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(REVIEW ARTICLE)

NEUROGENESIS: MECHANISMS, REGULATION, AND IMPLICATIONS FOR BRAIN FUNCTION AND DISEASE

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ABSTRACT

Adult neurogenesis, the continuous generation of functional neurons from neural stem cells in the mature mammalian brain, represents one of the most remarkable forms of structural plasticity in the central nervous system. Once considered impossible, adult neurogenesis is now recognized as a fundamental process occurring primarily in two canonical neurogenic niches: the subgranular zone (SGZ) of the hippocampal dentate gyrus and the subventricular zone (SVZ) of the lateral ventricles. This review synthesizes current knowledge on adult neurogenesis, covering the cellular and molecular mechanisms underlying neural stem cell maintenance and neuronal differentiation, the stages of neurogenesis from proliferation to synaptic integration, the functional contributions of adult-born neurons to learning, memory, and mood regulation, and the modulation of neurogenesis by intrinsic and extrinsic factors. We examine the impact of aging and disease on neurogenesis, with particular emphasis on the ongoing debate regarding adult human neurogenesis. Recent conflicting reports about the extent and persistence of neurogenesis in the adult human brain have highlighted critical methodological challenges and species differences that must be addressed for successful clinical translation. We discuss evidence for and against human adult neurogenesis, the methodological factors contributing to discrepancies, and the implications for understanding human brain function and developing therapeutic strategies.

This review also covers therapeutic strategies targeting neurogenic processes, including behavioral interventions, pharmacological approaches, and emerging cell-based therapies. Recent advances in molecular profiling, lineage tracing, and imaging technologies have deepened our understanding while revealing the complexity of neurogenic regulation across species and throughout the lifespan. This review aims to provide researchers, clinicians, and students with an integrative perspective on adult neurogenesis with special attention to translating findings from animal models to human applications.

Keywords: Adult neurogenesis; Neural stem cells; Brain plasticity; Neurogenic niches; Neuroregeneration

1 INTRODUCTION

1.1 Definition and Scope

Adult neurogenesis refers to the process by which new functional neurons are generated from neural stem and progenitor cells in the mature brain and successfully integrate into existing neural circuits [1][2]. Unlike the massive neuronal production that characterizes embryonic and early postnatal development, adult neurogenesis is spatially restricted to specialized microenvironments called neurogenic niches and occurs at a much lower rate. Nevertheless, this continuous addition of new neurons throughout life represents a remarkable form of structural plasticity with significant implications for brain function and dysfunction [3][4].

The term "adult neurogenesis" encompasses several distinct cellular processes: (1) the maintenance of a population of neural stem cells (NSCs) in a quiescent or slowly dividing state; (2) the activation and proliferation of these stem cells and their progeny; (3) the specification of neuronal fate and differentiation of progenitors into immature neurons; (4) the migration of newborn neurons to their final destination; (5) the morphological maturation of these neurons, including dendrite and axon elaboration; (6) the formation of synaptic connections with existing circuits; and (7) the activity-dependent survival and functional integration of mature adult-born neurons [5][6][7].

1.2 Significance in Neuroscience

The discovery and characterization of adult neurogenesis has fundamentally altered our understanding of brain plasticity and has important implications across multiple domains of neuroscience:

- Structural Plasticity: Adult neurogenesis demonstrates that the adult brain retains a capacity for structural remodeling beyond synaptic plasticity, challenging the long-held dogma that the adult brain is a static organ incapable of generating new neurons [8][9].
- Cognitive Function: Adult-born neurons in the hippocampus contribute uniquely to specific aspects of learning and memory, particularly pattern separation—the ability to distinguish between similar experiences or stimuli—and memory consolidation [10]
- Emotional Regulation: Hippocampal neurogenesis has been implicated in mood regulation and the pathophysiology of depression, with many antidepressant treatments shown to enhance neurogenesis in animal models [11]
- Disease Mechanisms: Alterations in adult neurogenesis have been documented in numerous neurological and psychiatric disorders, including Alzheimer's disease, Parkinson's disease, epilepsy, depression, and anxiety disorders, suggesting that impaired neurogenesis may contribute to disease pathology [12][13][14].
- Therapeutic Target: The identification of factors that promote or inhibit neurogenesis has opened new avenues for therapeutic intervention, with potential applications in neurodegenerative diseases, psychiatric disorders, and brain injury [15][16]

1.3 Historical Context

For most of the 20th century, neuroscience operated under the dogma that neurogenesis ceases shortly after birth and that the adult mammalian brain is incapable of generating new neurons. This belief was based on early anatomical studies and the influential teachings of Santiago Ramón y Cajal, who stated in 1913 that "in adult centers the nerve paths are something fixed, ended, immutable." However, evidence challenging this dogma began to emerge in the 1960s. Joseph Altman and colleagues published a series of pioneering studies demonstrating the incorporation of labeled nucleotides into newly formed neurons in the adult rat hippocampus and olfactory bulb [17][18]. Despite this groundbreaking work, the findings were initially met with skepticism and did not immediately overturn the prevailing view.

The field gained momentum in the 1980s and 1990s with the work of Fernando Nottebohm, who demonstrated robust adult neurogenesis in the avian brain associated with seasonal learning of new songs [19].

Another studies showed that adult neurogenesis in rodents is regulated by environmental factors and contributes to learning and memory. The development of new markers for proliferating cells (BrdU incorporation) and immature neurons (doublecortin) provided powerful tools for studying adult neurogenesis [20].

By the early 2000s, adult neurogenesis had become an established field of neuroscience research, with two primary neurogenic regions identified in the adult mammalian brain: the subgranular zone of the hippocampal dentate gyrus and the subventricular zone of the lateral ventricles [21][22].

1.4 Overview of Neurogenic Regions

In the adult mammalian brain, neurogenesis is primarily restricted to two canonical neurogenic niches:

- **Subgranular Zone (SGZ)** of the Hippocampal Dentate Gyrus:

This region, located at the border between the granule cell layer and the hilus of the dentate gyrus, harbors neural stem cells that give rise to excitatory granule neurons. These adult-born neurons integrate into the dentate gyrus circuitry and contribute to hippocampal-dependent learning and memory processes [23].

- **Subventricular Zone (SVZ)** of the Lateral Ventricles:

The SVZ, lining the walls of the lateral ventricles, contains neural stem cells that produce neuroblasts. In rodents and some other mammals, these neuroblasts migrate along the rostral migratory stream (RMS) to the olfactory bulb, where they differentiate into interneurons involved in olfactory processing [24].

While these two regions are the most well-characterized neurogenic niches, evidence for more limited neurogenesis or the presence of neural progenitor cells has been reported in other brain regions, including the hypothalamus, striatum, amygdala, and cortex, though the extent and functional significance of neurogenesis in these areas remains controversial and appears to be species-dependent [25].

2 NEURAL STEM CELLS AND NEUROGENIC NICHES

Neural stem cells (NSCs) are defined by their capacity for self-renewal and multipotency—the ability to generate neurons, astrocytes, and oligodendrocytes. In the adult brain, NSCs reside in specialized microenvironments called neurogenic niches and exhibit distinct properties compared to their embryonic counterparts [26].

