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Review

The Fate and Dynamics of Neural Stem Cells (NSCs) and Their Neurogenic Decline in Alzheimer's Disease

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ABSTRACT: Neural stem cells (NSCs) are crucial for neurogenesis in the mammalian brain, supporting the generation of neurons and glial cells during both development and adulthood. However, aging—driven by factors such as reduced growth factors, heightened inflammation, oxidative stress, and epigenetic modifications—leads to a decline in NSC activity, which is closely associated with cognitive decline. This article explores the significant reduction in neurogenesis observed in Alzheimer's disease (AD), where amyloid-beta (Aβ) accumulation, tau pathology, mitochondrial dysfunction, and chronic neuroinflammation disrupt NSC function in the hippocampus and subventricular zone (SVZ). These disruptions impair NSC proliferation, differentiation, and migration, contributing to the progression of cognitive deficits. Additionally, this article examines experimental studies suggesting that deficits in neurogenesis often precede amyloid plaque formation in animal models, positioning impaired neurogenesis as a potential early biomarker for AD. Therapeutic strategies targeting neurogenesis, epigenetics, and inflammation—such as anti-inflammatory treatments, environmental enrichment, and modulation of systemic factors—hold promise for reversing neurogenic deficits and enhancing cognitive function. Furthermore, this article discusses both pharmacological agents and non-pharmacological strategies that show potential in promoting neurogenesis, though further research is needed to evaluate their safety and efficacy. The decline of NSC is driven by many interconnected factors, making it challenging to understand and address fully. This highlights the need for ongoing research.

Keywords: Alzheimer's disease; Neural stem cells; Adult hippocampal neurogenesis; Subventricular zone (SVZ) neurogenesis; Amyloid-beta; Tau pathology; Neuroinflammation; Therapeutic strategies

1. Introduction: The Ongoing Debate on Adult Neurogenesis in Humans: Mechanisms, Evidence, and Potential Implications

The discovery of adult neurogenesis in mammals, first identified in the 1960s, remained largely overlooked until the late 1990s, when subsequent studies confirmed its occurrence in adult macaques and humans [1,2]. Despite these early findings, the question of whether neurogenesis continues throughout adulthood in humans remains a subject of ongoing debate. While some studies suggest a significant decline in hippocampal neurogenesis from childhood to adulthood, others assert that neurogenesis persists throughout life [3,4]. These conflicting views have fueled considerable discussion, with some studies supporting the former, while others challenge the methodology, citing issues such as postmortem delays and prolonged tissue fixation that may confound results [5].

Research investigating adult neurogenesis, particularly studies utilizing optimized techniques for its detection, has identified immature neurons in the dentate gyrus (DG) of individuals up to 90 years old [6,7]. However, some researchers suggest that these markers may represent a process known as "dematuration", in which mature neurons revert to a pseudo-immature state [8]. This possibility raises questions about the accurate estimation of neurogenesis and highlights the need for further investigation.

Recent advancements in single-nucleus RNA sequencing have cast doubt on the existence of adult hippocampal neurogenesis in humans. Limitations, such as small sample sizes and postmortem delays, are likely contributing factors to these findings [5]. Despite these challenges, compelling evidence from other studies continues to support the idea

that neurogenesis persists into old age [9,10]. Techniques like magnetic resonance imaging (MRI) have suggested the presence of neural stem cells (NSCs) *in vivo*, although concerns about their specificity and resolution remain unresolved [11]. Even if adult neurogenesis is absent in older individuals, the potential for therapeutic interventions to stimulate or reactivate neurogenesis persists.

Adult neurogenesis primarily occurs in the hippocampal DG and the subventricular zone (SVZ) of the lateral ventricles. Although neurogenesis has been observed in other brain regions, such as the neocortex and cerebellum, the hippocampus remains the focal point of research due to its well-established roles in learning, memory, and emotional regulation [12,13]. Environmental factors, such as exposure to enriched environments, have been shown to enhance neurogenesis, whereas age-related neurodegenerative diseases, including Alzheimer's and Parkinson's diseases, can impair hippocampal neurogenesis, potentially contributing to the pathophysiology of these conditions [14,15].

The dynamics of neurogenesis are influenced by both aging and neurodegenerative diseases [16]. In Alzheimer's disease (AD), for instance, the progressive decline in hippocampal neurogenesis correlates with cognitive deficits, suggesting that impaired neurogenesis may accelerate disease progression [17]. As a result, adult hippocampal neurogenesis holds potential as a valuable biomarker for neurodegenerative diseases.

To utilize adult neurogenesis as a biomarker in humans, it is essential to establish a physiological baseline in healthy individuals. Factors such as age, exercise, and caloric intake have been shown to influence neurogenesis rates [18,19]. Research suggests that approximately 700 new neurons are added to the hippocampus daily, representing a small but significant fraction of the DG neurons. However, this turnover decreases with age, and neurogenesis fails to keep pace with neuronal loss over time [20].

The potential to restore neurogenesis to baseline levels and its subsequent impact on cognitive function, particularly in the context of aging and neurodegenerative diseases, remains an unresolved question. This article emphasizes the critical role of NSCs in neurogenesis, highlighting how their function declines with age, contributing to cognitive impairment and the progression of AD. It examines the complex interactions between tau pathology, amyloid-beta accumulation, chronic neuroinflammation, and environmental factors in AD, which disrupt neurogenesis and impair NSC proliferation and differentiation, particularly within the hippocampus and SVZ. Furthermore, the article explores the potential of various pharmacological and non-pharmacological therapeutic strategies to restore neurogenesis and cognitive function.

2. The Role of Neural Stem Cells in Brain Development, Maintenance, and Aging

NSCs are fundamental to the formation, maintenance, and functional integrity of the mammalian central nervous system (CNS). They serve as the primary cellular source for neurogenesis, contributing to the generation of neurons and glial cells during both embryonic development and adulthood [21,22]. Beyond their critical developmental roles, NSCs support brain plasticity and cognitive resilience by facilitating cellular turnover and repair processes throughout life [17,23]. However, their functional capacity progressively diminishes with age, leading to a decline in neurogenic potential that has significant repercussions for cognitive functions, including memory retention, stress regulation, and adaptive neural remodeling [23,24].

2.1. The Developmental Origins of Adult NSCs

During early embryonic development, NSCs play a fundamental role in the rapid expansion of the CNS. These cells first emerge as neuroepithelial cells lining the ventricular zone (VZ), a region critical for brain development [25]. Neuroepithelial cells are highly proliferative and capable of symmetrical self-renewal, a process that not only expands the neuroepithelial population but also enlarges the VZ itself [26]. This expansion provides the structural and cellular foundation necessary for the generation of the brain's diverse cellular components [27,28].

As embryonic development progresses and the neural tube closes, neuroepithelial cells gradually transform into radial glial cells (Table 1) [29]. This transition is marked by the extension of long radial fibers from the ventricular surface to the pial surface. Radial glial cells shift from symmetrical to asymmetric cell division, a critical step in neural development [30,31]. Asymmetric divisions generate neural progenitor cells, which can differentiate into neurons and glial cells. This phase of neurogenesis continues until the final stages of brain development, after which radial glial cells differentiate into a range of mature cell types, including astrocytes with stem cell properties, ciliated ependymal cells, and other specialized glial subtypes that contribute to the structural and functional integrity of the mature brain [29,31–33].

Table 1. Stages of NSC Development and Key Outcomes in Brain Formation and Function.

Stage	Description	Key Outcomes	References
Embryonic Development	NSCs originate as neuroepithelial cells in the ventricular zone (VZ), undergoing symmetrical self-renewal to expand the neuroepithelial population and enlarge the VZ.	Formation of neuroepithelial cells and initial brain development.	[34,35]
Transition to Radial Glia	Neuroepithelial cells transition to radial glial cells, characterized by fibers extending from the ventricular to the pial surface, initiating asymmetric cell division to produce neural progenitors.	Generation of neurons and glial progenitors.	[31,36]
Radial Glial Differentiation	Radial glial cells differentiate into astrocytes with NSC properties, ependymal cells, and other glial types.	Formation of distinct CNS cell types contributing to brain architecture and function.	[29,32]
Adult Neurogenesis	NSCs in the adult brain reside in the ventricular-subventricular zone (V-SVZ) and subgranular zone (SGZ). They divide to form transit-amplifying progenitors (TAPs) and eventually neurons, integrating into existing circuits.	Sustained neurogenesis supports memory, learning, and behavioral adaptations.	[37–39]
Aging and Decline	NSC activity declines with age due to intrinsic and extrinsic factors, including reduced growth factors (EGF, FGF-2) and increased pro-aging systemic factors like inflammatory cytokines.	Decreased neurogenesis leads to cognitive deficits, reduced stress response, and diminished brain plasticity.	[40,41]

Following the peak neurogenic period, NSCs progressively enter a dormant or quiescent state (Table 1). This transition is regulated by intrinsic cellular mechanisms, including the expression of cell cycle inhibitors such as p57. By halting active proliferation, p57 helps preserve a reservoir of NSCs for potential future activation [42,43], primarily in specific regions where neurogenesis continues into adulthood.

In the adult brain, NSCs maintain their regenerative capacity in two primary neurogenic niches: the ventricular-SVZ (V-SVZ) lining the lateral ventricles and the subgranular zone (SGZ) of the hippocampal DG (Table 1) [44]. The persistence of NSCs in these regions ensures continued, albeit limited, neurogenesis throughout life. Notably, NSCs in the SGZ arise from a subset of progenitors responsive to Sonic Hedgehog (Shh) signaling. Gli1, a transcription factor activated by Shh, plays a key role in the maintenance and self-renewal of NSCs within this region [45,46]. This reliance on early developmental signaling pathways underscores the continuity between embryonic neurogenesis and adult brain plasticity [47].

2.2. Decline of Neurogenesis with Age

Neurogenesis declines significantly with age, a process attributed to a combination of intrinsic cellular changes and extrinsic environmental factors [16]. One of the primary contributors to age-related decline is the reduced availability of critical growth factors, such as epidermal growth factor (EGF) and fibroblast growth factor-2 (FGF-2) [48]. These signaling molecules are essential for maintaining NSC proliferation and ensuring a supportive microenvironment for neuronal differentiation. With age, the diminished presence of these factors restricts NSC activation and neurogenesis.

In addition to growth factor depletion, systemic inflammatory changes play a pivotal role in suppressing NSC activity. Aging is often accompanied by an increase in circulating pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) [49,50]. These molecules can impair the supportive microenvironment of the neurogenic niches by inhibiting NSC proliferation and differentiation while promoting gliosis, a reactive state of glial cells that further disrupts neurogenic capacity.

On a cellular level, intrinsic changes within NSCs themselves contribute to the decline in neurogenesis. Age-related alterations in metabolic pathways, mitochondrial dysfunction, and epigenetic modifications have been observed in quiescent NSCs [51,52]. For instance, increased oxidative stress and DNA damage accumulation can impair the regenerative potential of NSCs [53]. Additionally, changes in gene expression patterns related to cell cycle regulation and differentiation further diminish the ability of NSCs to sustain neurogenesis [54,55].

