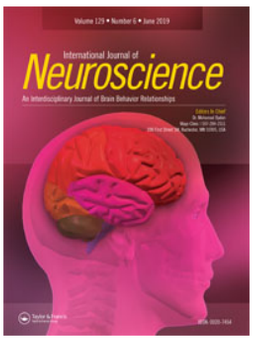

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REVIEW ARTICLE

Neurogenesis in the adult hippocampus: history, regulation, and prospective roles

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ABSTRACT

Background: The hippocampus is one of the sites in the mammalian brain that is capable of continuously generating controversy. Adult neurogenesis is a remarkable process, and yet an intensely debatable topic in contemporary neuroscience due to its distinctiveness and conceivable impact on neural activity. The belief that neurogenesis continues through adulthood has provoked remarkable efforts to describe how newborn neurons differentiate and incorporate into the adult brain. It has also encouraged studies that investigate the consequences of inadequate neurogenesis in neuropsychiatric and neurodegenerative diseases and explore the potential role of neural progenitor cells in brain repair. The adult nervous system is not static; it is subjected to morphological and physiological alterations at various levels. This plastic mechanism guarantees that the behavioral regulation of the adult nervous system is adaptable in response to varying environmental stimuli. Three regions of the adult brain, the olfactory bulb, the hypothalamus, and the hippocampal dentate gyrus, contain new-born neurons that exhibit an essential role in the natural functional circuitry of the adult brain.

Purpose/Aim: This article explores current advancements in adult hippocampal neurogenesis by presenting its history and evolution and studying its association with neural plasticity. The article also discusses the prospective roles of adult hippocampal neurogenesis and describes the intracellular, extracellular, pathological, and environmental factors involved in its regulation.

Abbreviations: AHN: Adult hippocampal neurogenesis; AKT: Protein kinase B; BMP: Bone Morphogenic Protein; BrdU: Bromodeoxyuridine; CNS: Central nervous system; DG: Dentate gyrus; DISC1: Disrupted-in-schizophrenia 1; FGF-2: Fibroblast Growth Factor 2; GABA: Gamma-aminobutyric acid; Mbd1: Methyl-CpG-binding domain protein 1; Mecp2: Methyl-CpG-binding protein 2; mTOR: Mammalian target of rapamycin; NSCs: Neural stem cells; OB: Olfactory bulb; P21: cyclin-dependent kinase inhibitor 1; RBPj: Recombination Signal Binding protein for Immunoglobulin Kappa J Region; RMS: Rostral migratory Stream; SGZ: Subgranular zone; Shh: Sonic hedgehog; SOX2: SRY (sex determining region Y)-box 2; SVZ: Subventricular zone; Wnt3: Wingless-type mouse mammary tumor virus

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1. Introduction

Neurogenesis, the process of producing functional neurons from precursor cells, was conventionally perceived to occur only during the embryonic and prenatal stages in mammals [1]. Altman's studies in the 1960s presented the first indication of the existence of newly formed dentate granule cells in the postnatal hippocampus of the rat [2]. Goldman and Nottebohm then reported on ventricular zone neurogenesis in the adult brain of the female canary [3]. Reynolds and Weiss, in the 1990s, extracted neural stem cells (NSCs) from the adult mammalian brain [4]. Ever since, the field of neurogenesis grew tremendously, especially after the introduction of bromodeoxyuridine (BrdU) – a synthetic analog of thymidine used as a lineage tracer in the detection of proliferating cells [5]. Soon, validations of permanent neurogenesis in many inspected mammals were published [6]. The last decade, specifically, witnessed substantial progress in the field of adult neurogenesis.

Active neurogenesis has been described and reported, under typical settings, in three definite "neurogenic" brain regions: (a) the subgranular zone (SGZ) in the dentate gyrus (DG) of the hippocampus where new dentate granule cells are produced; (b) the subventricular zone (SVZ) of the lateral ventricles whereby the newly generated neurons tend to travel

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through the rostral migratory stream (RMS) into the olfactory bulb to act as interneurons; and (c) the hypothalamus.

The hippocampus is part of the temporal lobe and the portion of the brain responsible for memory, learning, and emotion [8]. Several distinct regions characterize the mammalian hippocampus each with a different function, including areas called the Cornu Ammonis fields (CA1, CA2, and CA3) and the DG [8]. The newly formed DG neurons project to the CA2 region [9], which plays crucial roles in social memory and contextual discrimination [10,11]. The adult-born DG neurons promote excitation of the CA3 pyramidal neurons, mossy cells, and hilar interneurons [12], which is essential for memory recovery and for delivering feedback inhibition into the mature DG neurons [13].

