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The Silent Erosion: Neural Stem Cell Decline and the Fading Memory - A Commentary

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Abstract

Cognitive decline poses a major health concern, especially for older adults, as many do not notice the initial warning signs, which can result in decreased quality of life and increased financial strain on society. Neural stem cells (NSCs) play a crucial role in sustaining proper brain function by aiding in the production of new brain cells, enhancing neural connections, and providing the brain with the ability to withstand damage. The aging process hinders the functionality of the NSCs, leading to diminished neurogenesis and a decline in cognitive abilities. Factors such as DNA damage, changes in the epigenome, mitochondrial dysfunction, and the onset of cellular senescence contribute to this decline. Cognitive issues, especially in neurodegenerative conditions, are worsened by neuroinflammation and the inadequate elimination of waste products in the brain. This article investigates the function of NSCs in preserving cognitive abilities and examines how their reduction with age contributes to cognitive deterioration. The statement emphasizes the promise of stem cell therapies, small compounds that encourage the growth of brain cells, and lifestyle modifications to address age-related cognitive decline. The article supports the idea of launching a public health initiative that prioritizes early actions to promote neurogenesis, mitigate neuroinflammation, and improve waste clearance, which could greatly enhance cognitive abilities and overall well-being for elderly individuals. By leveraging these strategies, we can address both personal and societal challenges associated with cognitive decline.

Keywords: Vascular Endothelial Growth Factor (VEGF); Neural Progenitor Cells (NPCs)

Abbreviations

NSCs: Neural Stem Cells; NDs: Neurodegenerative Diseases; BDNF: Brain-Derived Neurotrophic Factor; Vascular Endothelial Growth Factor (VEGF); FGF: Fibroblast Growth Factor; NPCs: Neural Progenitor Cells; SVZ: Subventricular Zone; AD: Alzheimer's disease; Mitochondrial dysfunction (MD); SASPs: Senescence-Associated Secretory Phenotypes.

Introduction

Cognitive decline continues to be a critical issue linked to aging, affecting not just individuals with dementia but also the broader senior demographic [1-3]. Specialists anticipate that that by 2050, dementia will affect 152 million individuals globally, yet initial indications of cognitive decline are frequently disregarded [4,5]. Even in its early

phases, cognitive decline significantly impact people's autonomy, everyday tasks, and general wellbeing. Its effect reach further than individuals, putting pressure on public health systems, reducing workplace efficiency, and adding significant economic costs [6,7]. Without effective measures, early cognitive decline may escalate into more serious conditions such as dementia, adding strain to healthcare systems burdening healthcare systems and elevating societal costs. Consequently, prompt identification and action are critical for reducing these lasting public health and financial impacts.

Neural stem cells (NSCs) play a crucial role in preserving cognitive functions over a lifetime by facilitating neurogenesis-the ongoing production of new neurons [8-10]. This capacity to create new neurons enables the brain to adapt to novel experiences, acquire new knowledge, and establish memories [11,12]. NSCs function as a source for repplacing damaged or lost neurons and also preserve the structural and functional integrity of neural circuits, aiding in the fight against age-associated cognitive decline and neurodegenerative diseases (NDs) [13-15]. A fundamental aspect of this process is synaptic plasticity, which describes the ability of synapses to flexibly strengthen or diminish based on experiences, an essential mechanism for learning, memory consolidation, and preserving cognitive flexibility [16-18]. Moreover, NSCs secrete a range of trophic factors-such as brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF), and fibroblast growth factor (FGF)-that promote neuron survival, encourage neurogenesis, and aid in tissue repair, thus creating a neuroprotective microenvironment that supports enduring cognitive health [19-21].

In this commentary, we analyze the importance of NSCs in preserving cognitive abilities and their capability to reduce age-related deterioration. We explore how NSC-mediated neurogenesis, synaptic plasticity, and neuroprotection strengthen brain resilience and how these processes are influenced by aging. By accentuating the healing potential of NSCs, we underscore their ability to serve as targets for approaches designed to maintain cognitive abilities in aging populations while also tackling the broader societal and economic issues created by cognitive decline.