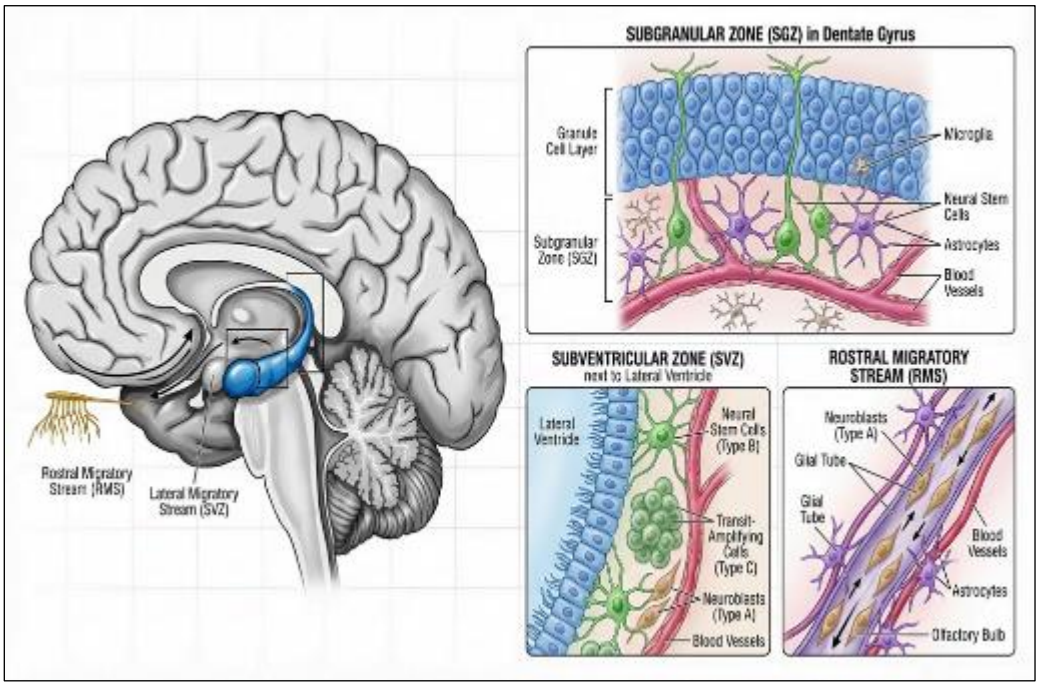


Figure 1: Neurogenic Niches

2.1 Neural Stem Cell Identity and Properties

Adult NSCs exist primarily in a quiescent (non-dividing) state, characterized by low metabolic activity and slow cell cycle progression. This quiescence is thought to preserve the stem cell pool over the lifespan by preventing stem cell exhaustion through excessive division. Quiescent NSCs (qNSCs) express markers such as GFAP (glial fibrillary acidic protein), nestin, and Sox2, and maintain their stemness through specific transcriptional programs and epigenetic signatures [27].

Upon receiving appropriate signals, qNSCs can become activated, entering the cell cycle and giving rise to transit-amplifying progenitors. Activated NSCs (aNSCs) show increased expression of proliferation markers such as Ki67 and

PCNA (proliferating cell nuclear antigen) while maintaining stem cell markers [28]. The transition between quiescence and activation is tightly regulated by intrinsic factors and niche signals, ensuring a balance between stem cell maintenance and neuronal output [29].

3 MOLECULAR MECHANISMS OF NEUROGENESIS

Adult neurogenesis is orchestrated by a complex interplay of signaling pathways, transcription factors, epigenetic regulators, and cell cycle control mechanisms. Understanding these molecular mechanisms is essential for elucidating how neurogenesis is regulated under physiological conditions and how it becomes dysregulated in disease [30].

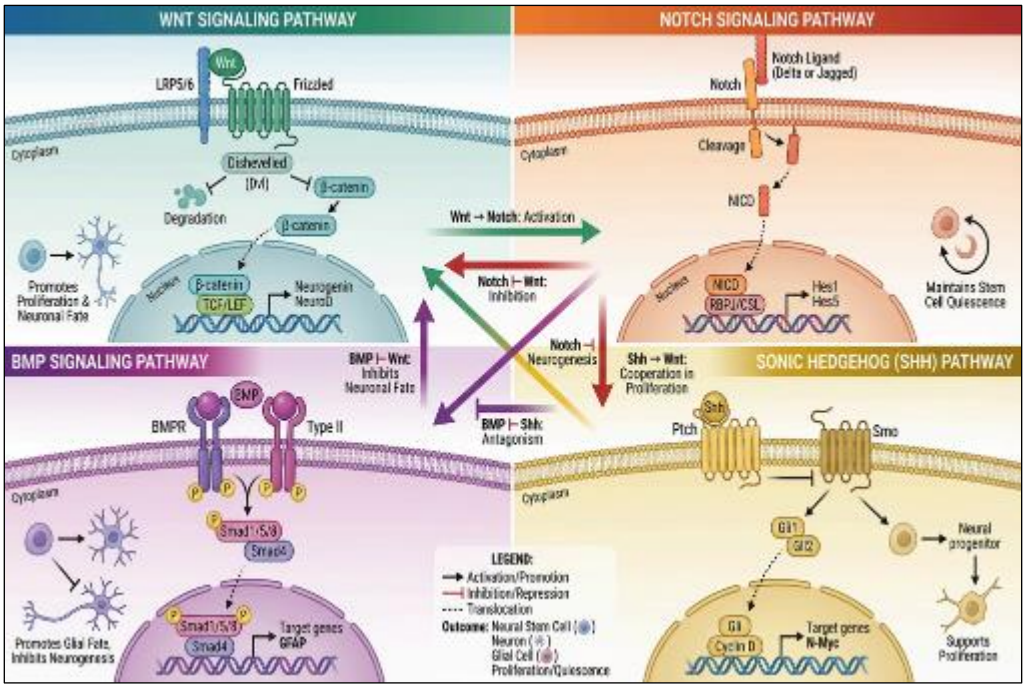


Figure 2: Signaling Pathways

3.1 Signaling Pathways

Several evolutionarily conserved signaling pathways play critical roles in regulating different stages of adult neurogenesis. These pathways often interact and cross-regulate each other to fine-tune neurogenic output [31].

3.2 Wnt Signaling

The Wnt signaling pathway is one of the most important pro-neurogenic pathways in adult neurogenesis. In the absence of Wnt ligands, β-catenin is phosphorylated by a destruction complex and targeted for degradation. When Wnt ligands bind to Frizzled receptors and LRP5/6 co-receptors on NSCs, β-catenin accumulates and translocates to the nucleus where it interacts with TCF/LEF transcription factors to activate expression of Wnt target genes involved in proliferation and neuronal fate specification [32].

Wnt ligands in the neurogenic niche are secreted by astrocytes, endothelial cells, and neurons. Canonical Wnt signaling promotes NSC proliferation and activation from quiescence, neuronal fate specification and differentiation, and dendritic development and synaptic integration of adult-born neurons [33].

3.3 Notch Signaling

Notch signaling is a key regulator of NSC maintenance and the balance between self-renewal and differentiation [34]. When Notch ligands bind to Notch receptors on NSCs, this triggers proteolytic cleavage releasing the Notch intracellular domain (NICD), which translocates to the nucleus and activates transcription of Notch target genes [35]. Notch signaling promotes maintenance of NSC quiescence, self-renewal of NSCs, and suppression of neuronal differentiation programs [36].

3.4 BMP Signaling

BMP signaling generally promotes glial fate and inhibits neuronal differentiation [37]. BMP ligands bind to BMP receptors leading to phosphorylation of Smad transcription factors. The neurogenic niche contains BMP antagonists such as Noggin which prevent BMP signaling, permitting neurogenesis [38].

3.5 Sonic Hedgehog Signaling

Sonic Hedgehog signaling supports proliferation of neural progenitors [39]. When Shh binds to Patched, it relieves inhibition of Smoothened, allowing activation of Gli transcription factors that promote proliferation of transit-amplifying progenitors and expansion of the progenitor pool [40][41].

4 STAGES OF ADULT NEUROGENESIS

Adult neurogenesis proceeds through a series of well-defined stages, from the activation of quiescent neural stem cells to the functional integration of mature neurons into existing circuits. Each stage is characterized by distinct morphological features, molecular markers, and regulatory mechanisms.

4.1 Stage 1: Quiescence and Activation

Adult NSCs spend most of their time in a quiescent state characterized by low metabolic activity [42]. Quiescent NSCs express GFAP, Nestin and Sox2 markers. Upon receiving appropriate signals such as increased Wnt signaling, growth factors, or neuronal activity, qNSCs become activated and enter the cell cycle [43].