Adult neurogenesis is an intricate process that is moderated and affected by numerous physiological and pathological stimuli. In the adult hippocampus, neurogenesis could be altered following stimuli that modulate its structural plasticity, such as environmental stressors and learning [14]. Today, we have unraveled some of the characteristics of the neural subtypes in the adult central nervous system (CNS), the supplementary indigenous microenvironment, and the successive stages of adult neurogenesis [15,16]. Several studies have shown the effects of new-born neurons on existing neural circuitries and their functional contribution to brain tasks under physiological and pathological conditions [17,18]. This comprehensive field of research has been booming lately, as it hovers over the principles of stem cell regulation, neuronal development, structural plasticity, and neuropathological mechanisms. Nevertheless, contradictory findings led to a number of debates and raised many questions on whether adult hippocampal neurogenesis does indeed occur in humans or not.

This article reviews current advancements in adult hippocampal neurogenesis by presenting the history of its discovery and evolution and studying its association with neural plasticity. The article also explores the prospective roles of adult neurogenesis in understanding neurophysiology and describes the numerous intracellular, extracellular, pathological, and environmental factors involved in its regulation.

2. History of neurogenesis discovery

More than a century ago, Santiago Ramon y Cajal [19] stated:

> *In adult centres the nerve paths are something fixed, ended, immutable. Everything may die, nothing may be regenerated. It is for the science of the future to change, if possible, this harsh decree.*

As perceived by Cajal, the mature nervous system was distinguished from the developing nervous system by the lack of growth and cellular regeneration. Nevertheless, contemporary progress in examining persistent neurogenesis in the adult brain has given hopes that self-renewal and structural repair may be possible in the mature CNS. Following recent advancements in neural plasticity, it has become gradually clear that environmental factors, involving explicit experiences, have an intense influence on adult brain structure and function [20]. In this aspect, attention has focused on the hippocampus due to its role in learning and memory and its notable capability for plasticity. However, questions arise on how the change in the number of neurons is contributing to the behavioral adjustments.

The field of neurogenesis has made significant progress during the past few decades [7,18,21,22]. In fact, the idea that new neurons continue to be integrated into the adult brain was not generally accepted until the mid-1990s [23]. However, numerous factors triggered this change in perception of adult neurogenesis. First, adult-born neurons were clearly identified through immunohistological techniques that allow labeling dividing cells with nucleotide analogs and protein markers specific to neurons, together with confocal imaging [6,24,25]. Second, these tracking techniques showed that the assimilation of young neurons was greatly controlled by genetics, age, stress, exercise, and other behavioral aspects [6,24,25].

Neurogenesis has been designated in numerous brain regions of various species. Early on, it was recognized in songbirds [3], sparrows [26], reptiles [27,28], and fish [29,30]. Nevertheless, neurogenesis seems to be substantially more limited in mammals. In fact, in the adult mammalian brain, it is currently well established that neural stem cells are retained in distinct structural regions involving the DG of the hippocampus [31], as well as the walls of the lateral ventricles [32]. Pilz et al. [33] were capable, through labeled individual progenitor cells in the mouse hippocampus, to watch the developmental progression as progenitor cells gave rise to mature cells of the DG.

In early 2018, a study by Sorrells et al. [34], and one of the biggest yet, completely failed to find any trace of young neurons in dozens of hippocampal samples collected from adult humans. They concluded that recruitment of young neurons to the primate hippocampus decreases rapidly during the first years of life, or is extremely rare, in adult humans.

They believed that the early decline in hippocampal neurogenesis raises questions about how the function of the DG differs between humans and other species in which adult hippocampal neurogenesis is preserved [34]. Shortly afterwards, another study by Boldrini et al. [35] reported that human hippocampal neurogenesis does not only exist but persists throughout aging. The study concluded that it is possible that ongoing hippocampal neurogenesis sustains human-specific cognitive function throughout life and that declines may be linked to compromised cognitive-emotional resilience [35]. Other reports have shown that adult-born neurons are involved in sensory learning through a specific involvement of adult-born neurons in facilitating odor–reward association during adaptive learning [36].

Newborn neurons have also been described in other brain regions such as the hypothalamus [37]. It is suggested that these hypothalamic neurons can integrate in neural pathways and contribute to physiological processes, like energy balance regulation [38]. Nevertheless, more studies and investigations are needed to unravel the complete mechanisms of neurogenesis in the adult hypothalamus [39].

3. Evolutionary perspective of adult neurogenesis

Understanding the significance of new neuron formation necessitates an accurate analysis of the evolutionary framework of adult neurogenesis [40–43]. This is rather important since the emergence of the notion of adult neurogenesis still seems to contradict long-term scientific belief. Rakic's controversial paper [44], 'Limits of Neurogenesis in Adult Primates', debated that sophisticated brains choose constancy over flexibility and that newborn neurons would disturb intricate neuronal networks. He further argued that validating adult neurogenesis in humans would put us at equal levels with lobsters, rodents, and perhaps birds [44]. Nowadays, adult hippocampal neurogenesis in humans has been relatively established [45]. Fairly, Rakic's dispute mainly targeted cortical neurogenesis; however, the hippocampus that is part of the archicortex, still was not totally discounted from the debate.