Neural Stem Cells (NSCs): Key Regulators of Brain Development and Function

NSCs are essential for the brain's development and operation, playing a vital role in forming and maturing the cerebral cortex [22,23]. In the early stages of brain development, NSCs are located in the ventricular zone next to the lateral ventricle, where they produce neural progenitor cells (NPCs) [24,25]. These NPCs develop into new neurons, which then travel from the ventricular surface to construct the cortical plate, a structure that will ultimately arrange into the functional layers of the adult brain [26,27]. Later-generated neurons migrate through the deeper cortical layers and settle in the upper layers near the pial surface [28,29]. This migration helps develop brain regions for sensory processing, cognition, and motor control, organizing cortical circuits that are vital for higher brain functions [30,31].

NSCs persist in the adult brain, particularly in regions like the hippocampus, where they generate new neurons throughout life [32,33]. Adult neurogenesis plays a critical role in synaptic plasticity and cognitive function [34,35]. While animal studies have firmly established this phenomenon, scientists are still exploring its extent and significance in the human brain, particularly concerning aging and neurological disorders [36,37]. In regions like the dentate gyrus (DG) of the hippocampus and the subventricular zone (SVZ) near the lateral ventricles, new neurons join existing networks, helping with memory and cognitive flexibility [38,39]. Although scientists are still gathering definitive evidence of ongoing neurogenesis in humans, studies suggest it persists in certain regions, even in older individuals and those with Alzheimer's disease (AD) [40,41]. The ability of adult neurogenesis to support cognitive health and potentially slow age-related cognitive decline highlights its therapeutic potential [42-44]. However, further studies are needed to fully understand its mechanisms and refine methods to harness it for clinical applications.

Aging and the Decline of Neural Stem Cells

Stem cells are uniquely defined by their remarkable ability for both self-renewal and the generation of specialized cell types. This division can happen in two ways: symmetrically, resulting in two daughter stem cells, or asymmetrically, yielding one stem cell and one specialized cell type. The latter process is essential for sustaining or increasing the stem cell population through self-renewal. These unique qualities make stem cells crucial during embryonic development, where they assist in forming tissues, and throughout adulthood, where they play an important role in maintaining tissue balance, repair, and regeneration [45-47].

A growing collection of evidence indicates that the decline in adult neurogenesis associated with aging significantly impacts cognitive abilities [41-43,48]. While various factors may influence the reduction of mature neurons incorporated into brain networks over time, the predominant evidence suggests that aging mainly affects the growth of NSCs [49,50]. Nevertheless, the exact mechanisms underlying this decline remain not fully understood. Proposed

contributing factors include NSC quiescence, cellular senescence, elongation of the cell cycle, or loss due to cell death or a change in cell fate [51-53]. The existing research is characterized by inconsistent findings and uncertainties regarding which of these mechanisms primarily drive the decrease in NSC proliferation as individuals age. To improve our comprehension in this developing field, it is essential to thoroughly investigate these differences.

In particular, the elements influencing NSC proliferation could greatly influence the reduction of neurogenesis linked to aging. Aging-related changes may disrupt the balance between symmetric and asymmetric divisions in NSCs [54,55]. For example, a rise in symmetric divisions, in which two differentiated cells are produced, could deplete the NSC pool and diminish the count of functional stem cells accessible for neurogenesis [56,57]. This disruption could especially affect regions like the hippocampus, which is crucial for learning and memory [58,59]. By investigating the impact of alterations in division patterns on NSC proliferation as we age, we can enhance our understanding of the essential mechanisms and uncover possible therapeutic strategies focused on preserving neurogenic capacity and mitigating cognitive decline related to aging.

Various fundamental hallmarks of aging result in cellular and tissue malfunction over time, facilitating the examination of the decrease in NSC function as people grow older [60-62]. A significant hallmark, genomic instability, is vital for comprehending the aging process of NSCs [63,64]. Studies have shown that DNA damage gradually builds up in NSCs over time, frequently due to oxidative stress and factors [65,66]. For instance, aging NSCs gather DNA damage, which impairs their self-renewal capabilities and diminishes their neurogenesis potential, especially in the hippocampus, an area essential for learning and memory. The build-up of DNA damage diminishes neurogenesis and is strongly associated with the cognitive deficits seen in older individuals [67,68]. Moreover, telomere shortening, a further hallmark of aging, also impacts NSCs [69,70]. The shortening of telomere length in NSCs limits their proliferation potential and shorten their lifespan, leading them to enter senescence or experience cell death, thereby decreasing the stem cell reservoir and hindering regenerative capabilities [71,72].