The decline in neurogenesis with aging has profound implications for cognitive health. Reduced NSC activity has been linked to memory deficits, impaired stress responses, and diminished brain plasticity [56]. For example, in the SGZ, where newly generated neurons contribute to hippocampus-dependent memory formation, age-related reductions in neurogenesis correlate with impaired spatial and episodic memory [57,58]. Similarly, in the V-SVZ, disruptions in

neuronal migration to the olfactory bulb may affect sensory processing and olfactory discrimination, functions essential for social behaviors in rodents [59,60].

3. Pathogenesis and Risk Factors of Alzheimer's Disease: An Integrated Perspective

AD is a progressive neurodegenerative disorder primarily affecting the elderly, and it remains the leading cause of dementia worldwide [61]. Projections suggest that by 2050, over 150 million individuals will be diagnosed with AD globally, highlighting the disease's profound social and economic impact [62]. Memory impairment is the hallmark clinical feature of AD, but as the disease progresses, it is accompanied by a range of cognitive and behavioral symptoms, including executive dysfunction, language deficits, sensory impairments, and mood changes [61,63,64]. AD is classified into two types: early-onset AD (EOAD), which typically manifests before 65 years of age and is often familial, and late-onset AD (LOAD), which generally affects individuals over 65 years of age and is frequently sporadic [65]. Genetic factors play a central role in the pathogenesis of AD, with mutations in the amyloid precursor protein (APP) and presenilins (PS1 and PS2) associated with EOAD, while the apolipoprotein E (APOE) gene is a significant susceptibility factor for LOAD [66,67].

The progression of AD is closely linked to aging, as the accumulation of DNA damage and the decline in DNA repair mechanisms accelerate disease onset in both human and animal models [68,69]. Mitochondrial dysfunction is central to neurodegeneration in AD patients, with a decline in nicotinamide adenine dinucleotide (NAD+), an essential mitochondrial coenzyme, observed in both aging and AD [70,71]. Inflammation further exacerbates the neurodegenerative processes, contributing to disease progression [72].

Females are disproportionately affected by AD, experiencing faster cognitive decline compared to males. Studies in animal models have shown that females exhibit earlier reductions in neurogenesis and mitochondrial dysfunction, which differences may influence sex hormones such as estrogen and testosterone [73,74]. Besides genetic and sex-related factors, lifestyle behaviors—particularly sleep disturbances and caloric intake—are linked to an increased risk of developing AD. For instance, caloric restriction has been shown to reduce amyloid-beta (Aβ) levels and improve memory in AD models [75–77]. However, despite identifying several risk factors, the precise mechanisms driving AD remain poorly understood, hindering the development of effective therapeutic strategies. Given the complexity of the disease, a multifaceted approach targeting aging, DNA repair, inflammation, mitochondrial function, and neurogenesis may offer new therapeutic opportunities.

3.1. The Role of Hippocampal Neurogenesis and Epigenetic Modifications in Alzheimer's Disease Progression

The hippocampus is one of the first areas affected by AD [78]. Amyloid plaques and neurofibrillary tangles develop early in the hippocampus and spread to other regions of the brain. Recent studies have observed disruption in neurogenesis-related genes in AD patients, including those involved in immune response, lipid processing, and the tau and APP pathways [79,80]. Additionally, genes essential for cell survival and growth, such as CDC42, brain-derived neurotrophic factor (BDNF), and VEGFA, are downregulated in AD, potentially impairing neurogenesis [81,82]. Epigenetic changes, including hypermethylation of genes related to neural differentiation and neurogenesis, have also been observed in the hippocampus of AD patients [83,84]. These findings suggest that targeting epigenetic modifications in neurogenesis-related genes may present novel therapeutic avenues for AD.

Although reduced adult neurogenesis is a common feature of healthy aging, its role in AD remains unclear. Some studies suggest that increased neurogenesis in the hippocampus of AD patients may represent a compensatory response to neuronal loss. However, prolonged neurogenesis may deplete the neural progenitor cell (NPC) pool [85,86]. In vitro studies have shown that NPCs derived from AD patients exhibit accelerated differentiation and reduced progenitor renewal [87]. Furthermore, hippocampal neurogenesis progressively declines in AD, correlating with cognitive impairments. A reduction in hippocampal volume and deficits in spatial memory further emphasize the relationship between neurogenesis decline and cognitive decline in AD [17,88,89].

In animal models of AD, both aged mice and transgenic AD models demonstrate decreased neurogenesis [90,91]. Human NSC transplantation has shown promise in restoring cognitive function in AD mouse models, supporting the idea that enhancing neurogenesis could be a viable therapeutic strategy. Risk genes such as APP, PS1, and APOE disrupt various stages of neurogenesis and influence neural precursor activity in AD models [92,93]. Interestingly, neurogenesis deficits can be detected before amyloid plaque formation in certain AD mouse models, suggesting that impaired neurogenesis may be an early indicator of the disease [94,95]. Studies using the 5xFAD mouse model reveal reduced newborn cells in the SGZ of the hippocampus, although neural stem cell proliferation remains unaffected [96]. This

suggests that the disruption of neurogenesis in AD occurs primarily during the differentiation stage [97]. Enhancing adult hippocampal neurogenesis (AHN) and elevating BDNF levels have been shown to improve cognitive function in AD mice, underscoring the importance of maintaining a healthy neurogenic environment [92,98,99]. Epigenetic modifications have been associated with cognitive improvements in AD models, suggesting that promoting neurogenesis may be a potential therapeutic strategy to treat or prevent the progression of AD [100,101].

3.2. DNA Damage and Oxidative Stress in Alzheimer's Disease: Implications for Neurodegeneration and Impaired Neurogenesis

DNA Damage and Neurodegeneration DNA damage and oxidative stress play a pivotal role in the pathogenesis of AD, with strong associations to both neurodegeneration and impaired neurogenesis [102,103]. DNA damage, particularly in the hippocampus, has been consistently observed in AD patients. The accumulation of such damage disrupts cell cycle progression, leading to neuronal apoptosis and synaptic dysfunction, both hallmarks of AD pathology [104,105].

Mutations in genes responsible for DNA repair processes further exacerbate these pathological features. Deficiencies in double-strand break (DSB) repair mechanisms, such as those involving ATM, BRCA1, and XRCC1, are linked to accelerated neuronal loss and cognitive decline in AD [106,107]. Compromised repair pathways not only fail to resolve existing DNA damage but also promote chronic oxidative stress, further amplifying cellular dysfunction [108].

Oxidative stress damages cellular components, including DNA, proteins, and lipids. In AD, oxidative stress is amplified by mitochondrial dysfunction and chronic inflammation, creating a feedback loop that perpetuates neurodegeneration [109,110]. Elevated oxidative stress markers, such as 8-oxo-2′-deoxyguanosine (8-oxo-dG), are frequently detected in post-mortem AD brain tissues, highlighting the persistence of oxidative damage [111,112].

Impaired DNA repair mechanisms have direct implications for neurogenesis as well [113,114]. NPCs rely on effective DNA repair for proper proliferation and differentiation [113,115]. In AD, the excessive DNA damage burden leads to premature depletion of NPCs and reduced neurogenic capacity in the hippocampus [16,116]. Additionally, epigenetic modifications driven by oxidative stress, such as histone modifications and DNA methylation changes, further disrupt neurogenesis regulatory pathways [117,118].

4. Neurogenesis Decline in Alzheimer's Disease: Clinical and Preclinical Insights

Recent research highlights the profound impact of impaired neurogenesis in AD, compounding the natural age-related decline in NSC activity. Evidence from postmortem studies and animal models reveals how tau pathology, inflammation, and environmental factors disrupt neurogenesis and suggests potential therapeutic approaches [119,120].

Postmortem analyses of AD patients across all Braak stages show a consistent reduction in neurogenesis, indicating early impairment in NSC proliferation and differentiation, possibly preceding amyloid plaque accumulation (Table 2) [17,93,121]. A study found significantly fewer doublecortin (DCX)-positive immature neurons, linking early cognitive decline to impaired neuronal lineage [122,123]. While earlier reports suggested compensatory hippocampal neurogenesis, their findings were limited by small sample sizes and inconsistent methodologies [10,124].

Table 2. Neurogenesis Impairment in Alzheimer's Disease: Insights from Various Study Models.

Study Type	Findings	Mechanisms Identified	Implications	Future Directions	References
Postmortem Studies	Reduced neurogenesis observed in AD patients across all Braak stages.	Early decline in NSC proliferation and differentiation before significant plaque deposition.	Neurogenesis impairment occurs early in AD progression, suggesting it as a potential biomarker for early detection.	Explore longitudinal studies linking neurogenesis decline with clinical and imaging biomarkers.	[17,88,93]
Mouse Models (3xTg, 5xFAD)	Decreased neurogenesis in hippocampal regions, including defects in NSC differentiation and survival.	Amyloid-β and tau pathology impair NSC maturation and migration.	Links neurogenesis impairment to cognitive deficits; enhancing neurogenesis may have therapeutic value.	Test novel therapeutic interventions (e.g., NSC transplantation, neurotrophic factors) in AD mouse models.	[96,125]
Tau Studies	Tau overexpression impairs neurogenesis, independent of NSC numbers.	Tau aggregation disrupts microtubule function and GABAergic signaling critical for NSC migration.	GABAergic modulation might alleviate tau-mediated neurogenesis defects.	Investigate tau-targeting therapeutics for restoring neurogenesis in tauopathy-related diseases.	[126,127]
Amyloid-β Studies	Amyloid-β accumulation reduces NSC proliferation and neuronal differentiation in hippocampal regions.	Oxidative stress, calcium dysregulation, and mitochondrial damage induced by Aβ contribute to neurogenesis loss.	Targeting Aβ toxicity may simultaneously preserve neurogenesis and cognitive function.	Develop Aβ-specific therapies aimed at NSC protection and differentiation support.	[103,128]
Environmental Enrichment	Inconsistent results; some studies show improved neurogenesis and cognitive performance in AD models.	Enrichment affects neurogenesis through increased levels of neurotrophic factors like BDNF.	Environmental factors can modulate disease progression, but the variability of outcomes warrants further research.	Conduct large-scale studies with standardized enrichment protocols across AD models.	[129,130]
Inflammation and Microglia	Microglial activation significantly reduces NSC proliferation and differentiation.	Overproduction of pro-inflammatory cytokines (e.g., TNF-α, IL-6, IL-10) creates a hostile NSC niche.	Anti-inflammatory therapies may restore neurogenesis and improve cognitive outcomes in AD patients.	Investigate the specific roles of cytokine signaling in neurogenesis and identify microglia-targeting therapies.	[131–133]
Neurovascular Impairment	BBB dysfunction correlates with reduced neurogenesis in AD models.	BBB dysfunction exposes NSCs to systemic factors, including toxins and inflammatory mediators.	Targeting BBB integrity may preserve NSC function and enhance neurogenesis in AD.	Develop therapeutic strategies to improve BBB repair and its role in neurogenic niches.	[134–136]
Oxidative Stress Studies	Elevated reactive oxygen species (ROS) reduce NSC survival and impair differentiation in the SGZ.	Amyloid-β oligomers exacerbate oxidative stress, causing mitochondrial dysfunction and calcium imbalance.	Antioxidant-based therapies could protect NSCs and preserve hippocampal neurogenesis.	Explore combinatorial treatments targeting oxidative stress and mitochondrial function.	[137,138]
Gut-Brain Axis Studies	Dysbiosis reduces hippocampal neurogenesis and impairs cognitive performance in AD models.	Altered microbial metabolites (e.g., SCFAs) impact NSC survival and differentiation via systemic signaling.	Gut microbiota modulation could serve as a novel therapeutic approach for neurogenesis preservation in AD.	Investigate the role of prebiotics, probiotics, and microbiota transplants in enhancing neurogenesis in AD.	[139,140]

Animal models offer valuable insights, although they fall short of fully recapitulating human disease. In 3xTg mice, which harbor APP, PS-1, and tau mutations, neurogenesis deficits emerge by four months of age, with substantial hippocampal SGZ impairment by 12 months (Table 2) (Figure 1) [125,141,142]. The 5xFAD model, encompassing five familial AD mutations, shows a decline in hippocampal neurogenesis beginning at two months, with virtually no new neurons detectable by seven months [143,144]. These models illustrate that neurogenesis deficits stem from both NSC proliferation and differentiation impairments, correlating with cognitive dysfunction. Experimental efforts to enhance neurogenesis in these models have shown modest but promising cognitive improvements.

