Neurogenesis, learning, and memory

Neurons are the building blocks of the brain, the cells most responsible for the ability to process and learn information. We receive most of our life's supply of neurons before we are born, losing many during adulthood. Happily, scientists have discovered that we also have a mechanism by which we can generate new neurons throughout our lives: neurogenesis.

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Executive summary

- More than ever before, world citizens of any age and most nationalities need or are forced to adapt to different environments and situations due to internal or external migration related to economic, political, and/or educational factors.
- For adequate adaptation to the changing environment and to self-induced change, the organization and functioning of our nervous system must be maintained. The gathering and analysis of information about our surroundings and ourselves ensure we can respond appropriately.
- Like in any other animal, this is possible due to the intricate relationship between the nervous system and our body, interconnected by neural networks.
- During early development, neural networks are formed by a process involving *neurogenesis* (the generation of new neurons), and *synaptogenesis* (the generation of interconnections between neurons, later refined by neuronal death and pruning of neural connections).
- The hippocampus, a brain center involved in learning, memory, and cognitive processes fundamental for early and continuous education, outstands for its plasticity, involving anatomic and functional changes spanning from synaptic connections to the cellular level.
- Learning and memory modulate cell proliferation, neurogenesis, and survival throughout postnatal life.
- Neurogenesis, learning, and memory are influenced by early experiences, feeding habits, the environment, sleep, and exercise.
- Teachers, school authorities, and policy makers can implement contingent classroom and school conditions for promoting brain plasticity to boost lifelong learning through, for example, physical exercise, multiprocess (e.g., musical) training, or mental (e.g., mindfulness) training.
- These initiatives are of utmost importance for disadvantaged populations such as those living in poverty or forced into internal or external migrations.
- Policy makers should be aware that their actions and decisions can have a wider and deeper impact on disadvantaged populations and consider implementing these and other interventions that promote lifelong impact on cognition.

Introduction

Nearly one billion world citizens of almost all nationalities and ages need or are forced to adapt to different environments and situations due to internal or external migration related to factors that include, amongst others, economic, political, and/or educational issues[1].

The appropriate adaptation to these environmental and self-induced changes depends, as in any animal, on the intricate relationship between the nervous system and the body. This is possible because the nervous system (from the most primitive chordates to mammals, including humans) is formed by networks of neurons that connect the nervous system with most parts of the body, as well as brain regions with each other. The activity of those neural networks enables, in one general direction of information flow, the sampling and interpretation of information related to the external world or from internal origin. In the other general direction, neural networks allow the efferent/motor control of body functions and the execution of actions that change the environment and/or allow adaptation. Moreover, neural activity produces emerging properties[2] such as sensation and perception, interpretation of incoming information for the selection and coordination of the most appropriate responses, and consideration of goals, motivations, and previous experience—thus also involving the recall of what was previously learned.

The formation of neural circuits involves the generation of neurons through a process called neurogenesis, and the subsequent formation of interconnections (synapses) between them. These processes result in overproduction of both neurons and synapses, and are followed by neuronal death and pruning of neural connections that refine the neural circuits[3].

Neurogenesis is influenced by learning as well as by external and internal factors such as early life environment (including enrichment or adverse childhood experiences), exercise, diet, and sleep[4].

In adulthood and in elderly people, the frequency of diseases caused by loss of particular groups of neurons caused by neurodegeneration, such as Parkinson's, Alzheimer's, and related diseases, is very high and is expected to continue increasing unless strategies to prevent neuronal cell death and/or promote neuro-regeneration are discovered[5,6]. While the most outstanding symptom of Parkinson's disease is rest tremble, memory is the most affected cognitive function in Alzheimer's disease.

Thus, neurogenesis emerges at the cellular level as a neural process subserving the construction and plasticity of the nervous system and emerging cognitive functions, particularly learning and memory. At the subcellular level, both learning and memory also depend on synaptic plasticity (activity-dependent changes on the efficacy of synapses within neural circuits). Synaptic plasticity is induced at appropriate synapses during memory formation and is both necessary and sufficient for the encoding and trace storage of memory[7]. This brief aims to summarise knowledge about neurogenesis, how it is regulated, and which preventive actions can be promoted from childhood by teachers in schools and by parents and caregivers within the family.