4.2 Stage 2: Proliferation and Amplification

Activated NSCs give rise to transit-amplifying progenitors (TAPs) that undergo several rounds of division to amplify the neuronal precursor pool [44]. These cells express Tbr2 and Ki67 markers and have limited self-renewal capacity [45].

4.3 Stage 3: Neuronal Fate Specification

Transit-amplifying progenitors give rise to neuroblasts committed to the neuronal lineage [46]. These cells express DCX (doublecortin), PSA-NCAM, and NeuroD1 markers and are highly migratory [47].

4.4 Stage 4: Migration

In the SGZ, neuroblasts migrate short distances into the granule cell layer [48]. In the SVZ, neuroblasts migrate long distances along the rostral migratory stream to the olfactory bulb [49].

4.5 Stage 5: Maturation

Neuroblasts mature into immature neurons over several weeks, extending dendrites and axons and beginning to form synaptic connections [50]. During a critical period of 2-4 weeks, these neurons exhibit enhanced plasticity and excitability [51].

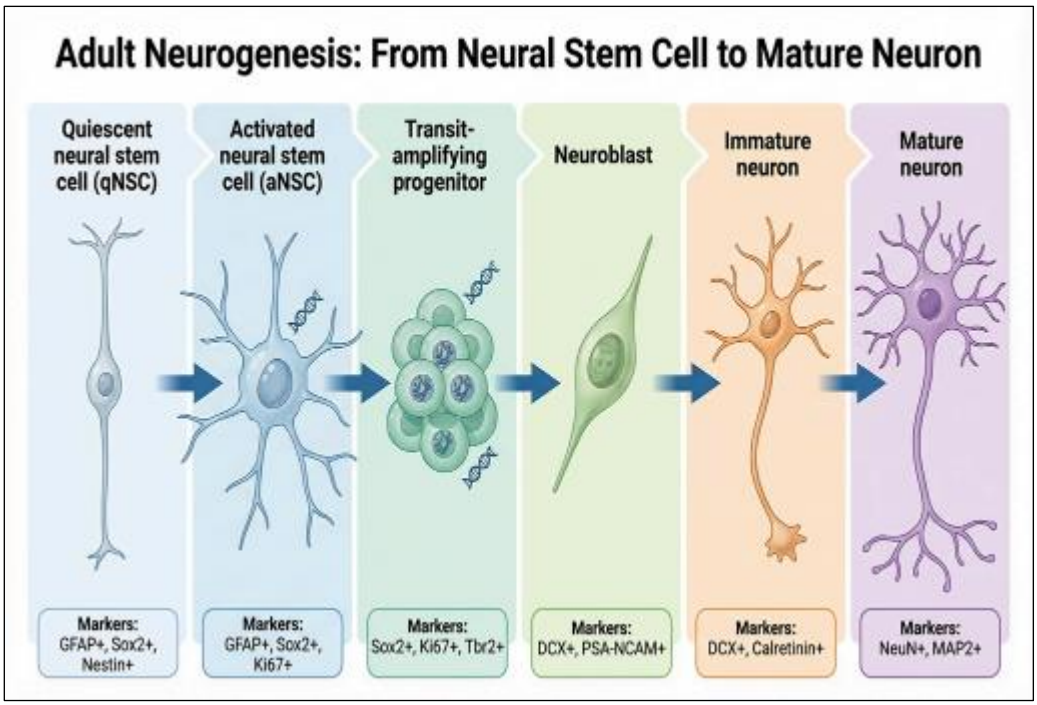


Figure 3: Neurogenesis Stages

4.6 Stage 6: Synaptic Integration

Adult-born neurons form synaptic connections with existing circuits through activity-dependent mechanisms [52]. Survival of newborn neurons depends on their successful integration and participation in network activity [53].

4.7 Stage 7: Maturation to Functional Neurons

By 6-8 weeks, adult-born neurons express mature markers (NeuN, Calbindin) and become functionally indistinguishable from developmentally born neurons [54].

5 HIPPOCAMPAL NEUROGENESIS

The hippocampus is a brain structure critical for learning, memory, and emotional regulation. Adult neurogenesis in the hippocampal dentate gyrus has been extensively studied and is one of the best-characterized examples of structural plasticity in the adult mammalian brain.

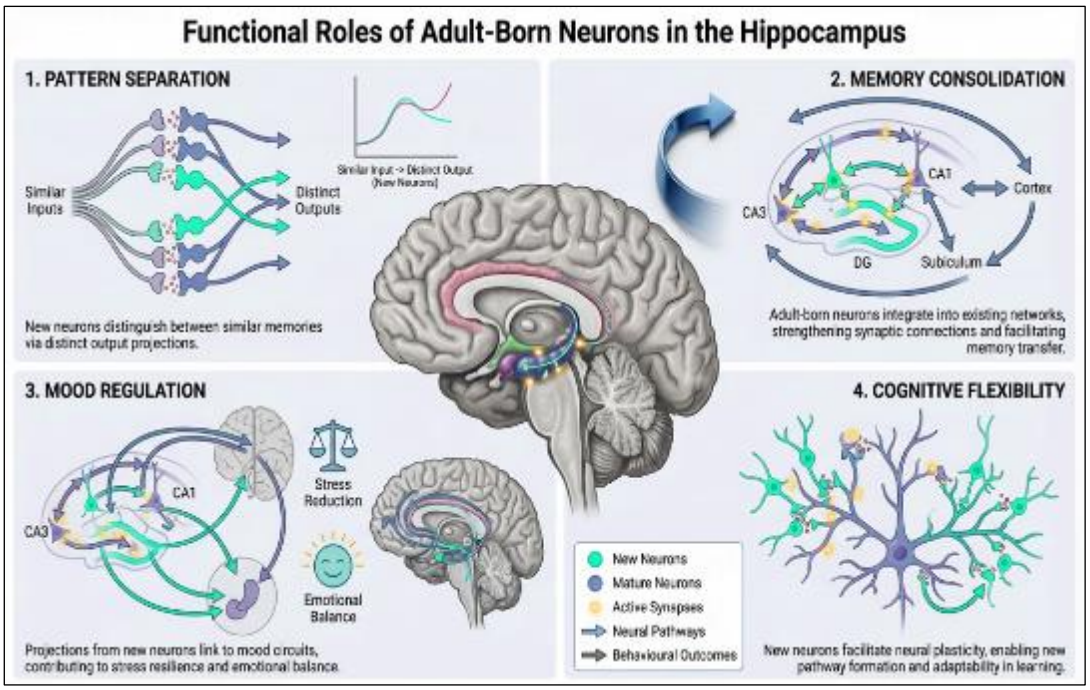


Figure 4: Hippocampal Functions

5.1 Anatomy and Organization

The dentate gyrus has a three-layered structure with the molecular layer, granule cell layer, and hilus. The subgranular zone at the border between the granule cell layer and hilus contains neural stem cells. Adult-born dentate granule neurons integrate into the trisynaptic hippocampal circuit, receiving input from the entorhinal cortex and projecting to CA3 [55].

5.2 Regulation of Hippocampal Neurogenesis

Hippocampal neurogenesis is dynamically regulated by activity-dependent mechanisms, behavioral experiences, and systemic factors[.

- Environmental Enrichment: Housing in enriched environments robustly increases hippocampal neurogenesis [56].
- physical Exercise: Voluntary running is one of the most potent stimulators of hippocampal neurogenesis, increasing proliferation, survival, and dendritic complexity [57].
- Learning: Hippocampus-dependent learning enhances survival of neurons born around the time of learning [58].

5.3 Functional Roles

5.3.1 Pattern Separation

Adult-born neurons contribute disproportionately to pattern separation—the ability to distinguish between similar experiences [59][60]. Ablation of neurogenesis impairs pattern separation tasks [61].

5.3.2 Memory Formation

Adult-born neurons participate in encoding new memories [62][63], with neurons born around the time of learning preferentially incorporated into memory traces [64][65].

5.3.3 Forgetting

Neurogenesis has also been linked to adaptive forgetting and memory clearance [66][67].