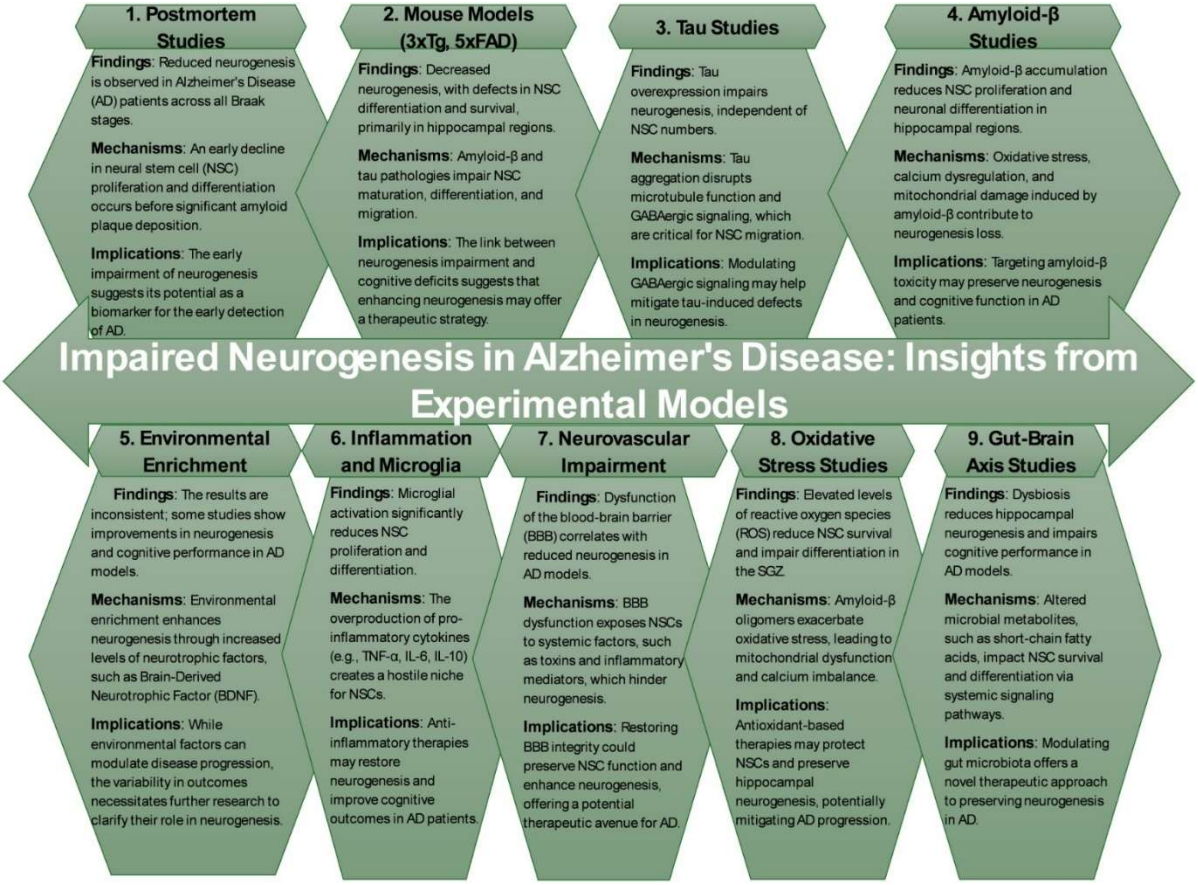

Figure 1. Neurogenesis Impairment in Alzheimer's Disease—Insights from Various Study Models.

Mechanistically, tau pathology disrupts microtubule dynamics critical for NSC maturation and axonal outgrowth. Tau hyperphosphorylation impairs GABAergic signaling and NSC morphology, exacerbating neurogenesis deficits (Table 2) [145,146]. Chronic neuroinflammation, mediated by activated microglia and elevated cytokines such as TNF-α and IL-6, creates a hostile NSC niche. Anti-inflammatory interventions, including interleukin-10 overexpression, have shown promise in restoring neurogenesis in animal models [132,147,148].

Environmental enrichment and systemic factors further modulate neurogenesis (Table 2) [149,150]. Environmental enrichment has been shown to enhance spatial memory, reduce amyloid and tau pathology, and promote neurogenesis in rodent models; however, the efficacy of these effects depends on the timing and duration of the intervention [151,152]. Additionally, systemic factors, including disruptions in the gut-brain axis and blood-brain barrier (BBB) dysfunction, can negatively impact hippocampal neurogenesis by exposing NSCs to systemic toxins and inflammatory mediators [153–155].

5. Molecular and Cellular Mechanisms Disrupting Hippocampal and SVZ Neurogenesis in Alzheimer's Disease

5.1. Mechanisms Impairing Hippocampal Neurogenesis in Alzheimer's Disease

AD is characterized by the progressive loss of cognitive function, primarily attributed to disruptions in AHN [17,156]. AHN is integral to learning, memory, and overall cognitive function. The decline in AHN in AD is driven by a complex interplay of molecular and cellular mechanisms, including mitochondrial dysfunction, calcium dysregulation, oxidative stress, neurotransmitter imbalances, and neuronal signaling alterations [69,88]. Additionally, pathological changes such as neuroinflammation, BBB dysfunction, and compromised neurovascular integrity further impair AHN and exacerbate cognitive deficits (Table 3) [157,158].

Table 3. Molecular Mechanisms Underlying Impaired Adult Hippocampal Neurogenesis in Alzheimer's Disease.

Mechanism	Key Impact	Molecular Pathways Involved	Experimental Evidence	Therapeutic Implications	References
Mitochondrial Dysfunction	Driven by amyloid-beta (Aβ) accumulation, leads to loss of mitochondrial membrane integrity, disrupts ion channel function, and causes dysregulated calcium (Ca^{2+}) influx, impairing neurogenesis processes like BDNF transport.	Mitochondrial membrane proteins, BDNF transport pathways	Studies with human neural progenitor cells treated with mitoAβ^{+} show reductions in BDNF levels and neural differentiation in SGZ of 5XFAD mice.	Targeting mitochondrial stability and enhancing mitochondrial biogenesis using antioxidants or mitochondrial-targeted peptides.	[70,159]
ApoE4 and Genetic Factors	ApoE4 isoform reduces AHN by disrupting GABAergic signaling, dendritic spine formation, and neurogenesis regulation, causing cognitive deficits. It also promotes tau hyperphosphorylation, impairing synaptic function.	ApoE4 isoform, Tau hyperphosphorylation	ApoE4 knock-in mice exhibit reduced AHN and dendritic complexity in dentate gyrus granule cells, alongside impaired memory in cognitive tasks.	Developing ApoE4-targeted therapies to improve synaptic function and restore neurogenesis.	[160,161]
Synaptic Plasticity	Impairments in LTP disrupt AMPA receptor insertion during synaptic plasticity, leading to unstable synaptic connections and memory deficits.	CaMKII, AMPA receptor trafficking	Aβ impairs CaMKII autophosphorylation, reducing AMPA receptor availability and synaptic plasticity in hippocampal neurons.	Enhancing CaMKII signaling or stabilizing AMPA receptor trafficking to restore LTP and memory consolidation.	[162–164]
Transcription Factor Dysregulation	Wnt signaling is suppressed (elevated Dkk-1 levels), impairing survival pathways, while BMP signaling is upregulated, leading to astrogliogenesis and reduced neurogenesis.	Wnt signaling, BMP signaling	Increased Dkk-1 levels suppress Wnt in AD mouse models, reducing synaptic density; upregulated BMP signaling promotes astrogliosis.	Targeting Dkk-1 antagonists or BMP inhibitors to restore Wnt signaling and promote neural differentiation.	[165–167]
Oxidative Stress and ROS	ROS accumulation leads to cellular damage and impairs neural progenitor cell functionality, exacerbating mitochondrial dysfunction and reducing AHN.	ROS-mediated signaling pathways	Aβ oligomers increase ROS production and calcium influx, causing oxidative damage and reduced neurogenesis in aged hippocampal neurons.	Using ROS scavengers or enhancing antioxidant defenses to protect neural progenitors and maintain AHN.	[128,168]
Neuroinflammation	Chronic neuroinflammation reduces neurogenesis by promoting astrogliogenesis and inhibiting neural progenitor proliferation and differentiation, leading to cognitive impairments.	Microglial activation, pro-inflammatory cytokines	LPS-induced inflammation in 3xTg-AD mice promotes astrogliogenesis, reducing neural progenitor survival and differentiation.	Anti-inflammatory treatments to shift microglial activation towards neuroprotective phenotypes and promote neurogenesis.	[169–171]
Blood-Brain Barrier Integrity	BBB dysfunction allows systemic factors to infiltrate the brain, disrupting neurogenesis and contributing to neurodegeneration in hippocampal regions.	Tight junction proteins, vascular factors	BBB disruption in AD models correlates with impaired neurogenesis and increased cognitive decline; plasma from exercised animals enhances neurogenesis in AD models.	Strengthening BBB integrity or targeting vascular factors to reduce permeability and maintain a supportive neurogenic environment.	[134,172]
Gut Microbiota	Alterations in microbiota composition influence brain health via the gut-brain axis, modulating systemic inflammation and impairing AHN in Alzheimer's disease.	Gut-brain axis signaling pathways	Microbiota from AD patients transplanted into wild-type rats reduce AHN and impair cognition, showing systemic effects on neurogenesis.	Modulating gut microbiota through probiotics or dietary interventions to restore balance and support hippocampal neurogenesis.	[140,173]

Mitochondrial dysfunction emerges as a hallmark of AD and plays a pivotal role in disrupting AHN (Figure 2) [71,173]. Amyloid-beta (Aβ) accumulation compromises mitochondrial membrane integrity and ion channel function, leading to dysregulated calcium (Ca^{2+}) influx [174,175]. This impairs essential neurogenic processes such as BDNF transport and increases neuronal susceptibility to excitotoxicity [174]. Experimental models with mitochondrial-targeted Aβ constructs reveal significant reductions in BDNF levels and impaired neural progenitor cell differentiation in the SGZ [88,128]. These findings underscore how Aβ-induced mitochondrial dysfunction disrupts AHN by hindering progenitor cell maturation and differentiation.