3.1. Neurogenesis in the olfactory bulb versus the hippocampus

A handful of differences exist between the two recognized neurogenic sections of the adult mammalian brain. Neurogenesis in the adult olfactory bulb produces various subtypes of interneurons that contribute to the sensory input processing [46,47]. In contrast, neurogenesis in the adult hippocampus creates only one type of excitatory neurons that contributes to adaptable memory development [48,49]. While adult neurogenesis in the hippocampus arise form precursor cell populations in the dorsal region of the hippocampus, adult neurogenesis in the SVZ/olfactory bulb arise from the precursor cell populations in the ventral region of the SVZ. In the SVZ, progenitor cells grow and migrate along the rostral migratory stream to the olfactory bulb where they differentiate and mature into interneurons. Interestingly, the neuroblasts and/or newborn neurons that originate from the SVZ in humans travel to multiple brain regions, such as the frontal cortex and the cingulate cortex in the infant brain and the striatum in the adult brain [50,51].

For a while, neurogenesis in the SGZ was debated. Some reported that adult hippocampal neurogenesis in the SGZ is extremely conserved in most mammals [52]. Still, others showed that in the DG, new neurons develop from neural precursor cells in the SGZ, as revealed through proliferation markers using BrdU [5]. It was established that produced neuroblasts travel to the superimposing granule cell layer and mature into excitatory neurons [5].

The two types of mammalian adult neurogenesis, in the DG and the olfactory bulb, evolved to handle considerably distinct challenges and demands, and were thus formed by relatively dissimilar evolutionary forces. Neurogenesis in the olfactory system is evolutionarily old and vastly preserved, whereas the DG is a young substructure of the hippocampus whose neuronal network and specific role is exclusive to mammals [53]. While it has been claimed that adult neurogenesis must be an atavism or, at best, a heritage from our ancestors, the notion may be true for the olfactory system but not for the hippocampus.

3.2. Neurogenesis and plasticity

A significant aspect of advanced brains is their plasticity, which is by definition their ability to regulate their network structure to meet real conditions. Edelman [54] has compared the means of plasticity underlying basically all learning functions to the mechanisms that theoretically control evolution and has invented the term 'neural Darwinism'. This term has been criticized since it is not entirely clear to which extent it is a true selection rather than arbitrary networks forming adaptive circuitry. Yet, plasticity is

certainly a selective process. In fact, at the synaptic level, networks that are being used are reinforced, while those that are not used are discarded [55]. Adult neurogenesis, in turn, adds another aspect to plasticity in which novel neuronal nodes are employed in the network, and it is precisely these new nodes that, notably for a temporary phase, convey synaptic plasticity [56–58]. Few weeks after birth, the newborn neurons exhibit an inferior threshold for potentiation, which allows their recruitment and thus yields a bias toward the most plastic neuronal cells [59].

It seems that adult neurogenesis offers methods of structural flexibility in many species other than mammals. Birds are among the most remarkable examples. Incessant neurogenesis is revealed throughout the songbird brain and is directly associated with plasticity [60]. For instance, adult male canaries create neurons seasonally as they learn and forget their songs [61], signifying that new neurons are immediately wired into brain function.

What we perceive in the bird as equivalent to the hippocampus can be comparable to the precursors of adult neurogenesis in the hippocampus of mammals [62]. However, the mammalian hippocampus is evidently distinct due to the presence of the DG that has precise connectivity and discrete function [41,43]. Given the fact that very few thorough comparative studies exist, more comprehensive descriptions of adult neurogenesis in more species are warranted. This would not directly clarify how adult neurogenesis has evolved but it would rather permit better understanding of the notion that adult hippocampal neurogenesis is regulated by environmental and behavioral factors. Nonetheless, if adult hippocampal neurogenesis is involved in the individual's compliance in response to various challenges through the adaptable incorporation of new information into preexistent networks [58], the same may pertain to other species. Hence, one would expect that species that need to adapt to challenging environments depend more on adult hippocampal neurogenesis than those living in restricted and steady environments [46].

Adult neurogenesis is also a customizing trait [63]. Elusive individual variances in early conditions and distinctive behavioral routes lead to an increase in phenotypic discrepancy with time. Yet, there are much more important concerns to be resolved for such a quantitative trait.

3.3. Neurogenesis in humans

Assessing neurogenesis in humans is significantly more challenging. Although human neurogenesis was initially established using BrdU, the sample sizes were very little [6]. Furthermore, studies using histological markers created some uncertainty concerning the general levels of neurogenesis in humans because samples are not always very well conserved after death [64].