Epigenetic alterations also contribute to the aging of NSCs. Research indicates that aging leads to significant changes in DNA methylation patterns, alterations in histones, and chromatin remodeling in NSCs [73,74]. These epigenetic alterations can hinder the expression of essential required for NSC upkeep, such as those governing the cell cycle and differentiation, rendering NSCs less reactive to external cues. Furthermore, the dysruption in proteostasis, a significant hallmark of aging, plays a role in the impairment of NSCs. As proteostasis deteriorates with age, misfolded proteins accumulate in NSCs, resulting in cellular stress that impairs their function and neurogenesis. The failure to ensure proper protein folding and sustain quality control processes further reduces the regenerative capacity of NSCs [75-77].

Mitochondrial dysfunction (MD) significantly contributes to the aging process of neural stem cells (NSCs) [78-80]. As we age, the efficiency of mitochondria diminishes, leading to a reduction in energy output that negatively impacts the growth and differentiation of NSCs. Increased oxidative stress damages mitochondria and disrupts the NSC cell cycle, reducing their ability to generate new neurons. Cellular senescence plays a considerable role in the decline of NSC function as we age. Aging NSCs, along with nearby niche cells, release pro-inflammatory cytokines and various factors that have a detrimental effect on the activity of adjacent healthy NSCs. These senescence-associated secretory phenotypes (SASPs) obstruct neurogenesis and tissue regeneration, contributing to cognitive decline associated with aging [81-83].

Ultimately, alterations in intercellular communication, which is a characteristic of aging, may influence NSC function [84]. The process of aging creates a pro-inflammatory environment that interferes with the interactions between NSCs and the supportive niche cells [85,86]. This increase in inflammation reduces the accessibility of essential growth factors, which may hinder the proliferation and differentiation of NSCs.

The findings collectively underscore the significance of aging-related traits in the dysfunction of neural stem cells (NSCs). The build-up of DNA damage, shortening of telomeres, modifications in epigenetics, disruptions in proteostasis, mitochondrial dysfunction, cellular senescence, and changes in intercellular communication all play a role in the reduction of neurogenesis as individuals age. Gaining a deeper understanding of these mechanisms paves the way for developing therapeutic strategies aimed at rejuvenating NSCs and maintaining cognitive function in older adults.

Memory and Neurogenesis: The Fragile Connection in the Aging Brain

The connection between memory and neurogenesis is essential yet delicate, particularly because the aging process diminishes neurogenesis in the hippocampus, a key area for memory development [40,41]. For memory and learning to function properly, new neurons must incorporate into the existing neural networks. Nevertheless, as one ages, the rate of neurogenesis decreases, resulting in difficulties with memory tasks such as spatial memory and pattern separation [87]. This drop is notably more pronounced in neurodegenerative diseases (NDs) like Alzheimer's, where disrupted neurogenesis accelerates memory deterioration.

In addition to the decline in neurogenesis, inflammation in the brain significantly contributes to memory deterioration associated with aging. As people get older, there is a rise in persistent, low-grade inflammation in the brain, commonly known as "neuroinflammation" [88,89]. Activated microglia, the immune cells of the brain, cause this type of inflammation and can produce pro-inflammatory cytokines over time. These cytokines interfere with neuronal function and impair the brain's capacity to facilitate neurogenesis [90-92]. Specifically, neuroinflammation disrupts the conditions essential for NSCs to multiply and differentiate, further restricting the formation of new neurons. This establishes a harmful feedback loop where neuroinflammation not only hinders neurogenesis but also leads to cognitive decline [93-95].

Additionally, the process of waste removal during sleep, mainly through the glymphatic system, is crucial for reducing both inflammation and neurodegeneration [96,97]. While we sleep, the glymphatic system aids in the elimination of harmful metabolites, such as β-amyloid, which can build up and intensify neuroinflammation. This waste removal mechanism is vital for NSC health and function, as it clears away debris that could trigger inflammation and cause harm. When aging or inadequate sleep disrupts this process, toxins build up, worsening neuroinflammation. This, in turn, further hinders neurogenesis and memory function [98,99].

Consequently, a variety of factors—decreased neurogenesis, heightened neuroinflammation, and compromised waste removal—plays a role in the age-related deterioration of memory. Prioritizing a healthy sleep pattern to facilitate effective waste clearance, along with controlling inflammation through lifestyle choices (such as diet and physical activity), are crucial approaches to maintain cognitive abilities [100,101]. By fostering conditions that encourage NSC growth and minimizing inflammation, it may be feasible to lessen the impact of aging on memory and neurogenesis, ultimately aiding brain health throughout one's life.