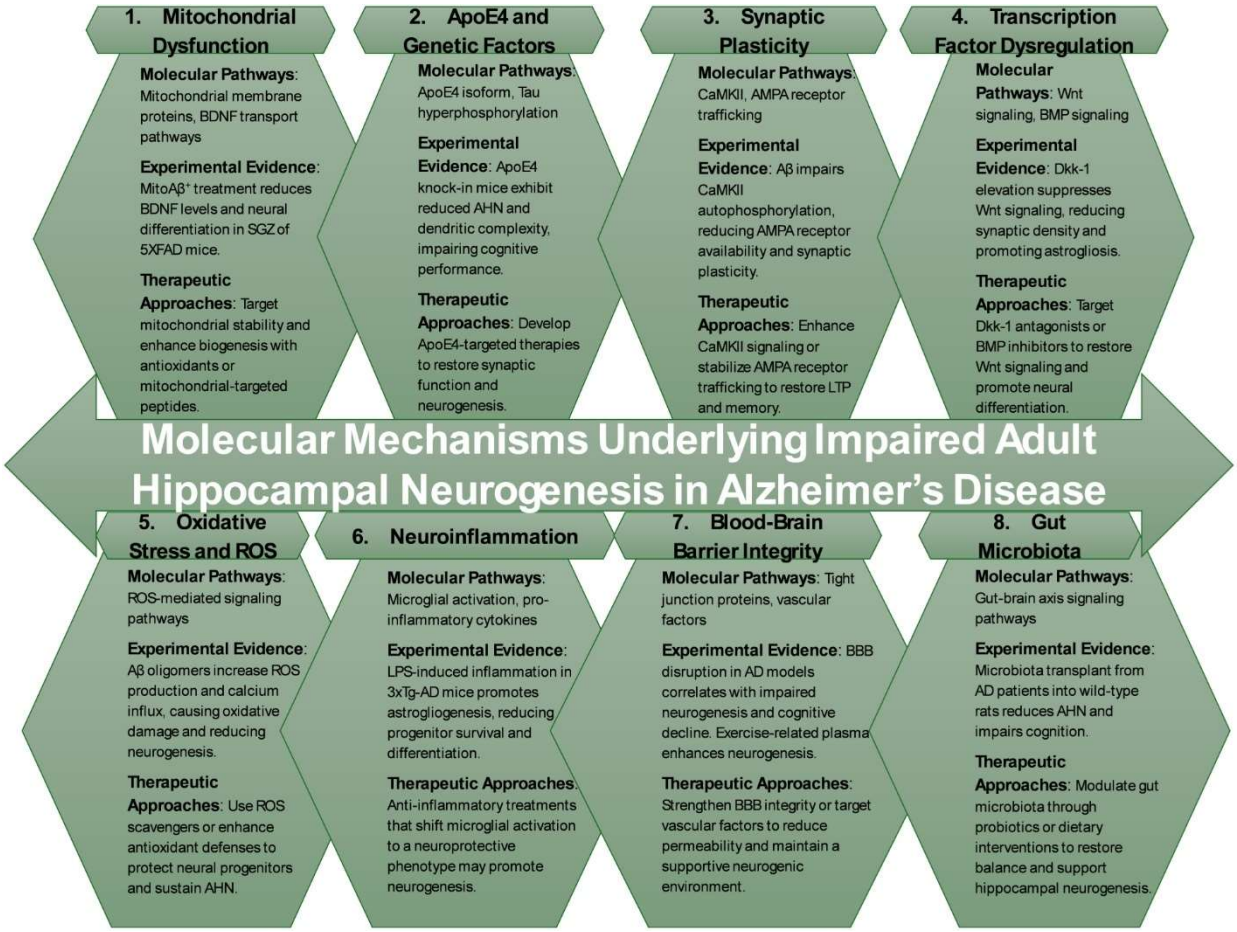

Figure 2. Molecular Mechanisms Underlying Impaired Adult Hippocampal Neurogenesis in Alzheimer's Disease.

The apolipoprotein E4 (ApoE4) isoform, a major genetic risk factor for AD, further exacerbates AHN deficits [176]. Studies demonstrate reduced AHN in ApoE4 knock-in mouse models compared to ApoE3 counterparts (Figure 2) [177]. Mechanistically, ApoE4 accumulation of hyperphosphorylated tau in parvalbumin-positive interneurons disrupts GABAergic signaling, reducing the survival and integration of adult-born dentate gyrus granule cells (DGCs) [17,160,178]. Furthermore, ApoE4 diminishes dendritic spine density and complexity, impairing synaptic connectivity and contributing to cognitive deficits observed in behavioral tasks [179].

Synaptic plasticity, particularly long-term potentiation (LTP) in adult-born DGCs, is another critical component of AHN that is disrupted in AD (Figure 2) [180,181]. Calcium/calmodulin-dependent kinase II (CaMKII), an essential enzyme for synaptic plasticity, is dysregulated in AD due to Aβ interference with autophosphorylation processes [182,183]. This impairs AMPA receptor insertion and synaptic strength, leading to memory consolidation deficits and accelerated cognitive decline [164,184].

The dysregulation of key neurogenic pathways, such as Wnt and bone morphogenetic protein (BMP) signaling, further exacerbates AHN impairment in AD. Wnt signaling, critical for neural progenitor survival, is inhibited in AD by elevated levels of Dickkopf-1 (Dkk-1), a Wnt antagonist, leading to synaptic loss [185–187]. Concurrently, upregulated BMP signaling promotes astrogliogenesis over neurogenesis, compounding the decline in AHN and exacerbating neuronal dysfunction [88,166,188].

Oxidative stress plays a substantial role in AHN impairment, with elevated reactive oxygen species (ROS) levels causing cellular damage in the hippocampus (Figure 2) [189,190]. Aβ oligomers amplify oxidative stress by inducing

mitochondrial damage, further impairing neurogenesis [191,192]. Studies show that Aβ oligomers in aged neurons increase ROS production and intracellular calcium levels, highlighting the vulnerability of neural progenitors to oxidative damage in the AD brain [193].

Neuroinflammation, a hallmark of both aging and AD, significantly disrupts AHN by altering the balance between neurogenesis and gliogenesis (Figure 2) [120,194]. Inflammatory mediators such as lipopolysaccharide (LPS) exacerbate AHN deficits, particularly in mouse models of AD, where pro-inflammatory microglial activation inhibits neural progenitor cell differentiation [195,196]. Chronic neuroinflammation shifts the microenvironment toward a state that favors astrogliogenesis, further impairing neurogenic processes and contributing to cognitive deficits [197].

BBB dysfunction is another pathological hallmark of AD that disrupts AHN [198]. The DG is particularly vulnerable to altered BBB permeability (Figure 2). This dysfunction permits systemic factors to influence neurogenesis [199]. For instance, plasma from exercised animals has been shown to enhance AHN in AD models, suggesting a role for systemic factors in modulating AHN and potentially mitigating cognitive decline [88,200].

Emerging evidence points to the gut microbiota as a key regulator of AHN in AD. Transplantation of microbiota from AD patients or 5xFAD mice into wild-type animals reduces AHN and impairs cognition, implicating gut dysbiosis in AD pathology [201–203]. This highlights the potential of the gut-brain axis as a therapeutic target for preserving AHN and cognitive function in AD.

The disruption of AHN in AD results from a multifaceted network of molecular, cellular, and systemic mechanisms. Therapeutic strategies targeting mitochondrial dysfunction, Wnt signaling, oxidative stress, neuroinflammation, and gut-brain axis modulation hold promise for preserving AHN and mitigating cognitive decline in AD. Further research into these interconnected pathways is critical for developing effective interventions to restore AHN and cognitive health in AD patients.

5.2. Mechanisms Impairing Subventricular Zone Neurogenesis in Alzheimer's Disease

The SVZ plays a dynamic role in maintaining brain plasticity through its contribution to neurogenesis, where NSCs generate new neurons and glial cells. However, in AD, this critical neurogenic niche becomes increasingly dysfunctional as pathological factors disrupt the ability of the SVZ to sustain neural regeneration [44,56,204]. Amyloid-β (Aβ) significantly diminishes NSC proliferation and migration, particularly during early disease stages (Table 4) [205]. Mechanistically, Aβ inhibits cell division by downregulating essential cell cycle regulatory proteins and upregulating inhibitors like p21 and p27 [206,207]. Furthermore, oxidative stress induced by Aβ directly damages NSCs and impairs their maturation into functional neurons, leading to a decline in the neurogenic capacity of the SVZ [53,208].

Table 4. Mechanisms and Impact of Pathological Factors on SVZ Neurogenesis in Alzheimer's Disease.