Analysis of the number of neuronal progenitor cells gives an indirect indication of the possible extent of neurogenesis. Carbon dating is a technique in which rates of young neuron birth in humans could be assessed by making use of the principle that ^{14}C in the atmosphere is taken up by plants that are food for animals, both of which are consumed by humans [65]. As ^{14}C is assimilated into DNA during cellular division, the ^{14}C content of a cell thus reflects ^{14}C levels in the atmosphere at the time of the birth of the cell. Between 1955 and 1963, an elevated atmospheric ^{14}C levels caused by above-ground nuclear bomb testing were recorded [66]. Since the Partial Nuclear Test Ban Treaty in 1963, atmospheric levels of ^{14}C have declined because of uptake by the biotope and diffusion from the atmosphere [67]. Spalding et al. [45] used the ^{14}C birth-dating technique on hippocampi dissected from post-mortem brains donated by people of different post-mortem ages during the 20th century to measure neuronal cell turnover in subjects. They then separated neuronal and non-neuronal hippocampal cells, filtered the neuronal DNA, and measured ^{14}C levels. Results showed that subjects born before 1955 had higher ^{14}C concentrations in neuronal DNA than were present in the atmosphere before 1955, which establishes that there has been DNA synthesis after 1955, indicating hippocampal neurogenesis [6].

Over the years, adult human neurogenesis has witnessed strides in development and progress [68–100]. Figures 1 and 2 show the major developments in the field of adult neurogenesis between 1970 and 2018.

4. Factors regulating adult neurogenesis

Adult hippocampal neurogenesis is tightly regulated. It has been demonstrated that cell-intrinsic molecular conduits precisely control self-renewal of adult neural progenitors and their differentiation into neurons [31]. Extracellular factors and cell-to-cell communications in the neurogenic niche also contribute to this control. Similarly, neurotransmitters such as GABA, glutamate, dopamine and serotonin [101], as well as cytokines and growth factors, exhibit significant modulatory functions in postnatal adult neurogenesis [31]. The physiological state of the hippocampus controls the recruitment of newborn DG neurons into neuronal