5.3.4 Mood Regulation

Hippocampal neurogenesis is implicated in mood regulation and depression pathophysiology, with many antidepressants enhancing neurogenesis [68][69][70][71].

6 SUBVENTRICULAR ZONE AND OLFACTORY BULB NEUROGENESIS

The SVZ represents the largest neurogenic region in the adult rodent brain. Unlike hippocampal neurogenesis, SVZ neurogenesis shows significant species differences, with important implications for translation.

6.1 SVZ Organization

The SVZ has a characteristic cytoarchitecture with ependymal cells lining the ventricle, type B cells (astrocyte-like NSCs), type C cells (transit-amplifying progenitors), and type A cells (neuroblasts) [72][73].

6.2 The Rostral Migratory Stream

Neuroblasts migrate along the RMS to the olfactory bulb, traveling several millimeters in chains ensheathed by astrocytic tubes [74]. Upon reaching the olfactory bulb, they differentiate into granule cells and periglomerular interneurons [75][76].

6.3 Functional Roles

Adult-born olfactory bulb interneurons contribute to odor discrimination and olfactory learning [77].

6.4 Species Differences

While robust in rodents, the extent of SVZ neurogenesis and olfactory bulb neurogenesis in humans remains controversial [78]. Evidence suggests minimal olfactory bulb neurogenesis in adult humans, with potential alternative destinations for human SVZ-derived cells [79].

7 REGULATION OF ADULT NEUROGENESIS

Adult neurogenesis is dynamically regulated by intrinsic factors, neurotrophic factors, neurotransmitters, hormones, immune signals, and metabolic state.

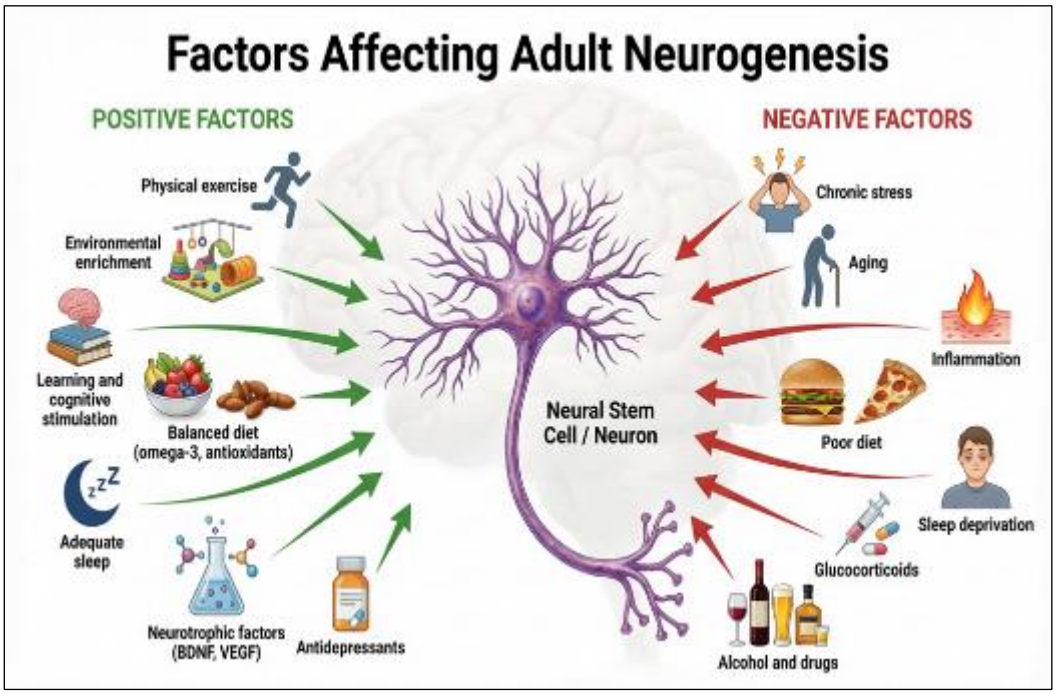


Figure 5: Factors Affecting Neurogenesis

7.1 Intrinsic Factors

Age is the most significant intrinsic factor, with neurogenesis declining progressively from development through aging [80]. Sex and genetics also influence baseline neurogenesis levels [81].

7.2 Neurotrophic Factors

- BDNF: Promotes NSC proliferation, neuronal survival, and synaptic integration; mediates effects of exercise and enrichment [82][83][84].
- VEGF: Links angiogenesis and neurogenesis; promotes proliferation and survival [85][86][87].
- IGF-1: Systemic growth factor that promotes proliferation and maturation [88][89].

7.3 Neurotransmitter Regulation

- GABA: Plays complex, stage-dependent roles, initially depolarizing immature neurons [90][91][92].
- Serotonin: Promotes proliferation and survival; mediates antidepressant effects [93][94].

7.4 Hormonal Regulation

- Glucocorticoids: Chronic elevation suppresses neurogenesis [95].
- Sex Steroids: Estrogen generally enhances neurogenesis [96].
- Thyroid Hormones: Essential for normal neurogenesis [97].

7.5 Immune and Inflammatory Signals

Microglia regulate neurogenesis through phagocytosis and cytokine secretion [98][99]. Pro-inflammatory cytokines (TNF-α, IL-1β) inhibit neurogenesis, while anti-inflammatory cytokines (IL-4, IL-10) support it [100][101].

7.6 Metabolic Regulation

Caloric restriction can enhance neurogenesis specially during fasting, while obesity reduces it [102][103][104].

8 FUNCTIONAL IMPORTANCE OF ADULT-BORN NEURONS BY NEUROGENESIS:

Despite representing a small fraction of total neurons, adult-born neurons make unique contributions to brain function through their distinct properties during maturation.

8.1 Pattern Separation

Adult-born neurons contribute disproportionately to distinguishing similar experiences, reducing representational overlap in dentate gyrus activity patterns [105].

8.2 Memory Formation and Consolidation

Adult-born neurons participate in encoding new memories and may facilitate systems consolidation [106][107].

8.3 Forgetting and Memory Clearance

Integration of new neurons may disrupt old memories, providing adaptive forgetting [108][109].

8.4 Mood and Emotional Regulation

Neurogenesis is implicated in depression and anxiety, with many antidepressants enhancing neurogenesis [110].

8.5 Cognitive Flexibility

Adult-born neurons contribute to behavioral adaptation and reversal learning and deep thinking for problems solving[111].

9 HUMAN NEUROGENESIS: EVIDENCE AND CONTROVERSY

The existence and extent of adult neurogenesis in humans has become one of the most contentious issues in neuroscience, with critical implications for translating animal research to human applications.