Pathological Factor	Impact on SVZ Neurogenesis	Mechanism	Associated Pathology	Therapeutic Interventions	Future Research Directions	References
Amyloid-β (Aβ)	- Significant reduction in NSC proliferation and migration, particularly in the early stages of AD. - Impaired maturation of NSCs into functional neurons.	- Downregulation of cell cycle regulatory proteins, leading to halted NSC proliferation. - Upregulation of inhibitory pathways like p21 and p27. - Induction of oxidative stress.	Amyloid plaques in hippocampus and cortex.	- Antioxidants to mitigate oxidative stress. - Small molecules targeting Aβ toxicity. - Immunotherapy to reduce amyloid burden.	- Longitudinal studies assessing NSC response to Aβ modulation. - Explore combinatorial therapies targeting oxidative stress and NSC proliferation.	[94,204]
Hyperphosphorylated Tau	- Impaired differentiation of NSCs into neurons and glial cells. - Reduced NSC migration to regions like the cortex and olfactory bulb.	- Destabilization of microtubule structures. - Impaired intracellular transport, causing energy deficits. - GABAergic signaling disruption by aggregated tau.	Neurofibrillary tangles in AD brain regions.	- Microtubule stabilizers like epothilones. - GABAergic interventions to restore migration. - Tau aggregation inhibitors.	- Investigate GABAergic pathways and tau-targeting therapies. - Examine links between tau pathology and NSC polarity.	[95,126]
Metabolic Dysregulation	- Diminished survival rates of NSCs in the SVZ. - Loss of energy production and structural maintenance in neural progenitors.	- Hyperactivation of the Akt/mTOR signaling pathway disrupts energy homeostasis. - Accumulation of toxic lipid intermediates damages NSCs and induces cellular stress responses.	Brain glucose hypometabolism in AD. - Lipid accumulation in neurons.	- mTOR pathway inhibitors to restore autophagy. - Therapies targeting lipid metabolism, such as lipid-lowering agents.	- Develop metabolic modulators to enhance NSC survival. - Explore autophagy restoration to support NSC energy balance.	[209,210]
Neuroinflammation	- Severe inhibition of NSC proliferation and differentiation. - Altered SVZ niche environment due to chronic inflammation.	- Overproduction of pro-inflammatory cytokines (e.g., IL-6, TNF-α, IFN-γ). - Microglial activation disrupting SVZ homeostasis and increasing NSC apoptosis.	Chronic microglial activation. - Increased cytokine levels in cerebrospinal fluid (CSF).	- Anti-inflammatory cytokines (e.g., interleukin-10 therapy). - Pharmacological microglia modulators (e.g., P2Y12 receptor agonists).	- Identify specific inflammatory cytokine pathways regulating NSCs. - Develop targeted microglial therapies to preserve the niche.	[132,211,212]
Calcium Dysregulation	- Reduced neurogenic capacity and NSC survival. - Exacerbation of cognitive deficits due to impaired synaptic integration of new neurons.	- Calcium homeostasis disruption alters proliferation. - Dysfunction of calcium-dependent pathways like CREB activity critical for NSC signaling and maturation.	Calcium overload in neurons. - Synaptic dysfunction in AD.	- Calcium channel blockers to restore homeostasis. - CREB activators to promote neurogenic signaling.	- Study calcium-dependent pathways affecting NSC function. - Evaluate the impact of calcium-modulating therapies on AD progression.	[213–215]

Hyperphosphorylated tau further exacerbates neurogenic impairments by disrupting the differentiation and migration of NSCs (Table 4) (Figure 3) [216]. Tau-induced destabilization of microtubules interferes with intracellular transport, resulting in energy deficits and loss of cellular polarity, which are essential for NSC migration to regions such as the cortex and olfactory bulb [217–219]. Additionally, metabolic dysregulation in AD further exacerbates these deficits. [220]. Hyperactivation of the Akt/mTOR signaling pathway disrupts energy homeostasis and autophagy, critical processes for NSC maintenance and survival [221–223]. Toxic lipid intermediates accumulate, inducing cellular stress responses that reduce NSC viability and impair structural integrity [224,225].

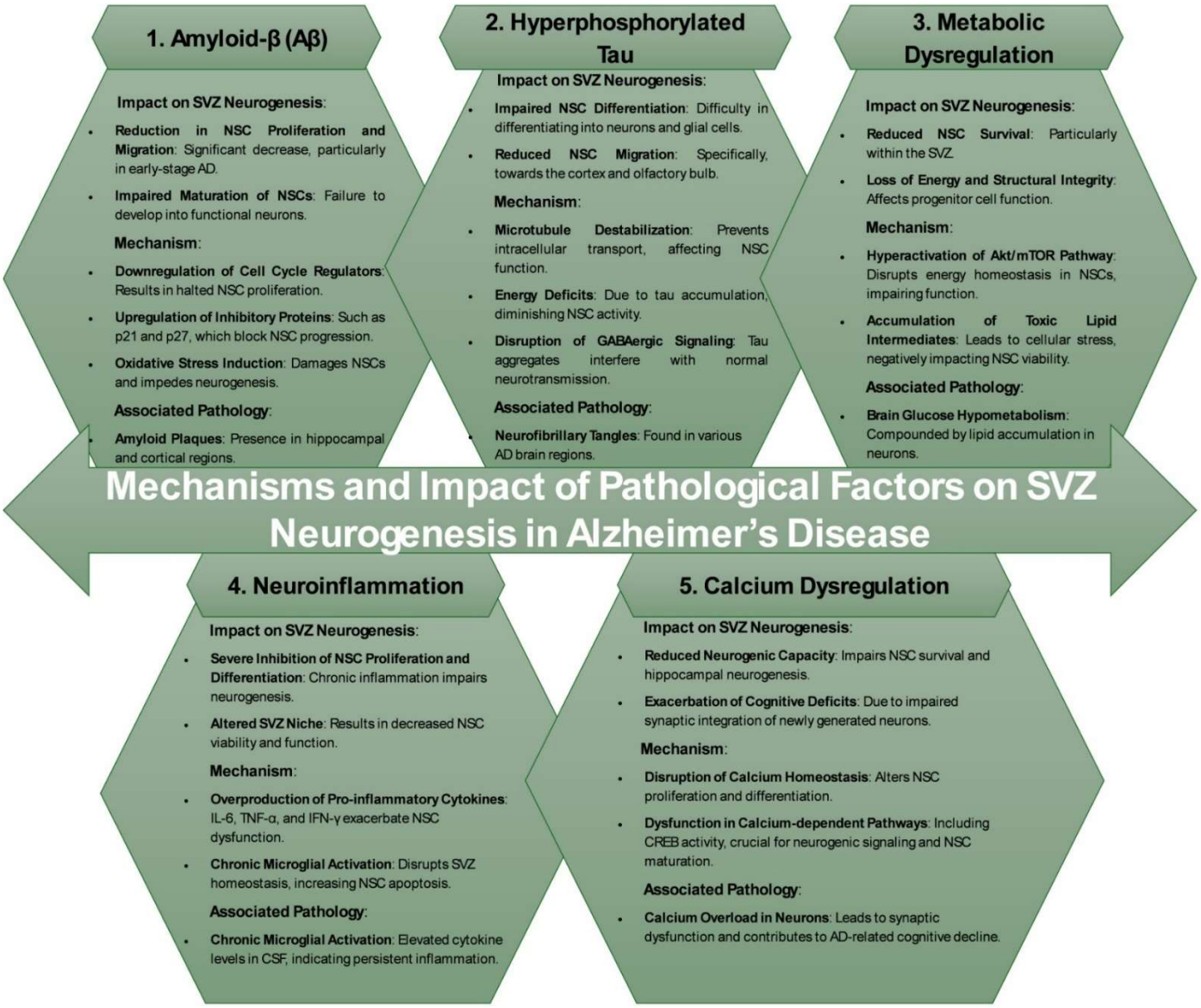

Figure 3. Mechanisms and Impact of Pathological Factors on SVZ Neurogenesis in Alzheimer's Disease.

Neuroinflammation and calcium dysregulation also significantly impair SVZ neurogenesis in AD (Table 4) (Figure 3). Chronic neuroinflammation reshapes the SVZ niche through the overproduction of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), creating a hostile environment for NSCs [132,226]. Activation of microglia further disrupts the SVZ's homeostasis, inhibiting NSC proliferation and differentiation [131,227]. Calcium dysregulation, often a downstream effect of Aβ and tau pathology, perturbs calcium-dependent signaling pathways critical for neurogenesis, including CREB-mediated transcription [88,228]. This imbalance reduces NSC survival and limits the integration of newly formed neurons into functional neural circuits, amplifying the cognitive deficits associated with AD. Exploring these interconnected mechanisms provides insight into potential therapeutic strategies aimed at restoring SVZ neurogenesis and mitigating the progression of AD.

6. Implications of Adult Hippocampal Neurogenesis in Humans for Cognitive Function and Alzheimer's Disease Pathophysiology

Adult hippocampal neurogenesis (AHN) has been extensively studied in rodent models, yet its presence and functional significance in humans remains a subject of ongoing debate. While neurogenesis appears absent in the adult human olfactory bulb and the ventral SVZ, evidence suggests that AHN persists in the hippocampus throughout the human lifespan [16,229]. This continued neurogenesis is associated with key cognitive functions such as spatial and contextual pattern separation, which are essential for learning and memory [230,231]. Furthermore, AHN has been implicated in the pathophysiology of AD, where it may either exacerbate or mitigate the disease's progression, depending on the context [17,92].

Various methodologies have been employed to investigate AHN, each offering unique insights while presenting distinct challenges. Techniques such as BrdU staining, radiocarbon dating, in vitro models, immunohistochemistry, and single-cell transcriptomics have been instrumental in advancing our understanding of AHN (Table 5). However, each approach has limitations that complicate data interpretation. For instance, BrdU staining is prone to age-related autofluorescence and false positives [232,233], while radiocarbon dating is hindered by background contamination and limited spatial resolution [234]. In vitro models, although valuable for studying underlying mechanisms, fail to replicate the complexity of the *in vivo* microenvironment. Single-cell transcriptomics has provided high-resolution molecular data, but it faces challenges such as technical variability and computational complexity [235,236]. Recognizing these limitations is critical to interpreting findings and improving methodological rigor in AHN research.

Table 5. Evaluation of Methodologies for Investigating Adult Hippocampal Neurogenesis.

Method	Description	Limitations	Applications	Advantages	Future Directions	References
BrdU Staining	5-bromo-2′-deoxyuridine (BrdU) is a thymidine analog that integrates into the DNA of proliferating cells, enabling the identification of newly generated neurons.	- Autofluorescence due to lipofuscin in aged tissues, interfering with BrdU detection. - Potential false positives from DNA repair or methylation processes. - Limited to short time windows, complicating long-term neurogenesis tracking.	- Tracking neurogenesis in animal models. - Evaluating neurogenic responses to therapeutic interventions.	- Direct identification of proliferating cells. - Quantitative analysis of neurogenesis at specific time points.	- Develop BrdU alternatives with lower autofluorescence sensitivity. - Combine BrdU with complementary techniques (e.g., transcriptomics) to improve temporal resolution and reliability.	[237–239]
Radiocarbon (14C) Dating	Uses atmospheric radiocarbon from nuclear bomb tests incorporated into DNA to retrospectively estimate the age of newly formed neurons.	- Background contamination from external carbon sources. - Limited spatial resolution; cannot measure neuron numbers. - Decline in radiocarbon levels with age complicates measurements in older individuals.	- Retrospective birth dating of neurons. - Estimating neurogenesis rates over a lifetime.	- Unique ability to date neurons over decades. - Requires no active incorporation of labels in living tissue.	- Refine contamination control methods. - Enhance spatial resolution to localize newly formed neurons. - Explore radiocarbon as a complementary method to track neurogenesis across life stages.	[20,240]
In Vitro Studies	Culturing hippocampal precursor cells derived from human tissues or induced pluripotent stem cells (iPSCs) to study neurogenesis mechanisms.	- Lack of physiological context due to the absence of *in vivo* microenvironment. - Potential cell culture artifacts affecting gene expression and differentiation. - Absence of synaptic connectivity limits functional insights.	- Mechanistic studies of NSC proliferation and differentiation. - Screening for neurogenic drugs.	- Direct control over experimental conditions. - Accessibility for genetic manipulation and drug testing.	- Develop organoid or co-culture systems to better replicate *in vivo* conditions. - Investigate synaptic interactions using advanced culture systems.	
Immunohistochemistry	Detects specific markers (e.g., DCX, PSA-NCAM) of immature neurons in brain tissue using antibodies, enabling visualization of neurogenesis in situ.	- Marker cross-reactivity with non-neurogenic cells. - Postmortem artifacts affecting antigen preservation. - Requires careful standardization of protocols to ensure reproducibility.	- Mapping spatial patterns of neurogenesis. - Correlating neurogenic activity with disease progression.	- High spatial resolution for neurogenic regions. - Visual identification of immature neurons.	- Develop highly specific markers to reduce cross-reactivity. - Standardize protocols for multi-center studies.	[241,242]
Single-Cell Transcriptomics	Analyzes gene expression at the single-cell level, providing detailed molecular insights into the developmental trajectory of individual neurons.	- High technical variability in sample prep and sequencing. - Requires advanced computational tools to interpret complex data. - Sample heterogeneity can obscure core signatures of adult hippocampal neurogenesis (AHN).	- Identifying neurogenic cell subtypes and their molecular signatures. - Elucidating pathways involved in neurogenesis.	- Provides molecular resolution for rare cell populations. - Identifies novel markers and pathways.	- Integrate single-cell transcriptomics with spatial transcriptomics to localize molecular changes. - Enhance computational pipelines for analyzing rare neurogenic cells in heterogeneous samples.	[243,244]