Neurogenesis definition and discovery

Neurons, the building blocks of the nervous system, are generated through neurogenesis, a paradigmatic example of the capacity of living organisms to self-generate and self-regulate[8]. The evolutionary origin of neurogenesis dates to 650 million years, about the time of origin of the nervous system in invertebrates. Nowadays, it is a process that lasts from early development to adulthood in all vertebrates, including humans[9], even though adult human neurogenesis has been recently at the center of a scientific debate[10,11].

Joseph Altman[12] discovered neurogenesis in mammals almost 60 years ago, but it took about 30 years for the scientific community to accept his challenge to previous dogmas. Altman described neurogenesis as a "prolonged process, one that begins during early embryonic development and proceeds through late embryonic, early fetal, perinatal, infantile, juvenile, and adult periods with distinctive age-related features and properties"[13].

Neurogenesis for nervous system formation and plasticity

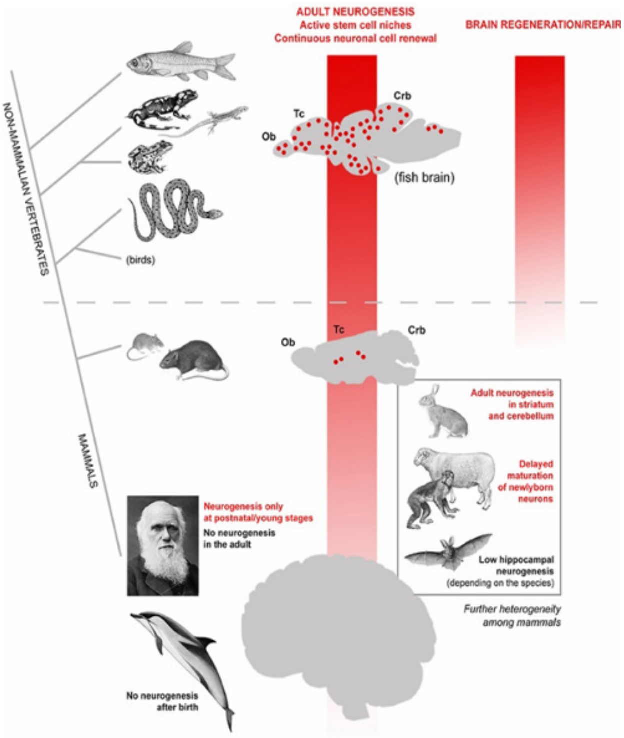

Figure 1. Vertebrate postnatal neurogenesis. Left: Phylogenetic relationship between some vertebrate

species used as animal models to study postnatal neurogenesis. Middle: The graded red bar indicates that more ancestral species (e.g., fish, reptiles, amphibians) have widespread adult neurogenesis, unlike mammals (e.g., rodents, humans, dolphins). Right: Regenerative capacity is also reduced along evolution. Despite these trends, differences among mammalian species also exist. Laboratory rodents have constitutive neurogenesis throughout life, whereas in humans the presence of adult neurogenic niches is very limited and even debated. The situation in nonrodent mammals is diverse. Some species show several neurogenic niches up to adulthood (rabbits), others show limited (bats) or do not show neurogenesis (dolphins). Modified from Ref. 16.

During development, neurogenesis contributes to the *novo* sculpturing and growth of the nervous system. Adult neurogenesis is, perhaps, the most outstanding form of whole-cell neural plasticity. It enables the most manifest modification of the nervous system's organization in response to changes in neural activity, as well as the repair of the nervous tissue after diverse forms of injury[14].