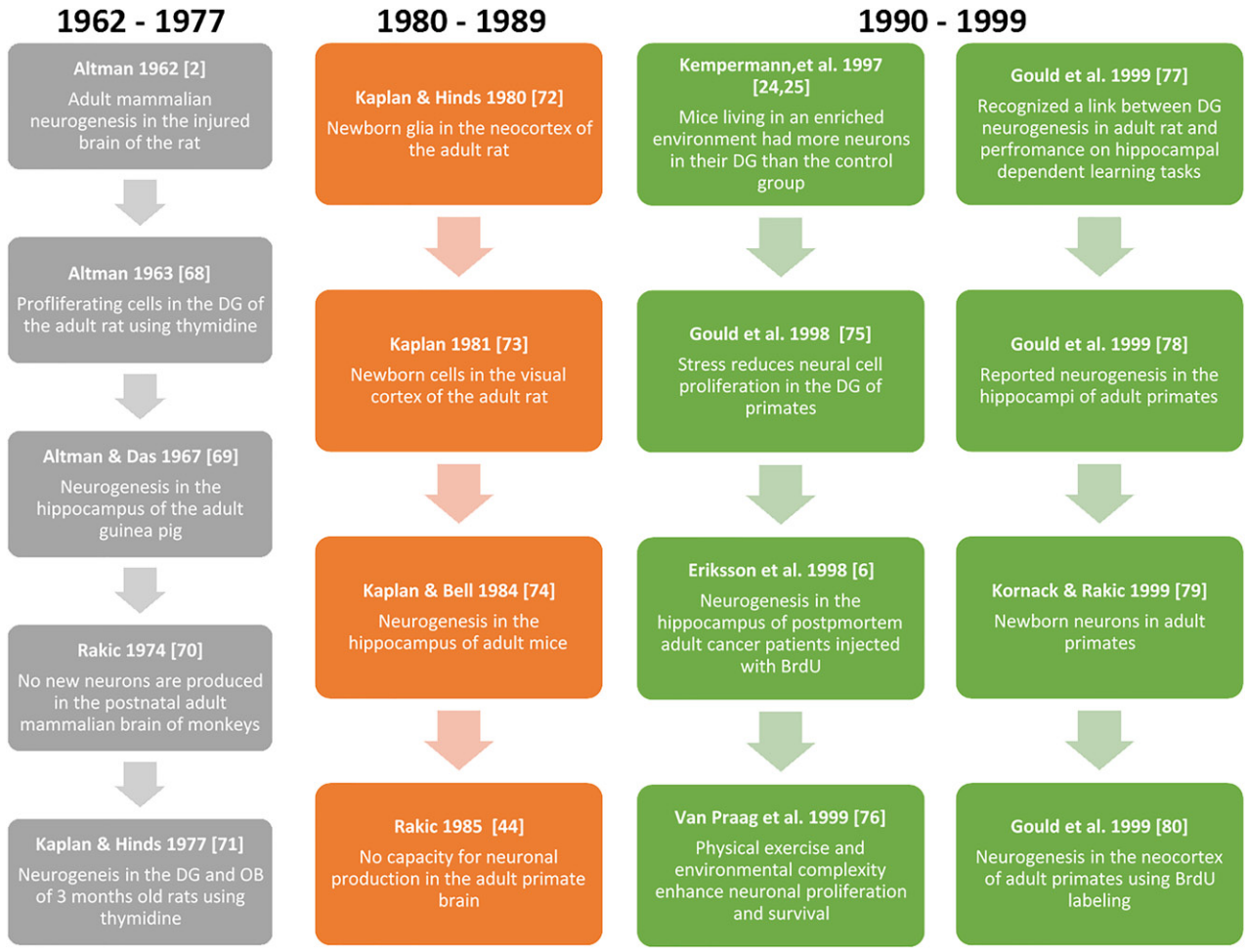

Figure 1. Timeline showing the major research discoveries in the field of adult neurogenesis between 1962 and 1999.

networks and their incorporation into the hippocampal circuits through GABAergic signaling [102]. In addition, researchers using optogenetics and chemogenetics have revealed that GABAergic inputs from parvalbumin-positive interneurons that produce gamma waves are crucial to augment the assimilation and maturation of young DG neurons [103]. A new report has demonstrated that diazepam binding inhibitor, an endogenous negative modulator of GABA receptors, regulates the proliferation of intermediate neural progenitors [104]. Furthermore, neural stem cells are very reactive to environmental molecular signals. This contributes to the formation of the neurogenic niche in neonates, which preserves its functions in the adult [105].

Numerous extracellular actors play roles as signaling factors to control maintenance, activation, and fate of adult neural precursors [106–118]. Studies demonstrate that the neurogenic activity in the SVZ/SGZ is dynamically regulated by a complex interplay between different extracellular factors. Adult neurogenesis, also, is largely influenced by intracellular factors, including cell cycle regulators, transcription factors, and epigenetic regulators [115–126] (Table 1).

Many neurological-disease-risk genes control adult neurogenesis [15,128–135] (Table 2). Such outcomes raise the interesting prospect that deviant postnatal neurogenesis might contribute to the juvenile and adult onset of several mental disorders. Moreover, adult neurogenesis has been documented to be vigorously modulated by numerous physiological stimuli [5,62,75–77,87,136–162] (Table 3). In 2018, a murine study by Choi et al. [163] showed that inducing hippocampal neurogenesis alone did not improve cognition in mice with Alzheimer's Disease, whereas inducing neurogenesis while simultaneously ameliorating the neuronal environment via exercise did.

5. Prospective roles of adult neurogenesis

While the olfactory bulb is involved in olfaction, the dorsal and ventral parts of the hippocampus of the adult brain have been associated with learning/memory and affective behaviors, respectively. Directly after