One of the primary challenges in studying AHN in humans is the absence of reliable, non-invasive *in vivo* assessment techniques. Animal studies benefit from genetic ablation and precursor cell culture models, but these approaches are not feasible in human research. Neuroimaging techniques, such as magnetic resonance imaging (MRI), lack the resolution required to detect newly generated dentate granule cells (DGCs) during neurogenesis. As a result, much of human AHN research relies on postmortem brain tissue and neural progenitor cell cultures derived from patient samples or induced pluripotent stem cells (iPSCs) [245–247]. However, postmortem studies have yielded inconsistent results due to variations in experimental protocols, such as differences in postmortem intervals, tissue preservation methods, and fixation techniques. For example, while Boldrini et al. observed stable expression of neurogenesis markers such as PSA-NCAM and DCX in human DG tissue across various ages [9], Sorrells et al. failed to detect similar markers in comparable age groups [4]. These discrepancies underscore the need for standardized methodologies to improve reproducibility and reliability in AHN research.

Recent advances in single-nucleus and single-cell transcriptomics have provided transformative opportunities to study AHN at the molecular level. These technologies enable the identification of gene expression profiles in immature DGCs, offering insights into age-related changes in neurogenesis [5,248]. Despite their promise, challenges such as sample preparation variability, sequencing depth, and computational pipeline differences complicate the interpretation of transcriptomic data, especially in studies involving aging and neurodegenerative diseases. Nonetheless, immunohistochemistry and single-nucleus transcriptomic analyses of postmortem human brain tissues have provided compelling evidence for ongoing AHN in adults and its disruption in AD [249,250]. These findings suggest that impaired neurogenesis may contribute to the pathogenesis of AD and emphasize the therapeutic potential of targeting AHN pathways to mitigate disease progression.

Understanding AHN in humans is crucial for advancing our knowledge of AD. Enhancing neurogenesis or preventing its decline may hold the key to slowing or even reversing some aspects of cognitive deterioration in AD patients. By focusing on AHN, researchers may uncover new molecular targets that could pave the way for innovative treatments aimed at preserving cognitive function in aging and neurodegenerative diseases like AD.

7. Comparative Mechanisms of Neurogenesis Decline in Normal Aging and Alzheimer's Disease: Implications for Cognitive Function and Pathophysiology

The decline in neurogenesis during normal aging contrasts sharply with the more rapid reduction seen in AD (Figure 4). In normal aging, hippocampal neurogenesis gradually decreases, leading to mild cognitive impairments such as slight memory difficulties and reduced learning efficiency [251,252]. Despite this, brain adaptive mechanisms, including functional plasticity and neural circuit reorganization, help compensate for these changes, allowing continued cognitive function. Although neurogenesis declines, the hippocampus retains sufficient structural integrity and neuroplasticity to support relatively high cognitive performance, with NSCs maintaining limited proliferative and differentiative capacity [16,253].

In AD, neurogenesis is impaired much more rapidly and severely, driven by Aβ accumulation, tau hyperphosphorylation, neuroinflammation, and vascular dysfunction. These pathological changes disrupt NSC proliferation, survival, and differentiation, leading to significant neurogenesis reduction and accelerated cognitive decline [17,126]. Cognitive impairments in AD, including severe memory loss, disorientation, language difficulties, and executive dysfunction, are irreversible and cannot be compensated by other cognitive processes, unlike in normal aging [254].

The mechanisms underlying neurogenesis decline differ between aging and AD. In aging, mitochondrial dysfunction, oxidative stress, reduced BDNF signaling, and cellular homeostasis alterations contribute to reduced neurogenic capacity, but do not cause catastrophic dysfunction. Some hippocampal plasticity remains to support mild cognitive function [255,256]. In contrast, AD involves additional pathological factors, such as Aβ plaques, tau tangles, oxidative stress, and disrupted calcium signaling, which further hinder neurogenesis [257]. Tau hyperphosphorylation destabilizes microtubules, impairing axonal transport and NSC migration, creating a toxic microenvironment in the hippocampus that accelerates neurodegeneration and cognitive decline [217].

Genetic factors, including mutations in APP, PS1, and APOE, exacerbate the decline in neurogenesis in AD [258]. These mutations predispose individuals to early depletion of NSCs, increasing amyloid-beta production and tau pathology, which accelerates cognitive decline in genetically predisposed individuals.

Vascular dysfunction and BBB disruption contribute to neurogenesis impairment in AD. A compromised BBB increases permeability, exposing neurogenic regions to peripheral immune cells, inflammatory mediators, and toxins,

which further damage NSCs and promote neurodegeneration [259]. Impaired vascular function also disrupts nutrient and oxygen delivery to the hippocampus, while pro-inflammatory cytokines and oxidative molecules worsen the toxic environment, further exacerbating cognitive decline [260].

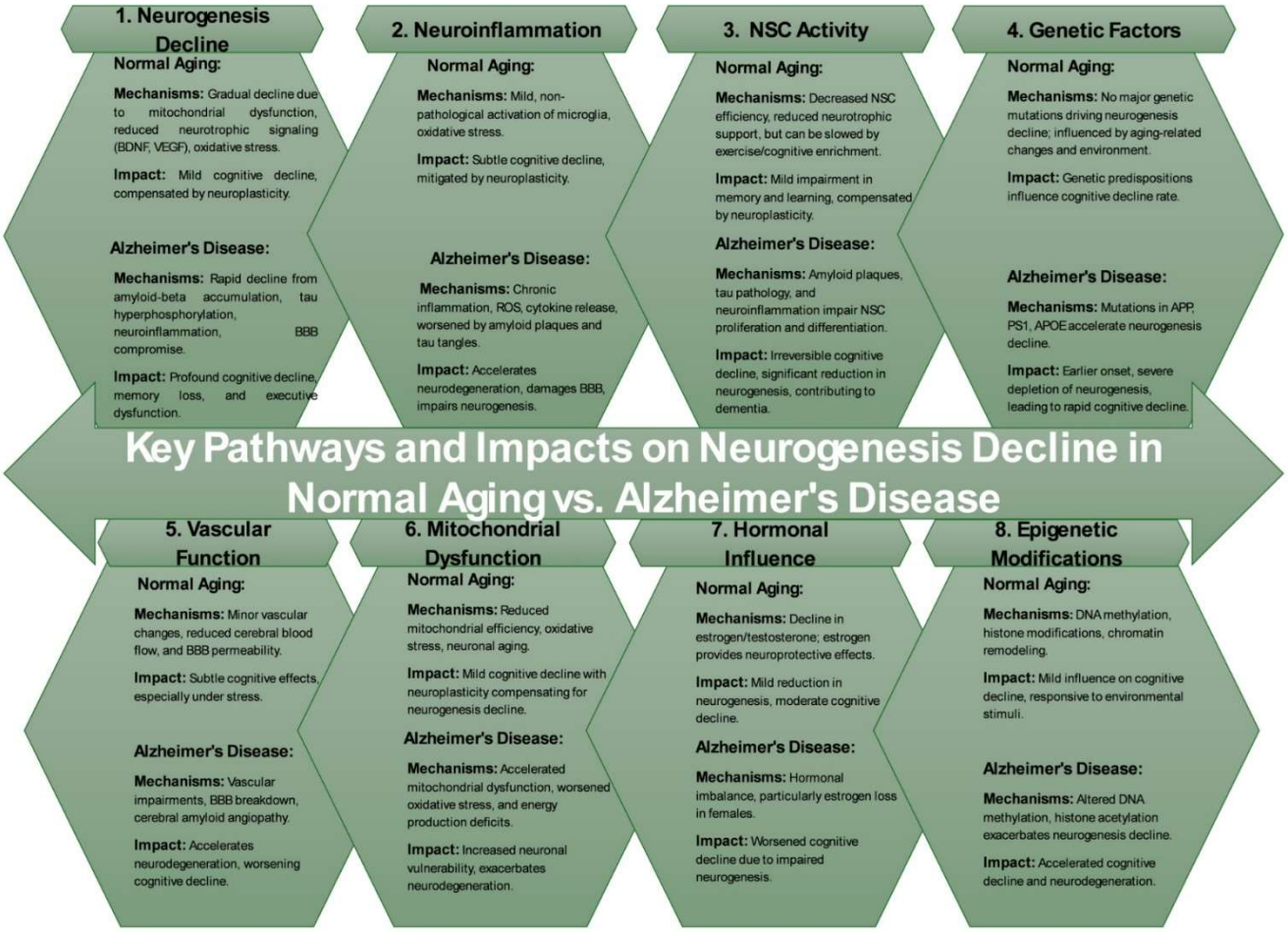

Figure 4. Key Pathways and Their Impact on Neurogenesis Decline in Normal Aging and Alzheimer's Disease.

8. Disruptions in Adult Hippocampal Neurogenesis as an Early Contributor to Alzheimer's Disease Pathology

AHN is critical for cognitive functions such as learning and memory, and its disruption is an early feature of AD [17,156]. Notably, impairments in AHN often precede hallmark Aβ plaques and tau tangles [88]. Animal models of AD, including 3XTg-AD, APP/PS1, and 5XFAD mice, consistently demonstrate deficits across various stages of AHN, including neural precursor proliferation, neuroblast differentiation, and dentate granule cell maturation (Table 6). These disruptions strongly correlate with cognitive impairments assessed through behavioral paradigms such as contextual fear conditioning and the Morris water maze [88,261].

Table 6. Comparison of AHN Deficits Across Alzheimer's Disease Models.