Neurogenesis may serve multiple functions, depending on multiple factors such as the species, age, and physiological or pathological state. In some species, as in the case of nonmammalian vertebrates, neurogenesis enables the extended brain development and growth that continue along postnatal life up to adulthood. Neurogenesis is also involved in the constant addition of new neurons and/or neuronal turnover. Another function is the regeneration after neuronal loss due to different causes during postnatal life, including adulthood[15,16].

During early development, the nervous system of vertebrates is a tube whose wall is made of multipotent cells that produce the main neural cell types, both neurons and glia, in all brain regions. Neurogenesis is progressively limited in extension and amount along animal development and evolution (see Figure 1 left, middle). This is paralleled by a loss in regenerative capacity that, in humans, is associated with the inability to replenish neurons lost due to several reasons, including age-related neurodegenerative diseases, stroke, or trauma[16] (see Figure 1, right) and the consequent appearance of symptoms of various diseases.

Adult neurogenesis

Cell proliferation and postnatal neurogenesis persist up to adulthood in very few and restricted regions of the mammalian brain called neurogenic niches (see Figure 2A)[13]. There are two most remarkable neurogenic niches in the brain hemispheres of mammals[18,19], including humans[20]. One neurogenic niche occupies part of the subventricular zone of the telencephalic ventricles (SVZ). The other is the subgranular zone of dentate gyrus (SGZ) of the hippocampus (see Figure 2), an ancestral part of the brain cortex involved in learning and memory (both declarative* and spatial**[21]).

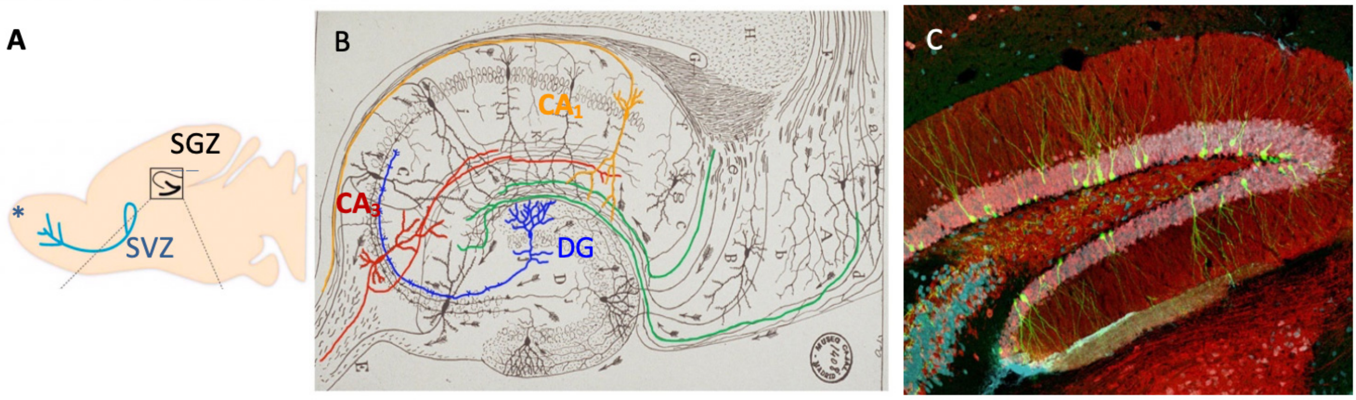

Figure 2. Hippocampal neurogenesis. (A) Schematic representation of the lateral view of a rodent brain indicating the location of adult mammalian neurogenic niches, at the wall of the telencephalic ventricles (the subventricular zone, SVZ) and the hippocampus subgranular zone (SGZ). Neurons generated in SVZ migrate to the olfactory bulb (asterisk) whereas those generated in SGZ migrate locally. (B) Modified drawing from Cajal to highlight the organization of the hippocampal circuitry and flux of information (arrows) in the mouse brain. The hippocampus receives projections from other parts of the cerebral cortex (the entorhinal cortex -EC-, green) that contact directly the principal cells (pyramidal neurons) of regions CA1 (orange)

and CA3 (red), or indirectly (through projections to granular neurons of the dentate gyrus) granule neurons (DG, blue). CA1 pyramidal neurons project back to EC. (C) Image obtained by confocal microscopy, corresponding to the DG of mice hippocampus showing newborn neurons (21 days) labelled by viral particles attached to a green fluorescent molecule. Accessed from:
http://www.leloir.org.ar/blog/cientificos-argentinos-descubren-un-proceso-clave-en-el-funcionamiento-de-la-memoria/.