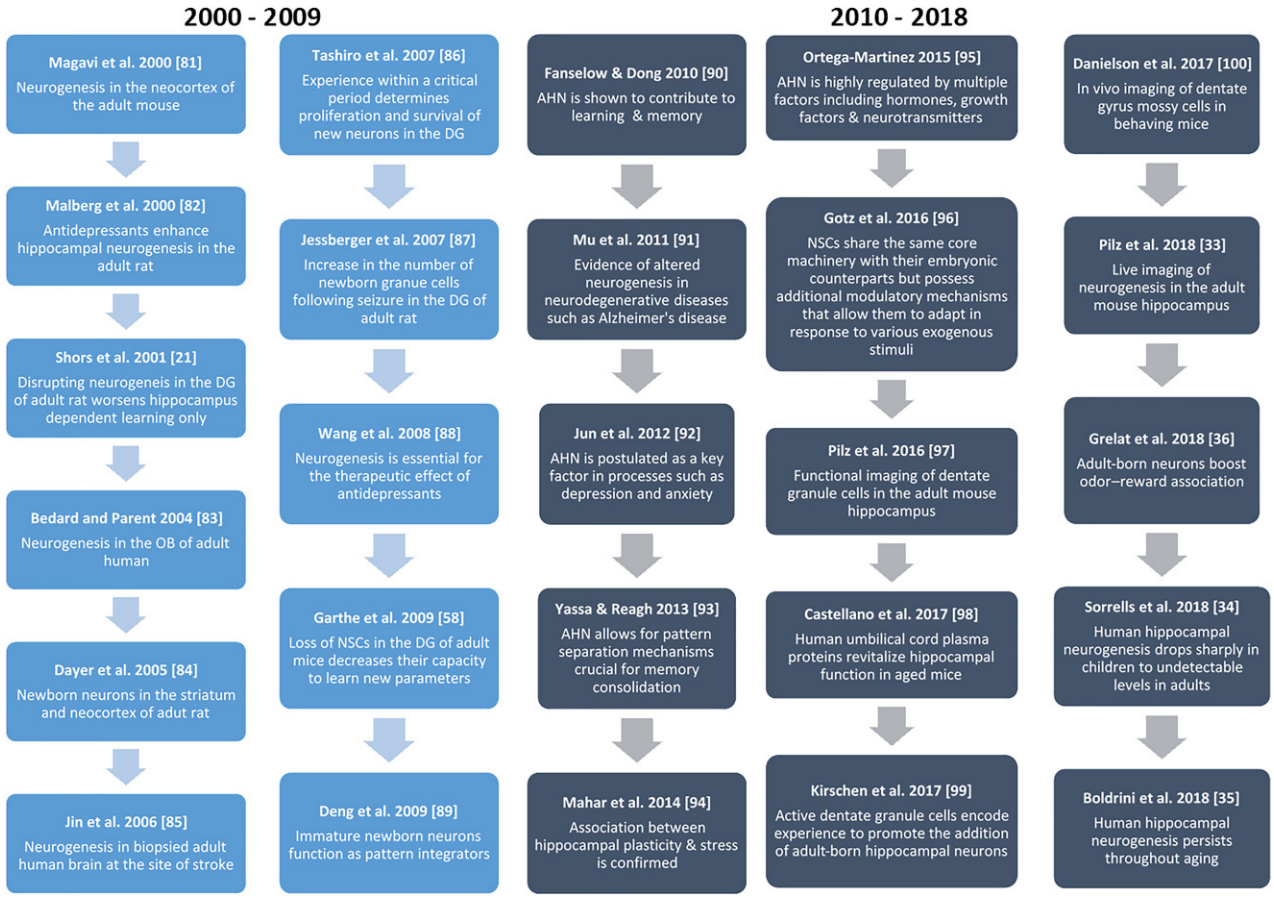

Figure 2. Timeline showing the major research discoveries in the field of adult neurogenesis between 2000 and 2018.

the initial detection of neurogenesis in the postnatal rat hippocampus, Altman [164] proposed that new neurons are imperative for learning and memory. The enhanced integration of adult-born neurons in aged animals enhances contextual memory [165], hinting that augmenting adult hippocampal neurogenesis can increase memory precision in aged humans. Although still under rigorous discussion, investigations at the cellular, circuitry, system, and behavioral levels over the past few years have created rising proof supporting significant contributions of adult-born neurons to hippocampal functions [18,166].

At the cellular level, newfound neurons exhibit unique properties that are distinctive from mature cells [12,56,57,167]. Newborn neurons that are connected through synapses display hyper-excitability and superior synaptic plasticity of their glutamatergic inputs in both the hippocampus and the olfactory bulb, which allows them to make an exceptional influence on information processing [168].

At the circuitry level, adult-born neurons are accountable for specific distinct features of the local network. One characteristic is a diminished sensitivity of new neuronal cells to potent perisomatic GABAergic inhibition from interneurons during periods of stress [167].

At the system level, numerous computational replicas of adult neurogenesis have offered evidence on how new neurons can adjust neural network individualities. They have proposed different roles for adult-born neurons at the various phases of neuronal maturation [169]. Such computational advances can direct future trials to explicitly examine new predictions.

At the behavioral level, findings using radioactivity in rodents and lately using genetically modified mice to eradicate adult neurogenesis have presented considerable proof that newborn neurons in the adult brain are essential for certain hippocampal or olfactory bulb-dependent tasks such as learning, memory, pattern separation, olfactory associative memory, habituation, fear conditioning, and discrimination learning [18,166]. A 2016 study has found that enhanced integration of adult-born dentate granule cells transiently reorganized their local afferent connectivity and promoted global remapping in the DG [165]. Furthermore, rejuvenation of the DG by enhancing integration of adult-born dentate granule cells in adulthood, middle age, and aging enhanced memory

Table 1. Extracellular and intracellular factors and their effects on adult neurogenesis.