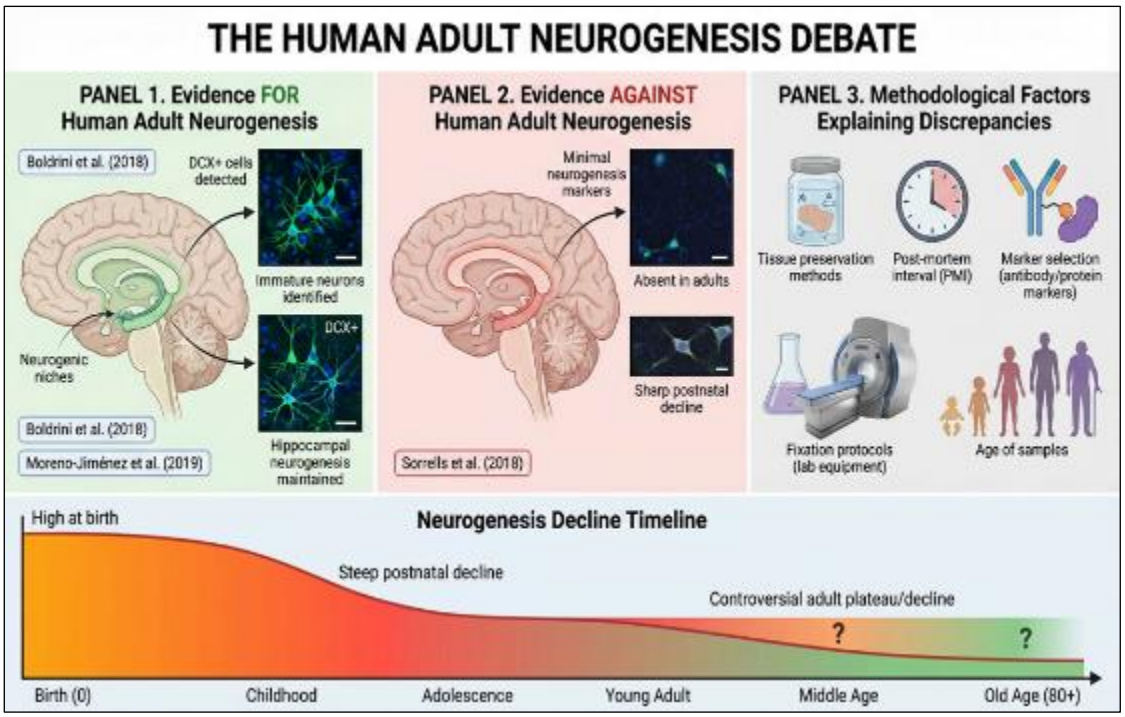


Figure 6: Human Neurogenesis Debate

9.1 Historical Context

Eriksson et al. (1998) collected postmortem Human brain tissue from patients who had been treated with the thymidine analog (BrdU), that labels DNA during the S phase and also used neuronal markers. He demonstrated that new neurons, were generated from dividing progenitor cells in the dentate gyrus of adult humans. So, he stated that the human hippocampus retains its ability to generate neurons throughout life [112]..

9.2 The Controversy: Conflicting Reports

In 2018-2019, three high-profile studies reached contradictory conclusions which are:

Sorrells et al. (2018) conducted a comprehensive examination of human hippocampal tissue across a wide age range to evaluate the persistence of neurogenesis in the dentate gyrus (DG). Their analyses showed that the population of proliferating progenitor cells and newly generated neurons declines steeply during the earliest years of life. By the time children reach 7 to 13 years of age, only a very small number of young neurons can still be identified, and these appear as isolated cells rather than as part of a robust neurogenic process. When the researchers examined surgically resected hippocampal samples from adults aged 18 to 77 years—including both individuals with epilepsy and neurologically healthy controls—they found no detectable young neurons in the DG. Based on these findings, the authors concluded that the recruitment of new neurons into the primate hippocampus diminishes rapidly after infancy. [113].

Boldrini et al. (2018) examined entire autopsy-derived hippocampi from healthy individuals aged 14 to 79 years. Their analysis revealed consistent numbers of intermediate neural progenitors, thousands of immature neurons in the dentate gyrus (DG), and stable counts of glial cells and mature granule neurons across the lifespan, along with a relatively unchanged DG volume. However, they observed age-related reductions in angiogenesis, neuroplasticity, and the size of the quiescent progenitor pool within the anterior–mid DG, while the posterior DG remained unaffected. Despite these changes, older adults without cognitive impairment, neuropsychiatric conditions, or medical treatments still showed evidence of preserved neurogenesis. Based on these findings, the authors proposed that ongoing hippocampal neurogenesis may support uniquely human cognitive functions throughout life, and that reductions in this process could contribute to diminished cognitive-emotional resilience[114].

Moreno-Jiménez et al. (2019): Reported thousands of immature neurons in healthy older adults but dramatic reduction in Alzheimer's disease [115].

9.3 Methodological Factors Explaining Discrepancies

- Tissue Preservation: Postmortem interval and fixation methods critically affect marker detection.
- Marker Selection: may label non-neuronal cells.

- Cohort Differences: Age distribution, cause of death, and health status vary across studies.
- Anatomical Sampling: Different hippocampal subregions may show varying neurogenesis levels [116].

9.4 Current Consensus

Robust adult human hippocampal neurogenesis as seen in rodents is unlikely. Some neurogenesis may persist at much lower rates, declining substantially with age and disease. Methodological standardization is critical for resolving remaining questions [117].

10 NEUROGENESIS ACROSS THE LIFESPAN AND AGING

10.1 Developmental Trajectory

Neurogenesis is highest during fetal and early postnatal development, the newly formed nerve cells showed growth of their axons and dendrites then integrate with each other to form circuits that can carry out their specific functions. Neurogenesis then show declining rapidly during childhood and adolescence, followed by continued gradual decline in adulthood [118][119].

10.2 Age-Related Decline

A progressive reduction in neural stem cell (NSC) number and proliferative capacity accompanies aging. Although studies show that overall production of new neurons declines with age, the actual quantity and phenotype of core neural stem and progenitor cells in the dentate gyrus—the hippocampus's primary neurogenic niche—remain relatively stable. The age-related decrease in neurogenesis instead appears to stem from difficulties these cells face in exiting their quiescent state, reduced proliferative potential, and a microenvironment that becomes increasingly less supportive. As a result, fewer neurons are generated, while astrocyte production rises, indicating a shift from a neurogenic to a more astrocyte-biased output [120].

Niche inflammation and pro-inflammatory cytokines, Vascular dysfunction reducing trophic support growth factors like IGF-1, VEGF promoting neural stem/progenitor cell growth significantly decline in the hippocampus by middle age [121][122].

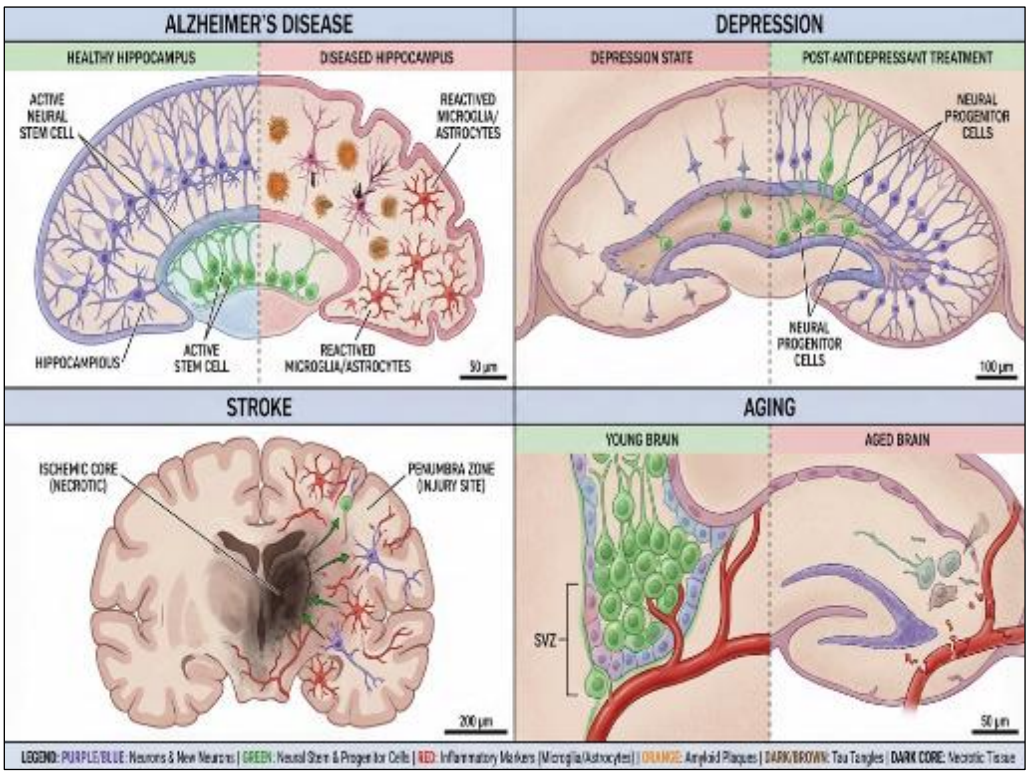


Figure 7: Aging Effects

10.3 Functional Consequences

As age passes the hippocampal environment undergoes marked changes, including increased niche inflammation and elevated pro-inflammatory cytokines. At the same time, vascular dysfunction reduces the availability of key trophic growth factors—such as IGF-1 and VEGF—that normally support neural stem and progenitor cell growth, leading to a significant decline in this supportive signaling [123][124].