Neurogenesis takes time. It is a process that involves several main steps (see Figure 3) from proliferation of stem or precursor cells, migration of newborn cells to their destination, and differentiation into specific cell types. During this process, many cells die but others become new neurons that form new circuits—mainly during early ontogeny—or insert into preexisting neural circuits—mainly during late postnatal development and adulthood[22,23].

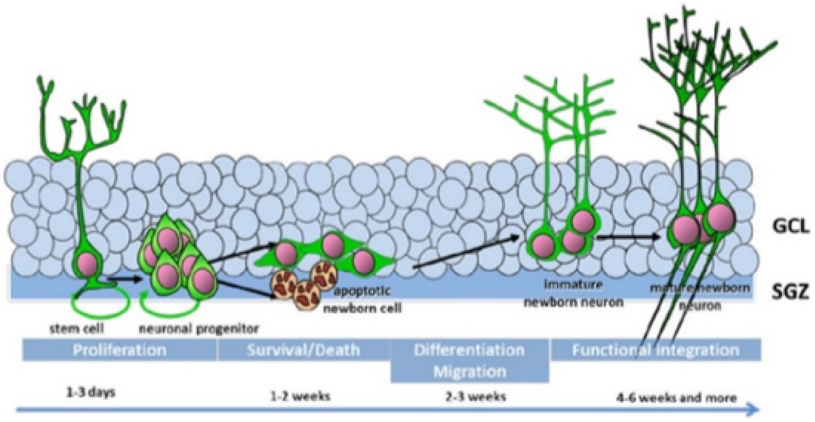

Figure 3. Schematic representation of adult steps in the process of neurogenesis. New neurons that integrate the granule cell layer (GCL) of the dentate gyrus originate from stem and precursor cells at the subgranular zone (SGZ). In the course of their maturation, they exhibit specific properties that confer them a unique behavioural function. [Image from Koehl (2015) licensed under
https://creativecommons.org/licenses/by/4.0/
Koehl, M. Gene-environment interaction in programming hippocampal plasticity: focus on adult neurogenesis. *Front. Molec. Neurosci*. 8, 8, doi:10.3389/fnmol.2015.00041 (2015).]

Neurogenesis to remember, neurogenesis to forget…

Almost twenty years after the discovery of postnatal and adult neurogenesis by Altman, another group headed by Nottebhom[24] discovered seasonal changes in the size of the high vocal center (HVC) of birds paralleled by modulation of neurogenesis. Their contributions were not only fundamental for the clarification of a long-lasting scientific controversy, but also for proposing a functional role of postnatal neurogenesis in learning. In fact, the peak of neurogenesis of HVC—the avian homologous of the mammalian hippocampus—also correlates to song learning[24].

Hippocampal mammalian neurogenesis is a process that maintains hippocampal plasticity. The addition of new neurons contributes to improved cognitive functions including learning and memory throughout life in rodents and humans[23,25] and memories that involve this brain region, such as declarative memory and spatial memory. Conversely, the integration of new neurons into existing circuits also involves the formation of new connections between neurons that may destabilize the established networks and make previously formed memories more labile and prone to decay faster[26]. Consistent with this, a high rate of childhood hippocampal neurogenesis may represent a mechanism underlying accelerated forgetting of contextual fear memory[26], even though "oblivion is full of memory"[27].

Considering the involvement of neurogenesis in human brain plasticity, a property that makes the human brain so flexible and successful[28], it is important to know if this process can be modulated through intervention, and if it is possible to implement contingent classroom and school conditions and appropriate habits for promoting brain plasticity to boost lifelong learning.