Factor	Classification	Effect on Adult Neurogenesis	References
nestin-CreER^{T2}	Extracellular	Mediates deletion of RBPj, which triggers radial glia-like cells to differentiate into temporary amplifying cells, decreasing inactive neural precursors in the SVZ	Imayoshi et al. [106]
Notch1 &/or RBPj	Extracellular	Regulates proliferation and differentiation of neural progenitor cells in the SGZ, and exhibits central roles in several aspects of developmental and maintenance processes of the adult brain	Imayoshi and Kageyama [107]
Ephrins &/or Ephrin receptors	Extracellular	Adjust cell proliferation in the SVZ	Genander and Frisén [108]
Shh	Extracellular	Stimulated in radial glia-like cells, and vital for their formation and preservation in the adult SVZ and SGZ	Ahn and Joyner [109] Balordi and Fishell [110]
Wnt3	Extracellular	Stimulates proliferation and neuronal fate commitment of precursor cells in the SGZ	Lie et al. [111]
Wnt/β-catenin	Extracellular	Plays a major role in the regulation of adult neurogenesis	Gonçalves et al. [112]
BMP	Extracellular	Support glia differentiation and impede neural differentiation in the adult brain Obstructing BMP signaling in adult SGZ neural precursors results first in neural stem cell stimulation and a rise in neurogenesis, however afterwards it contributes to the depletion of precursors and loss of neurogenesis	Bonaguidi et al. [113] Mira et al. [114]
Glutamate GABA Acetylcholine	Extracellular	Regulate relocation, maturation, incorporation and endurance of newborn neurons	Zhao et al. [115]
Serotonin Norepinephrine	Extracellular	Expand neural progenitor proliferation, accelerate dendritic growth, and improve persistence of newborn neurons in the adult hippocampus	Warner-Schmidt and Duman [116] Sahay and Hen [117]
Noggin	Intracellular	Facilitates the effect of antidepressant treatment in enhancing adult neurogenesis	Brooker et al. [118]
p21	Intracellular	Preserves the latency of adult neural precursors. p21 deletion results in increased hippocampal cell proliferation and consequent reduction in the precursor pool	Pechnick et al. [119] Marqués-Torrejón et al. [120]
Sox2	Intracellular	Moderates Notch signaling to maintain the precursor pool in the adult SGZ. Sox2 obliteration in adult mice leads to the loss of hippocampal neurogenesis	Favaro et al [121] Ehm et al. [122]
Nup153	Intracellular	Collaborates with Sox2 to preserve the cellular state of neural stem cells. Partnership with Sox2 is fundamental in conserving the identity of neural progenitor cells	Toda et al. [123]
Methyl-CpG binding proteins	Intracellular	Binds to methylated DNA to employ other factors to moderate gene expression. MBD1-knockout mice were found to have deficiencies in adult neurogenesis. Phosphorylation of Methyl-CpG binding protein regulates adult neurogenesis	Li et al. [124] Hsieh and Zhao [125] Jobe et al. [126]
FGF-2	Intracellular	Regulates the equilibrium between proliferation and differentiation during adult hippocampal neurogenesis	Li et al. [127]

precision [165]. Due to divergences in numerous factors, like timing, duration, and cell types of animals used (age, sex, and genetic background), it is expected to find obvious inconsistencies in the literature. Still, these studies have implied substantial impact of adult hippocampal neurogenesis on spatial-navigation learning, lasting spatial memory retention, clearance of hippocampal memory traces, and reorganization of memory to extra-hippocampal substrates [18,165,166].

It has also been proposed that neurogenesis is needed for some anti-depressant provoked behavioral reactions in certain strains of mice [116]. In addition, human umbilical cord plasma proteins were found to revitalize hippocampal function in aged mice [98]. Therefore, identifying the positive and negative factors that influence adult neurogenesis would allow researchers to develop therapeutic strategies for age-dependent cognitive decline and mood disturbances.

Collective evidence has suggested the role of adult olfactory bulb neurogenesis in sustaining long-standing fundamental integrity of the olfactory bulb, temporary olfactory memory, olfactory fear conditioning, and long-term associative olfactory memory, including

Table 2. Neurological-disease factors and their effects on adult neurogenesis.

Factor	Neurological Disease	Effect on Adult Neurogenesis	References
Presenilin	Alzheimer's disease	Damages proliferation and neuronal fate commitment of microglia. Presenilin-1 mutations in mice disrupt neurogenesis through abnormal beta-catenin signaling pathway	Chevallier et al. [129] Choi et al. [130] Fuster-Matanzo et al. [131]
Mecp2	Rett Syndrome	Controls growth and development of new neurons in the adult hippocampus	Smrt et al. [132]
DISC1	Schizophrenia	Endorses production of neural progenitors through the GSK3β/β-catenin pathway, whereas restraining dendritic growth and synapse growth of new neurons through Protein kinase B (Akt) and mammalian target of rapamycin (mTOR) signaling	Duan et al. [133] Faulkner et al. [15] Mao et al. [134] Kim et al. [137]

Table 3. Environmental/external factors and their effects on adult neurogenesis.

