 2008; Lee et al., 2003).

## 5. Conclusion

In summary, adult neurogenesis is extensively considered essential for memory consolidation. Numbers of papers related with neurogenesis and learning has exponentially increased since AHN discovery, 50 years ago (To review see Ortega-Martinez, 2015). Even recently, adult neurogenesis process has been described to occur in more brain areas, the link between memory and related neurogenesis primarily occurs in the DG of the hippocampus and OB. By the other hand, the adult hippocampus has been widely studied for its implications in numerous neurodegenerative and neuropsychiatric disorders, such as depression, anxiety, or Alzheimer´s disorder, among others. All these brain disorders also share, between other physiological features, its decreased AHN. In fact, andbecause hippocampus-dependent memory processes arealtered in such diseases, understanding the underlying molecular mechanisms is important for restoring normal brain function. In this regard, recently it has been proposed the possible role between CREB family of transcription factors and its implication in memory through its relation with AHN (see review Ortega-Martinez, 2015). Indeed, some recent drug discovery efforts have focused on increasing AHN (Ortega-Martinez, 2015). To reach this functional *'in vivo'* increase in hippocampal neurogenesis within the human brain, constitutes nowadays, an essential key target in neuroscience, for the future advance and development of new treatments in brain disorders, with all the societal and economic implications associated.

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