Is it possible to modulate neurogenesis?

Studies in animals indicate that several factors influence brain cell proliferation, neurogenesis, and/or a newborn neuron's survival. Interestingly, memory itself is one of the factors that modulate neurogenesis[24,29]. Also, exercise[30,31] and environmental factors[32,33], including exposure to music[34], affect hippocampal neurogenesis.

Learning, when particularly involving the hippocampus (e.g., learning about space and time) has a trophic effect on adult-generated hippocampal neurons[35]. Learning increases the survival of newly born cells, mainly neurons, which remain for months, longer than the period that the hippocampus is required for the memory[29]. Moreover, Sisti and collaborators[36] showed that information that is spaced over time is better remembered than the same amount of information massed together and relates to the number of cells that reside in the hippocampus.

All these factors also affect human brain plasticity, including in some cases neurogenesis, impacting learning and other cognitive functions.

For example, regular and intensive training affects brain plasticity and produces anatomical and functional changes related to experience as shown in London taxidrivers[37]. Compared to control subjects who do not drive taxis, the volume of the caudal region of the hippocampus increases, and that of the rostral hippocampus decreases (in both cases correlating with the time spent as a taxi driver).

Learning skills[38,39](either sequential motor skills or meditation—a form of "pure" mental training) increases hippocampal volume and has an impact not only on the specific skill but also on other cognitive functions, indicating that this learning might produce more general reorganization of brain neural networks.

Musical training, particularly playing a musical instrument (a complex multimodal and multiprocess activity that requires the use of higher order thinking), not only improves specific sensory-motor skills, it also elicits widespread functional and anatomical plasticity, particularly in the hippocampus. It impacts a wide range of nonspecific cognitive functions throughout development[40-42], adulthood, and aging [43,44].

Short- and long-term meditation training produces stable structural changes of several regions including the hippocampus and large-scale neural networks (the default mode network, the attentional network, as well as connections between both of them). Regions that are active during meditation are the most affected by these structural changes and, in some cases, expertise has been reported to correlate with the magnitude of morphological changes. Furthermore, meditation affects all components of attention (mainly executive attention, and to a lesser extent orienting and alerting attention) and other cognitive functions such as executive functions (verbal fluency, cognitive inhibition, and working memory), conflict resolution, and emotional regulation. Interestingly, the improvements can also be transferred to other tasks[36.]

Suggestions for teachers, school administrators, and authorities

The evidence reviewed here has focused on neurogenesis and brain plasticity, their modulation, and their roles in learning and memory. This suggests it should be emphasized that teachers, school administrators, and policy makers have "in their hands" the invaluable opportunity to contribute to implementing contingent classroom and school conditions enabling habits for promoting brain plasticity to boost lifelong learning.

As previously remarked, it is desirable that schools in low socioeconomic status communities shift the needle of the balance of their schedules toward activities that foster physiology such as naps, exercise, and meals to surpass one of the major bottlenecks of school learning among students with low socioeconomic status[45].

From this platform, and as a second turn of the screw, teachers, school administrators, and policy makers may promote the inclusion in schools' schedules those activities that promote brain plasticity as well as cognitive improvement and adaptability.

Global inclusion of skills training (either only physical, multiprocess such as musical training, or mental training—such as mindfulness) may allow one more step of the staircase to be climbed towards the promotion of wider and deeper exploitation of educational resources.

These actions would be relevant not only to low socioeconomic status communities but also for children and families forced to change life circumstances as a result of migration that demands adaptability. Furthermore, according to the long-term effects on cognition, these activities may elicit lifelong benefits for future encounters with other challenging environments.

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**Declarative (explicit or episodic) memory* concerns our ability to consciously recollect personally experienced events, changes in the world that we can localize in time and space. It is a type of memory that can be recalled or declare its content either verbally or not[21].

***Spatial memory* refers to the memory for location within an environment, involving the spatial references, the dimensionality of the world, the orientation (mainly in relation to external references), and the consequences of self-motion[21].