Regulatory factor	Effect on adult neurogenesis	References
Sex	Higher cell proliferation in the SGZ of females	Tanapat et al. [142]
Aging	Decreased cell proliferation in the SGZ and SVZ	Kuhn et al. [5] Cameron and McKay [143] Enwere et al. [145]
Enriched environments	Increased rate of adult neurogenesis and survival of newborn neurons in the SGZ	Barnea and Nottebohm [62] Rosenzweig and Bennett [145] Nilsson et al. [146] Brown et al. [147]
Physical exercise	Enhanced cell proliferation and survival in the SGZ	Van Praag et al. [75] Brown et al. [147] Holmes et al. [148]
Physical and psychosocial stress	Decreased cell proliferation in the SGZ	Gould et al. [75] Duman et al. [149]
Learning	Increased adult hippocampal neurogenesis	Gould et al. [77] Waddell and Shors [150]
Antidepressants	Increased cell proliferation and survival in the DG	Chen et al. [151] Wu and Castren [152] Chamaa et al. [153]
Drugs of abuse	Decreased cell proliferation and survival in the SGZ	Eisch et al. [154] Crews et al. [155]
Dietary/caloric restriction	Increased survival of new born neurons	Bondolfi et al. [156] Kitamura et al. [157]
Ethanol	Decreased cell proliferation	Nixon et al. [158] Crews et al. [159]
Seizures	Increased cell proliferation in the SGZ and SVZ	Jessberger et al. [87]
Stroke	Increased neurogenesis in the SVZ	Zhang et al. [160]
Estrogen	Enhanced neurogenesis in the SGZ	Tanapat et al. [142]
Glucocorticoids	Decreased neurogenesis in the SGZ	Gould et al. [161]
Prolactin	Increased neurogenesis in the SGZ and SVZ	Wang et al. [162]

active learning [164]. However, abnormal adult neurogenesis leads to pathophysiological states. For instance, seizure-induced SGZ neurogenesis might result in epileptogenesis and enduringness of cognitive impairment [87,138].

One important question arises: in what way can a trivial number of adult-born neurons influence overall brain function? The answer is found in the ability of these neurons to encrypt and effectively modify the firing and harmonization of mature neurons. First, new neurons are triggered by precise inputs as evidenced by instant early gene expression in both of the hippocampus and the olfactory bulb [170–172]. Second, new neurons can actively hinder local circuitry output [173]. Third, adult-born neurons can also amend the local neural network through their selective stimulation of modulatory pathways [91].

6. Future studies

There is mounting evidence that hippocampal neurogenesis in adult humans exists. Now, whether its extent is sufficient to have functional significance is questioned. Still, it's real in infants and in other animals. If adults really don't make any new neurons, how can they learn new things? And is there any way of restoring that lost ability to create new neurons in cases of neurodegenerative diseases? Adult neurogenesis is what needs to be induced in cases of stroke and brain damage. Therefore, developing modern technology will contribute to the advancement and better understanding of adult neurogenesis, especially in animal models. Numerous sophisticated genetic models permit targeting of definite subtypes of neural progenitors and/or adult-born neurons at precise maturation phases. Optogenetic methods warrant influencing the activity of newborn neurons with a great spatial and temporal accuracy and avoiding the obstacles of injury and homeostatic responses associated with the physical eradication of adult neurogenesis. Multiple groups have been developing new live-imaging methods to measure neuronal activity in the DG in awake and behaving mice using a multi-photon

microscopy or microendoscopy [97,99,100]. Additional technical advancements, such as 3-photon microscopy, may one day permit complete imaging of the DG [174].

With a collective approach at the cellular, circuitry, system, and behavioral stages, future studies will elucidate how adult neurogenesis can add to learning, memory, and mood regulation. They may also detect novel tasks of adult neurogenesis under physiological states and illustrate how irregular neurogenesis could lead to mental disorders and other degenerative neurological conditions. Such promising studies will not only address key questions involving adult neurogenesis but will also disclose central principles of neuronal plasticity and propose innovative approaches for the treatment of several neurological and psychiatric disorders.

7. Conclusion

The breakthrough of incessant neurogenesis in the adult mammalian brain has postulated a new perception on the plasticity of the mature nervous system. This discovery has also updated our knowledge on the brain's control of mood and cognition, as well as its response to illness and injury. The transformations that occur in neurogenic progenitor cell populations in response to stress, psychiatric disorders, and neurodegenerative disease imply that these cells exhibit a therapeutic potential for these pathologies. Neurogenesis in the SVZ has been verified to be essential for successful treatment of psychiatric disorders. In fact, failed or distorted neurogenesis has been associated with several psychiatric diseases, such as major depressive disorder.

Our understanding of adult neurogenesis and neural stem cell regulation has developed gradually over the last 20 years. Nevertheless, we still lack a comprehensive understanding of the neurogenic process. Based on the current advancements and the development of new methods, the adult neurogenesis research field will surely make another giant leap forward.

Disclosure statement

No potential conflict of interest was reported by the authors.

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