11 NEUROGENESIS IN NEUROLOGICAL DISEASES

Alterations in neurogenesis have been documented in numerous neurological disorders, suggesting both pathogenic roles and therapeutic opportunities.

11.1 Alzheimer's Disease

Multiple studies report reduced hippocampal neurogenesis in Alzheimer's disease patients and animal models [125][126]. Reduction occurs early in disease progression and correlates slowly destroys memory, thinking skills, and eventually the ability to carry out daily tasks, leading to significant cognitive and behavioral changes [127][128]. Mechanisms include amyloid-β toxicity, tau pathology, and chronic neuroinflammation [129][130][131].

11.2 Parkinson's Disease

Dopamine depletion and neuroinflammation affect neurogenesis in Parkinson's disease with progressive brain disorder causing involuntary movements like tremors, stiffness, and balance disturbance [132][133]. SVZ neurogenesis may be altered [134][135].

11.3 Stroke

Ischemic stroke transiently increases neurogenesis the brain's natural attempt to repair itself after a stroke by generating new neurons from neural stem cells in areas like the Subventricular Zone (SVZ) and Hippocampus, with these new cells migrating to the damaged zone to potentially restore function, though this process is complex, varies by region, and often needs enhancement.[136][137][138]. Strategies to enhance post-stroke neurogenesis are being investigated [139][140][141].

11.4 Traumatic Brain Injury

TBI riggers both damage and a complex response in neurogenesis, primarily in the hippocampus, initially increasing cell proliferation but often leading to long-term deficits, cell death, and impaired integration of new neurons due to inflammation and stem cell exhaustion. While early increases in new neurons (neurogenesis) might seem beneficial, they can paradoxically worsen outcomes, potentially by promoting seizure development (epileptogenesis) or depleting stem cell reserves [142].

11.5 Epilepsy

Temporal lobe epilepsy is the most common focal epilepsy, it is started with aura followed with confusion, sometimes leading to generalized seizures [143]. Acute seizures often increase cell production, but this leads to abnormal new neurons (ectopic migration) potentially triggering more seizures, while chronic seizures reduce overall neurogenesis, contributing to cognitive deficits, memory issues, and increase in the disease's severity144][145].

12 NEUROGENESIS IN PSYCHIATRIC DISORDERS

12.1 Major Depression

Reduced hippocampal neurogenesis is associated with depressive-like behaviors in animal models as the hippocampus is involved in emotion regulation [146][147]. An important study demonstrate that unpredictable chronic mild stress in mice not only reduces hippocampal neurogenesis, but also dampens the relationship between hippocampus and the main stress hormone system, the hypothalamo-pituitary-adrenal (HPA) axis. Moreover, this relationship is restored by treatment with the antidepressant fluoxetine, in a neurogenesis-dependent manner [148].

12.2 Schizophrenia

In schizophrenia, the hippocampus consistently shows both structural and functional disturbances that contribute to the cognitive symptoms of the disorder. One of the most prominent features is impairment in hippocampal-dependent memory processes, particularly those involving declarative memory, which includes the ability to consciously recall facts and events. Individuals with schizophrenia often struggle with tasks that require episodic memory retrieval, and

these behavioral deficits are closely linked to reduced activation of the hippocampus during such tasks. At the same time, the hippocampus can become abnormally hyperactive in other contexts—most notably during episodes of auditory hallucinations—suggesting dysregulated neural signaling rather than a simple loss of function. This combination of underactivation during memory tasks and overactivation during hallucinatory experiences reflects a broader disruption in hippocampal circuitry. As a result, patients frequently exhibit measurable declines in both verbal and spatial memory performance, highlighting the central role of hippocampal dysfunction in the cognitive profile of schizophrenia. According to animal models, there were altered neurogenic processes implicated, but causal relationships remain unclear [149] [150].

12.3 Addiction

Drug abuse and addiction are widely recognized as chronic, relapsing disorders characterized by compulsive drug seeking and drug taking, along with a progressive loss of control over consumption. This dysregulation is typically conceptualized through three interconnected stages of the addiction cycle—binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation—each of which reinforces the next and contributes to the persistence of addictive behavior. A recent review explores how adult-born neural and glial progenitors influence behavioral vulnerability across these stages. The authors highlight that newly generated cells, particularly those arising in the hippocampus, may play a crucial role in regulating learning, memory, and stress responses that shape drug-seeking tendencies. Evidence from rodent models suggests that chronic drug exposure reduces the survival and proliferation of these progenitors, and that such losses may heighten susceptibility to relapse by impairing hippocampal-dependent cognitive and emotional processes. The review further proposes that restoring drug-induced deficits in neurogenesis or gliogenesis—either through behavioral interventions, pharmacological treatments, or environmental enrichment—could help reverse maladaptive neuroplastic changes that accumulate during abstinence. By normalizing the function of these progenitor populations, it may be possible to reduce relapse vulnerability and support more stable, long-term recovery [151][152][153].

13 FACTORS MODULATING NEUROGENESIS

13.1 Exercise

Voluntary running robustly enhances hippocampal neurogenesis through multiple mechanisms including increased BDNF, VEGF, IGF-1, and improved vascular function [154][155].

13.2 Environmental Enrichment

Complex environments with social interaction, novelty, and cognitive challenges enhance neurogenesis [156][157][158].

13.3 Diet

- Detrimental: High-fat diet, obesity, alcohol [159][160]
- Beneficial: Omega-3 fatty acids, antioxidants, caloric restriction [161][162]

13.4 Sleep

Sleep deprivation significantly inhibits this new cell production, partly due to stress hormones (glucocorticoid) increases, while recovery from sleep loss can trigger a temporary surge in neurogenesis, suggesting sleep directly supports brain plasticity, mood, and cognitive health, with deficits linked to depression and cognitive decline [163].

13.5 Stress

Chronic stress and stress hormones, glucocorticoids exert widespread actions in central nervous system, ranging from the regulation of gene transcription, cellular signaling, modulation of synaptic structure, and transmission and glial function to behavior. Their actions are mediated by glucocorticoid and mineralocorticoid receptors which are nuclear receptors/transcription factors. While glucocorticoids primarily act to maintain homeostasis by inducing physiological and behavioral adaptation, prolonged exposure to stress and elevated glucocorticoids levels may result in neuro- and psychopathology. There is now ample evidence for cause-effect relationships between prolonged stress, elevated glucocorticoids levels, and decrease in neurogenesis that is associated with cognitive and mood disorders [164][165].

13.6 Drugs and Medications

- Pro-neurogenic: Antidepressants (SSRIs), mood stabilizers, some antipsychotics [166][167]
- Anti-neurogenic: Alcohol, opioids, some chemotherapy agents [168][169]

14 FUTURE DIRECTIONS AND PRACTICAL APPLICATIONS

14.1 Resolving the Human Neurogenesis Debate through

- Standardized tissue collection and processing protocols
- Development of neurogenesis-specific biomarkers [170].
- Advanced imaging technologies by MRI and PET. [171]

14.2 Enhancement of the neurogenesis

14.2.1 Pharmacological Enhancement

Neurogenesis drugs that enhance neural stem cell proliferation [172] or survival. Lead candidates include:

- BDNF mimetics: (7,8-dihydroxyflavone)
- Anti-inflammatory agents (NSAIDs, minocycline)
- Metabolic modulators: (metformin, NAD+ precursors)

14.2.2 Cell-Based Therapeutic enhancement

- Neural Stem Cell Transplantation: Direct transplantation of neural stem cells into damaged brain regions shows promise for stroke, traumatic brain injury, and neurodegenerative diseases. Challenges include cell survival, integration, and differentiation into appropriate neuronal subtypes.[173][174]
- Endogenous Stem Cell Activation: Rather than transplanting cells, mobilizing endogenous neural stem cells through targeted interventions may be more practical. Approaches include gene therapy, and focused ultrasound to activate quiescent stem cells [175].