Model	Age of Onset of AHN Deficits	Key Pathological Features	Affected AHN Stage	Observed Cognitive Impairment	References
3XTg-AD	Postnatal day 5 and 1 month	Amyloid-beta (Aβ) plaques, tau tangles	Neural precursor cell proliferation, differentiation, and maturation	Impaired contextual fear conditioning, Morris water maze	[88,262]
J20	3 months	Aβ oligomers and plaques	Initial increase in precursor cell proliferation, followed by a decline	Decreased cognitive performance	[263,264]
5XFAD	6 weeks (early Aβ accumulation)	Aggressive Aβ deposition, tau pathology	DCX+ cell reduction, impaired neuron differentiation	Impaired memory retrieval, reduced dendritic spine density	[265,266]
PS1 Mutant	1-3 months	Familial AD mutations (presenilin-1)	Decreased BrdU incorporation in DG	Deficits in hippocampal pattern separation	[267,268]

Interestingly, some models exhibit an initial increase in hippocampal precursor proliferation or differentiation before an eventual decline. In the 3XTg-AD model, which carries mutations in amyloid precursor protein (APP) and tau, hippocampal proliferation is impaired as early as postnatal day 5 and at one month—before Aβ and tau pathology emerge. $Sox2^+$ and DCX^+ reductions at these early stages suggest neurogenic deficits precede amyloid deposition [92,125,169]. Similarly, hippocampal proliferation is disrupted three months before Aβ pathology appears.

In contrast, the J20 mouse model, which harbors APP mutations, initially shows increased hippocampal precursor proliferation at three months, as indicated by enhanced BrdU incorporation and elevated Ki67, NeuN, and PSA-NCAM expression in the SGZ (Table 6) [93,269]. This early neurogenic boost occurs prior to Aβ oligomer and plaque formation at two and seven months, respectively. However, by five months, proliferation markers decline, suggesting transient compensatory mechanisms that ultimately fail as the disease progresses [270,271].

The 5XFAD model, which exhibits aggressive Aβ deposition and tau pathology, further highlights the impact of AD on AHN (Table 6) [272–274]. Intraneuronal Aβ accumulation in the SGZ appears as early as six weeks, preceding extracellular plaque formation at 16 weeks. Despite intact precursor cell proliferation ($PCNA^+$ and $Sox2^+$ markers remain unchanged), DCX^+ neuroblasts are significantly reduced, indicating impaired neuronal differentiation [275–277]. Consequently, immature DGC numbers and dendritic spine density decrease, leading to memory retrieval deficits.

The presenilin-1 (PS1) mutant model of familial AD also demonstrates hippocampal pattern separation deficits alongside reduced BrdU incorporation in the DG, supporting the role of AHN disruptions in AD pathology (Table 6) [268,278].

AHN Alterations in Human AD

Post-mortem studies corroborate these findings, revealing significant reductions in DCX^+ neurons in the DG, particularly in $calbindin^+$ DCX^+ cells at Braak stage IV and beyond, suggesting compromised DGC maturation and survival [7,279,280]. Interestingly, the percentage of DCX^+ neurons expressing calretinin remains unchanged, implying early neurogenesis stages may be less affected. A positive correlation between cognitive performance and DCX^+ $PCNA^+$ cell numbers in hippocampal tissue further links AHN deficits to cognitive decline [88,279,281].

Single-nucleus RNA sequencing of post-mortem hippocampal tissue reveals a substantial reduction in immature DGCs, constituting only approximately 1% of the total DGC population in AD patients, compared to about 3.5% in healthy controls [5,282]. Additional studies highlight decreased $calretinin^+$ $Prox1^+$ and $calretinin^+$ DCX^+ DGCs, alongside an increase in $Nestin^+$ cells, indicating heightened astrogliogenesis [5,283,284]. These changes correspond with deficits in spatial memory and pattern separation, reinforcing the role of AHN dysfunction in AD-related cognitive decline.

Immature DGCs, characterized by enhanced plasticity, are particularly vulnerable to calcium dysregulation and excitotoxicity in AD [285,286]. Their functional impairment—whether through reduced numbers or compromised integration—disrupts AHN-dependent cognitive processes such as pattern separation [97,287,288]. Additionally, post-mitotic DGCs may undergo de-maturation and re-enter the cell cycle, potentially adopting a senescence-like phenotype that exacerbates AD pathology [289,290]. Investigating senescence markers in the DG neurogenic niche and exploring ion transporters like NKCC1 and KCC2, which regulate GABAergic signaling during DGC maturation, may provide further insights into AHN dysfunction in AD.

9. Strategies for Enhancing Neurogenesis in Alzheimer's Disease: A Multifaceted Approach to Mitigating Cognitive Decline

Neurogenesis in the SVZ and hippocampus plays a critical role in maintaining cognitive function, particularly in aging populations such as those affected by AD. Strategies aimed at enhancing neurogenesis in these regions have shown promising potential in mitigating cognitive decline and improving disease outcomes. However, challenges remain in translating these approaches into clinically effective therapies. Among the various strategies, antipsychotics have garnered attention for their ability to stimulate neurogenesis in the SVZ. These medications, commonly prescribed for psychiatric disorders, have been observed to promote neural stem cell proliferation and enhance brain repair mechanisms (Table 7) [291–293]. Despite these promising effects, the translation of antipsychotic use into AD therapy is hindered by a lack of clarity regarding their mechanisms of action and insufficient evidence regarding their long-term effects. As a result, their impact remains moderate, with additional research needed to understand their therapeutic potential for AD patients fully.

Table 7. Strategies for Enhancing SVZ and Hippocampal Neurogenesis in Alzheimer's Disease: Mechanisms, Challenges, and Potential Impact.

Approach	Mechanism	Challenges	Potential Impact	Targeted Brain Region	References
Antipsychotics	Stimulate neurogenesis in SVZ	Limited translational insights; need for mechanism clarification	Moderate—may enhance neurogenesis but requires more validation	SVZ (Subventricular Zone)	[294,295]
Allopregnanolone	Modulates GABA type A receptors	Long-term efficacy and safety; understanding of optimal dosing	High—potentially restores GABAergic balance and enhances neurogenesis	SVZ, Hippocampus	[296,297]
Sovateltide (IRL-1620)	Enhances neurotrophic factor expression (VEGF, NGF)	Mechanism validation; assessment of broad applicability for AD	High—could stimulate neurogenesis and improve cognitive function	SVZ, Hippocampus, Cortex	[298,299]
NNI-362	Activates p70S6 kinase, promoting neurogenesis	Unexplored SVZ-specific effects; optimization for clinical use	Moderate—could promote neurogenesis but needs further development	SVZ, Hippocampus	[300,301]
Environmental Enrichment	Improves SGZ neurogenesis and cognitive function	Limited data on direct SVZ impact; variability in EE models	Moderate—promotes neurogenesis but varies by model and population	SGZ (Subgranular Zone), Hippocampus	[93,302,303]
Polyphenol-Rich Diet	Promotes neurogenesis, reduces cognitive deficits	Scalability to human trials; long-term effects in AD populations	Moderate—may reduce inflammation and promote neurogenesis	SVZ, Hippocampus, Cortex	[304–306]
Non-Invasive Stimulation	Enhances SVZ/SGZ neurogenesis in animal models	Validation in AD-specific neurogenesis; optimal stimulation protocols	Moderate—needs human-specific data and protocol standardization	SVZ, SGZ, Hippocampus	[14,307,308]
Growth Factor Supplementation	Enhances mitogenic factors (EGF, FGF-2) to restore NSC proliferation	Replenishing factors in aged brain; ensuring target specificity	High—could potentially restore neurogenic niches in aged brains	SVZ, Hippocampus	[309–311]
Anti-Inflammatory Interventions	Reduces inflammation and mitigates effects of pro-aging cytokines (IL-6, TNF-α)	Balancing inflammatory response and NSC activity; potential side effects	High—reducing neuroinflammation may sustain NSC activity in AD	SVZ, Hippocampus	[312–316]
Gene Therapy and Signaling Modulation	Reactivates critical pathways (Shh-Gli1) and modulates epigenetic regulators (HDAC inhibitors)	Translating gene therapies to human trials; delivery and targeting mechanisms	High—reactivating key pathways may reverse age-related neurogenic decline	SVZ, Hippocampus, Cortex	[12,117,317]
Metabolic and Lifestyle Modifications	Promotes neurogenesis via caloric restriction and exercise, increases BDNF	Sustainability of lifestyle changes in aging populations; individual variability	Moderate—may enhance neurogenesis with long-term lifestyle commitment	SVZ, Hippocampus, Cortex	[19,318,319]

Allopregnanolone, a neurosteroid known for its ability to modulate GABA type A receptors, represents another promising avenue for enhancing neurogenesis in both the SVZ and hippocampus (Table 7) (Figure 5) [320,321]. This compound has demonstrated the potential to restore the GABAergic balance, a key factor in supporting cognitive health and neuronal function [322]. By improving neurogenesis in the hippocampus and SVZ, allopregnanolone may help reverse some of the neurogenic deficits associated with AD [323]. However, challenges remain in establishing its long-term safety and efficacy, particularly regarding optimal dosing strategies. If these challenges are overcome, allopregnanolone could play a significant role in ameliorating cognitive decline in AD patients by promoting neurogenesis in critical brain regions involved in learning and memory.