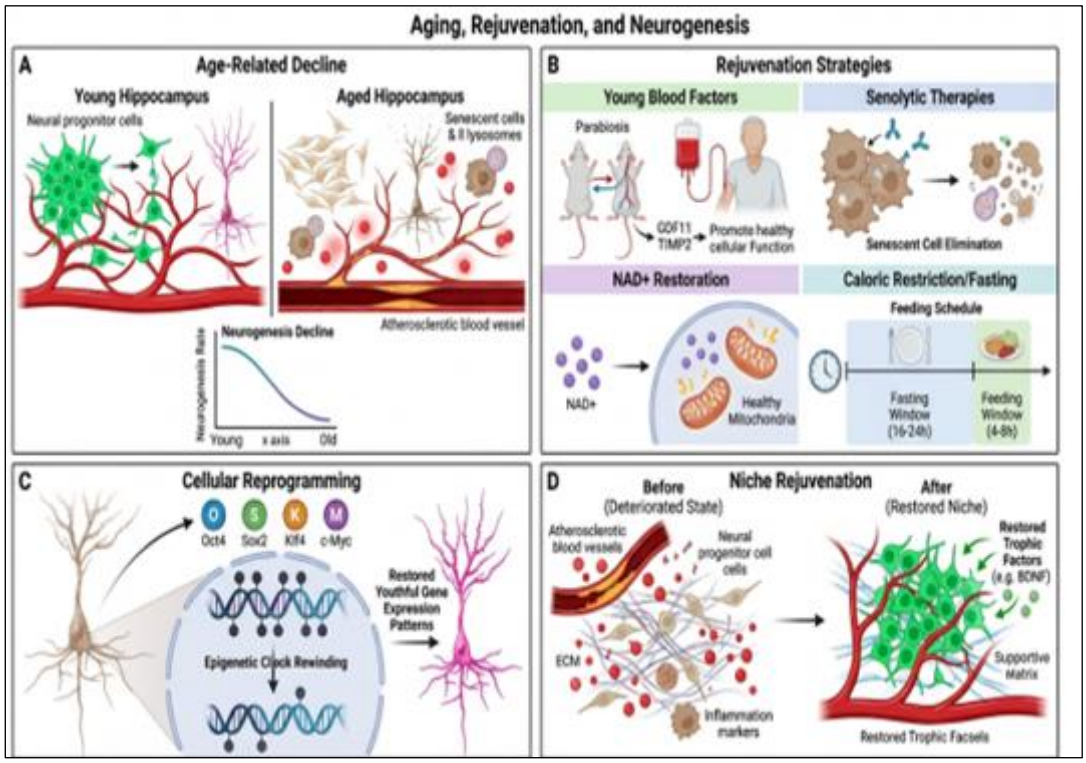


Figure 8: Aging, Rejuvenation and neurosis

14.3 Systemic Rejuvenation Approaches

14.3.1 Young Blood Factors

The young blood contains factors that can rejuvenate aged neural stem cells [176]. Identified factors include, oxytocin, and TIMP2 . Clinical trials are testing young plasma transfusions for cognitive decline [177][178].

14.3.2 Senolytic Therapies

Elimination of senescent cells using senolytics (dasatinib + quercetin, fisetin) reduces inflammation and improves neurogenesis in aged mice. Human trials are underway for age-related cognitive decline [179][180].

14.3.3 NAD+ Restoration

Age-related decline in NAD+ impairs mitochondrial function and stem cell activity [181]. NAD+ precursors restore neurogenesis and cognitive function in aged animals [182].

14.3.4 Metabolic Reprogramming

Caloric restriction, intermittent fasting, and ketogenic diets enhance neurogenesis and extend healthspan. Mimetics such as rapamycin and metformin show similar benefits [183][184].

14.3.5 Cellular Reprogramming and Epigenetic Rejuvenation

Resetting age-related epigenetic changes restores neural stem cell function [185][186].

14.4 Niche Rejuvenation

Aging affects not only stem cells but also the neurogenic niche (vasculature, extracellular matrix, immune cells) [187]. Comprehensive rejuvenation strategies must target all niche components:

- Vascular restoration using VEGF, exercise, or pro-angiogenic factors
- Extracellular matrix remodeling using matrix metalloproteinases
- Immune modulation to reduce chronic inflammation

14.5 Neurogenesis in Non-Traditional Brain Regions

While adult neurogenesis is well-established in the hippocampus and subventricular zone, emerging evidence suggests neurogenic potential in other brain regions (188):

- Hypothalamus:: Regulates metabolism and energy balance (189)
- Amygdala:: Involved in emotional processing [190].
- Striatum:: Enhanced after injury or in disease [191]
- Cortex:" Controversial but potentially important for learning [192].

14.6 Environmental and Lifestyle Interventions

14.6.1 Exercise Optimization

Different exercise modalities (aerobic, resistance) affect neurogenesis differently. Personalized exercise prescriptions based on age, fitness level, and genetic factors will maximize neurogenic benefits [193][194].

14.6.2 Dietary Interventions

Specific nutrients and dietary patterns enhance neurogenesis:

- Omega-3 fatty acids: [195]
- Polyphenols: (resveratrol, curcumin) [196].
- Ketogenic diet and intermittent fasting. [197].
- Mediterranean diet. [198]

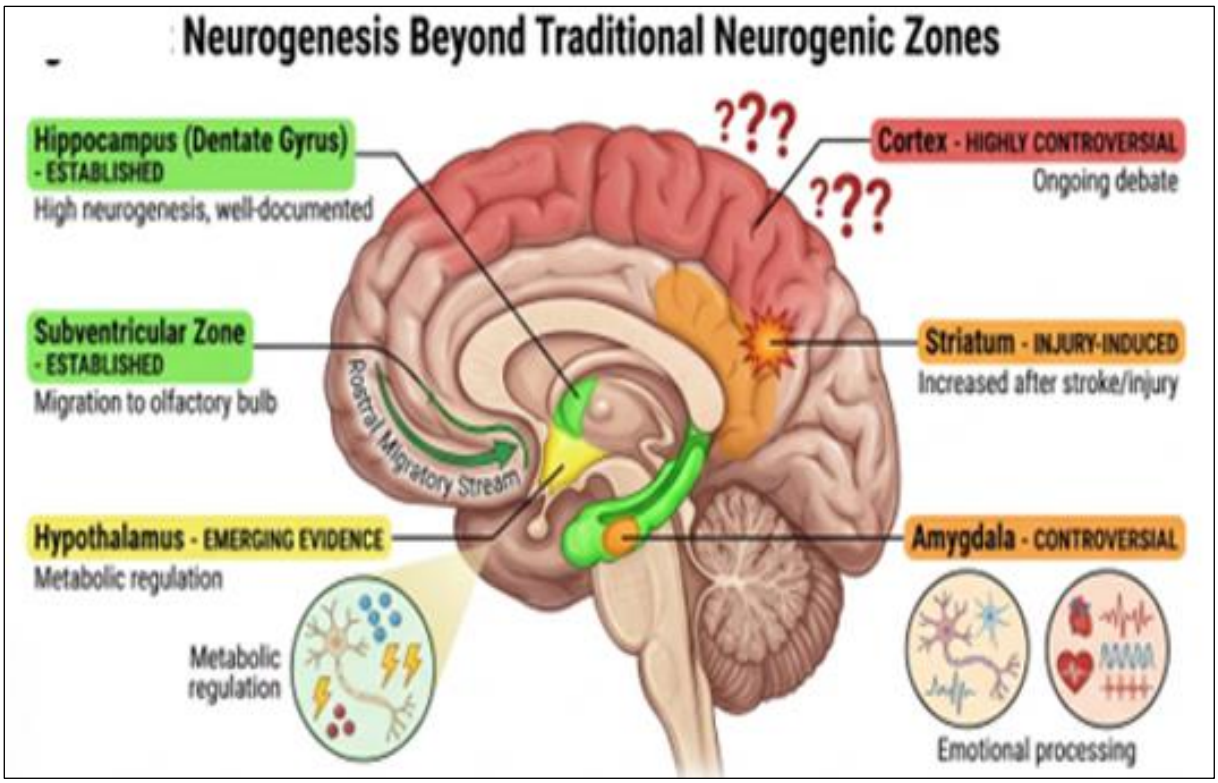


Figure 9: Neurogenesis in Non-Traditional Brain Regions

14.6.3 Cognitive Enrichment

Cognitive training, learning new skills, and environmental enrichment stimulate neurogenesis . Optimized cognitive interventions combining novelty, challenge, and social interaction will enhance neurogenic responses [199][200].