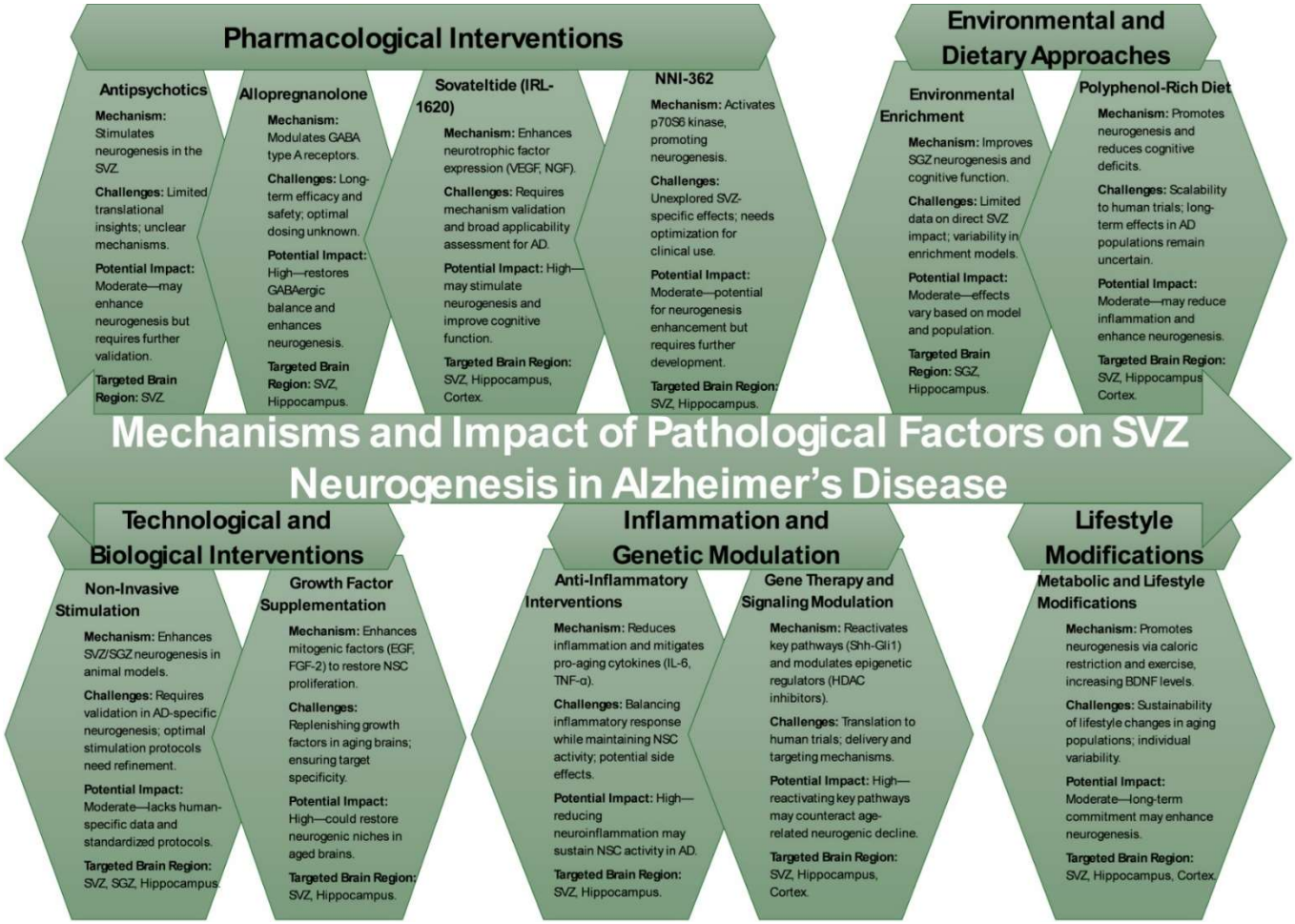

Figure 5. Strategies for Enhancing SVZ and Hippocampal Neurogenesis in Alzheimer's Disease—Mechanisms, Challenges, and Potential Impact.

Sovateltide, an endothelin B receptor agonist, offers another promising approach for stimulating neurogenesis in AD (Table 7) (Figure 5) [324]. Sovateltide works by enhancing the expression of neurotrophic factors such as vascular endothelial growth factor (VEGF) and nerve growth factor (NGF), both of which support neuronal survival and promote neurogenesis [325,326]. This strategy holds high potential, not only for stimulating neurogenesis in the SVZ and hippocampus but also for improving cognitive function in AD patients. However, further studies are required to validate the underlying mechanisms and explore the broader applicability of sovateltide as a therapeutic option for AD. Its ability to target neurogenic processes that are compromised in AD provides a potential pathway for improving outcomes and expanding treatment options for individuals with the disease.

In addition to pharmacological interventions, non-pharmacological approaches such as environmental enrichment have shown promise for enhancing neurogenesis in AD [327] (Table 7) (Figure 5). Environmental enrichment, which involves exposing animals to stimulating environments that promote physical and mental activity, has been shown to improve neurogenesis in the SGZ of the hippocampus [303,328]. Although the direct effects of Environmental enrichment on SVZ neurogenesis remain less understood, it has demonstrated the ability to enhance brain plasticity and cognitive function in AD animal models [327]. One challenge with this approach is the variability in effectiveness across different models and populations, which complicates its translation into human therapies. Nevertheless,

Environmental enrichment remains a moderately effective and non-invasive strategy for promoting neurogenesis and cognitive function in AD patients, offering an accessible therapeutic option.

Dietary interventions, particularly those rich in polyphenols, emerge as potential strategies for promoting neurogenesis and reducing cognitive deficits in AD (Table 7) (Figure 5) [305,306]. Diets high in polyphenols, such as those rich in omega-3 fatty acids and flavonoids, have been shown to enhance neurogenesis in the SVZ and hippocampus while also reducing inflammation, a key contributor to AD progression [329,330]. Despite challenges in scaling these dietary interventions for human clinical trials, particularly in terms of assessing long-term effects, they hold considerable potential for broad implementation as part of preventive or adjunctive treatment for AD. The moderate impact of polyphenol-rich diets on neurogenesis and cognitive function, combined with their ability to address inflammation, makes them an attractive option for AD management [304], especially when used in conjunction with other therapeutic strategies.

Collectively, these diverse therapeutic strategies provide a multifaceted approach to enhancing neurogenesis in Alzheimer's disease (AD) and mitigating cognitive decline. By targeting multiple pathways involved in neurogenesis and cognitive function, these interventions offer a promising avenue for therapeutic development. While challenges remain in optimizing their efficacy and translating them into clinical practice, these strategies hold significant potential to restore cognitive function, promote healthier brain aging, and improve outcomes for individuals living with AD.

Advancements and Challenges in Stem Cell Therapy for Alzheimer's Disease: From Initial Promise to Future Hope

Stem cell therapy initially generated significant optimism as a potential treatment for AD and other neurodegenerative disorders, driven by the promise of regenerating damaged brain tissue and promoting neural repair. Stem cells, with their ability to differentiate into various cell types, including neurons, were considered promising for restoring lost functions in neurodegeneration-affected regions [331]. Preclinical studies demonstrated their potential to replace dead neurons, enhance synaptic plasticity, and reduce inflammation—key features of AD pathology [266]. These promising results raised hopes that stem cell-based therapies could reverse cognitive deficits and slow disease progression by replenishing critical brain regions like the hippocampus and SVZ. The advent of induced pluripotent stem cells (iPSCs) further fueled optimism, offering personalized treatment possibilities by using patient-specific cells for transplantation [332].

Despite the early promise, the clinical translation of stem cell therapies for AD has encountered significant challenges, leading to numerous trial failures. One key issue is the difficulty of ensuring that transplanted stem cells integrate effectively into the brain, differentiate into the desired neuronal types, and establish functional connections with existing neural circuits. In many cases, the transplanted cells fail to survive or are rejected by the immune system, limiting the long-term benefits [333,334]. Even when cells integrate, their contribution to cognitive restoration is often limited, potentially due to the complexity of the brain's cellular environment and the advanced stage of neurodegeneration in AD patients. Additionally, concerns about tumorigenesis, immune rejection, and the ethical implications of stem cell-based therapies have compounded these challenges. A lack of standardized protocols and inconsistent study results have further hindered the progress of stem cell-based treatments for AD, preventing them from becoming a viable therapeutic option despite their initial potential.

However, recent advances in stem cell technology offer renewed hope for treating AD and other neurodegenerative diseases. iPSCs have revolutionized personalized medicine by enabling the creation of patient-specific stem cells, minimizing immune rejection risks and facilitating more tailored therapies. iPSCs can be differentiated into various neuronal subtypes, providing invaluable models to study neurodegenerative diseases in vitro and offering insights into disease mechanisms and potential therapeutic targets [335,336]. Advances in optimizing iPSC-derived neural networks are yielding more robust models for studying AD and testing treatments. Furthermore, the development of brain organoids—three-dimensional, miniaturized brain models derived from iPSCs—has provided a powerful tool to replicate human brain structure and function better. These organoids offer a more accurate representation of disease mechanisms and have the potential to simulate complex brain interactions, providing a platform for testing regenerative therapies [337,338]. As these technologies continue to evolve, they hold promises for overcoming previous obstacles, paving the way for more effective, targeted therapies for AD and other neurodegenerative diseases in the near future.

10. Concluding Remarks

NSCs are essential for brain development and the maintenance of cognitive flexibility throughout life. However, the age-related decline in neurogenesis, driven by diminished growth factor availability, increased inflammation, and

intrinsic cellular changes, poses a significant challenge to cognitive health. In neurodegenerative diseases such as AD, these issues are further exacerbated by mitochondrial dysfunction, calcium dysregulation, oxidative stress, and genetic predispositions, such as the presence of ApoE4. Additionally, impairments in synaptic plasticity, BBB integrity, and transcriptional regulation contribute to the cognitive deficits observed in AD.

Research into the developmental origins and regulatory mechanisms of NSCs has highlighted potential therapeutic approaches to mitigate the decline in neurogenesis and its associated cognitive impairments. Gene therapy, anti-inflammatory agents, and metabolic interventions represent promising strategies to enhance adult hippocampal neurogenesis (AHN) and SVZ neurogenesis. Targeting these pathways may offer innovative solutions to address cognitive decline associated with aging and AD.

However, therapeutic strategies face several challenges. While pharmacological agents, neurotrophic factors, and systemic approaches targeting the gut microbiome and BBB integrity hold promise, their translation into clinical practice requires refinement. Current limitations include an incomplete understanding of the molecular pathways involved, variability in preclinical models, and the lack of robust biomarkers to monitor neurogenesis in humans. These challenges necessitate further research to optimize interventions for safety, efficacy, and long-term outcomes.

In AD, neurogenesis is disrupted at multiple stages, including the proliferation, differentiation, and maturation of neural precursor cells and dentate granule cells. These disruptions, driven by amyloid-beta deposition, tau hyperphosphorylation, chronic inflammation, and metabolic dysregulation, hinder the brain's regenerative capacity. A comprehensive mechanistic understanding of how these pathways interact remains incomplete. Contradictions in findings, especially across different disease models and stages of the disease, underscore the complexity of this relationship. Standardized approaches and improved disease models that capture the multifactorial nature of AD are crucial to bridging these gaps.

Furthermore, longitudinal studies are needed to clarify the sequence of neurogenesis impairments relative to amyloid and tau pathology. Such investigations would provide critical insights into whether early interventions targeting neurogenesis could slow or reverse cognitive decline in AD.

Advancing therapeutic strategies will require a multidisciplinary approach that integrates pharmacological, lifestyle, and regenerative medicine interventions. For instance, combining NSC transplantation with systemic anti-inflammatory therapies or metabolic modulation may enhance the efficacy of treatments. Similarly, lifestyle modifications such as exercise and dietary interventions, which influence systemic inflammation and neurogenesis, should be explored as complementary strategies.

A major limitation in current research is the difficulty of studying neurogenesis in humans due to technical constraints. However, advancements in transcriptomic techniques and postmortem tissue analyses provide robust evidence for AHN in adults and suggest its impairment in neurodegenerative diseases. Future research should prioritize the development of non-invasive imaging biomarkers to monitor neurogenesis and track therapeutic outcomes in real-time.

Understanding the cellular and environmental factors that regulate neurogenesis offers a promising avenue for developing therapeutic strategies for AD and other neurodegenerative diseases. While significant progress has been made, there is still a need for deeper mechanistic insights and more effective interventions. By addressing these challenges, future research can unlock innovative approaches to preserve cognitive function, improve quality of life, and advance efforts to combat neurodegeneration. The integration of pharmacological, lifestyle, and regenerative approaches has the potential to transform neurogenesis-targeted therapies from experimental strategies into clinical realities.

Author Contributions

M.M.N. contributed to the design and writing of the main manuscript text. This manuscript is a comprehensive review article, and no AI was utilized in its research, writing, or preparation.

Ethics Statement

Not applicable.

Informed Consent Statement

Not applicable.

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