14.6.4 Social and Emotional Factors

Social isolation reduces neurogenesis while social interaction enhances it [201]. Stress management, mindfulness meditation, and positive social connections promote neurogenesis [202][203]

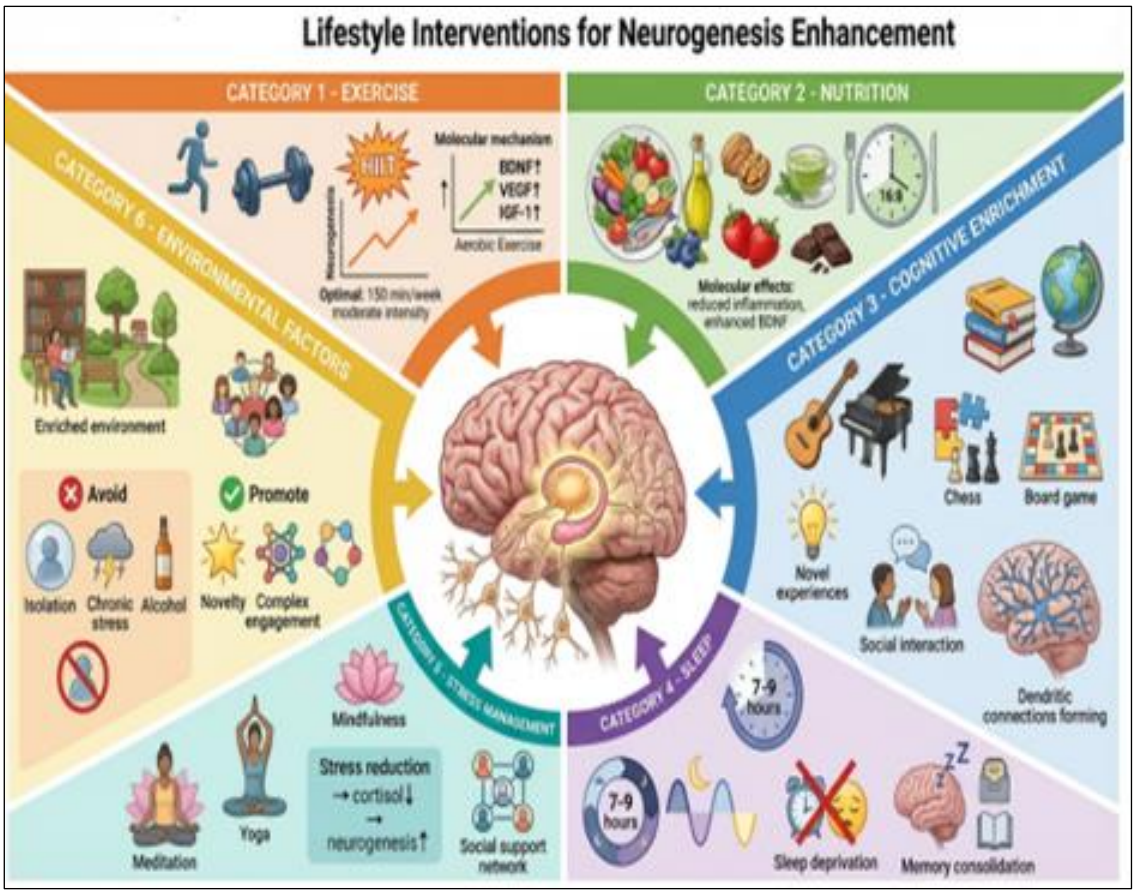


Figure 10: Lifestyle Interventions for Neurogenesis

14.6.5 Sleep and Circadian Rhythms

Sleep deprivation impairs neurogenesis while adequate sleep enhances it. Circadian rhythm optimization through light exposure, meal timing, and sleep hygiene supports neurogenesis [204][205].

15 CONCLUSION

Adult neurogenesis represents one of the most remarkable forms of plasticity in the mammalian brain. Over the past two decades, research has revealed the cellular and molecular mechanisms governing neurogenesis, the functional contributions of adult-born neurons, and the regulation of neurogenesis by experience, aging, and disease.

In rodents and other laboratory animals, adult hippocampal neurogenesis is well-established and contributes to pattern separation, memory formation, mood regulation, and behavioral flexibility. The continuous addition of new neurons throughout life provides the brain with a unique form of structural plasticity that complements synaptic mechanisms.

However, the field faces a critical challenge regarding human adult neurogenesis. Conflicting evidence about the extent and persistence of neurogenesis in the adult human brain has emerged from methodological differences in tissue processing, marker selection, and cohort characteristics. While robust neurogenesis as seen in rodents is unlikely in adult humans, some capacity for neurogenesis may persist at much lower levels. Resolving this controversy is essential for translating preclinical findings to human applications.

Regardless of the ultimate resolution of the human neurogenesis debate, the study of adult neurogenesis has provided fundamental insights into brain plasticity, disease mechanisms, and potential therapeutic strategies. Neurogenesis is altered in numerous neurological and psychiatric disorders, including Alzheimer's disease, depression, epilepsy, and stroke. Understanding these alterations may reveal disease mechanisms and therapeutic targets.

Looking forward, the field must address several key challenges:

- **Standardization:** Developing standardized protocols for human tissue studies to enable reliable cross-study comparisons
- **Biomarkers:** Creating validated biomarkers to non-invasively measure human neurogenesis in vivo
- **Translation:** Carefully considering species differences when extrapolating from animal models to human biology
- **Therapeutics:** Developing and testing pro-neurogenic interventions with realistic expectations based on human neurogenic capacity
- **Integration:** Understanding how neurogenesis interacts with other forms of plasticity and overall brain function

The study of adult neurogenesis has fundamentally changed our view of the adult brain from a static organ to one capable of ongoing structural remodeling. Whether robust adult human neurogenesis exists or not, the insights gained from studying this process in animal models have deepened our understanding of brain plasticity and opened new avenues for therapeutic intervention. As methodologies improve and our understanding grows, adult neurogenesis research will continue to provide valuable insights into brain function, aging, disease, and the potential for brain repair and regeneration.

The journey from the initial skepticism of Altman's findings in the 1960s to today's sophisticated understanding of neurogenic mechanisms exemplifies the power of persistent scientific inquiry. While important questions remain, particularly regarding human neurogenesis, the field has made remarkable progress and stands poised to contribute to the development of novel therapeutic strategies for neurological and psychiatric disorders. The coming years will likely see resolution of current controversies, development of better tools for studying human neurogenesis, and translation of pro-neurogenic strategies from bench to bedside, ultimately benefiting patients suffering from conditions affecting brain plasticity and function.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

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The authors disclose that artificial intelligence tools were utilized during the preparation of this manuscript. Specifically, AI was used for grammatical editing, text-cohesion enhancement, and formatting support to improve the narrative flow. Additionally, AI tools were employed to generate the illustrative figures. The authors maintain full accountability for the scientific accuracy, intellectual integrity, and final judgment of both the text and the visual content.

Disclosure of conflict of interest

The authors declare that they have no conflict of interest or competing financial relationships to disclose.

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