Public Health Approach to Age-Related Memory Decline

A comprehensive public health strategy to address age-related cognitive decline integrates stem cell therapy, small molecule treatments, and lifestyle changes. Stem cell therapy holds promise for regenerating NSCs and encouraging the process of neurogenesis, which could potentially reverse cognitive decline by reinstating lost neurons. Small molecules that target neurogenesis, inflammation, and waste management—such as those that boost BDNF or assist the glymphatic system—can play a role in safeguarding brain health. Lifestyle elements, including regular physical activity, a diet abundant in antioxidants, mental engagement, and adequate sleep, are crucial for sustaining cognitive function by promoting neurogenesis, reducing oxidative stress, and enhancing memory. Together, these strategies can offer a holistic approach to preventing and alleviating cognitive decline, with public health initiatives focusing on early intervention and prevention to improve the quality of life for seniors.

Conclusion

Cognitive decline associated with aging presents a significant challenge for both individuals and worldwide public health systems. As neurogenesis, particularly in the hippocampus, declines with age, the brain becomes increasingly prone to memory issues and reduced cognitive flexibility. Elements like neuroinflammation, mitochondrial impairment, and cellular aging exacerbate this deterioration, highlighting the need for specific treatments. The potential of NSC therapy, along with small molecules that boost neurogenesis and lifestyle changes, presents a complete approach to mitigate these impacts. Promoting healthy aging via early actions aimed at maintaining neurogenesis, reducing inflammation, and enhancing waste clearance may significantly improve cognitive results [102-104]. As progress in these areas persists, adopting a public health strategy that includes these treatment techniques could not only decelerate cognitive decline associated with aging but also rejuvenate brain health, resulting in enhanced quality of life for elderly populations worldwide [105,106].

References

1. Langa KM (2018) Cognitive Aging, Dementia, and the Future of an Aging Population. In: Majmundar MK, et al. (Eds.), National Academies of Sciences, Engineering, and Medicine; Division of Behavioral and Social Sciences and Education; Committee on Population. Future Directions for the Demography of Aging: Proceedings of a Workshop.

2. Brito DVC, Esteves F, Rajado AT, Silva N, Nobrega C (2023) Assessing cognitive decline in the aging brain: lessons from rodent and human studies. NPJ Aging 9(1): 23.

3. Murman DL (2015) The Impact of Age on Cognition. Semin Hear 36(3): 111-121.

4. GBD 2019 Dementia Forecasting Collaborators. (2022) Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. Lancet Public Health 7(2): e105-e125.

5. Shin JH (2022) Dementia Epidemiology Fact Sheet 2022. Ann Rehabil Med 46(2): 53-59.

6. Tahami AA, Byrnes MJ, White LA, Zhang Q (2022) The

Humanistic and Economic Burden of Alzheimer's Disease. Neurol Ther 11(2): 525-551.

7. Tahami AA, Khachatryan A, Hummel N, Kopiec A, Martinez M, et al. (2024) Assessing Quality of Life, Economic Burden, and Independence Across the Alzheimer's Disease Continuum Using Patient-Caregiver Dyad Surveys. J Alzheimers Dis 99(1): 191-206.

8. Chang J, Li Y, Shan X, Chen X, Yan X, et al. (2024) Neural stem cells promote neuroplasticity: a promising therapeutic strategy for the treatment of Alzheimer's disease. Neural Regen Res 19(3): 619-628.

9. Zanirati G, Shetty PA, Shetty AK (2023) Neural stem cells persist to generate new neurons in the hippocampus of adult and aged human brain - Fiction or accurate? Ageing Res Rev 92: 102133.

10. Yang L, Liu SC, Liu YY, Zhu FQ, Xiong MJ, et al. (2024) Therapeutic role of neural stem cells in neurological diseases. Front Bioeng Biotechnol 12: 1329712.

11. Marzola P, Melzer T, Pavesi E, Mohapel J, Brocardo PS (2023) Exploring the Role of Neuroplasticity in Development, Aging and Neurodegeneration. Brain Sci 13(12): 1610.

12. Puderbaugh M, Emmady PD (2025) Neuroplasticity. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing.

13. Jimenez P, Urbach A (2023) From Youthful Vigor to Aging Decline: Unravelling the Intrinsic and Extrinsic Determinants of Hippocampal Neural Stem Cell Aging. Cells. 12(16): 2086.

14. Kesidou E, Theotokis P, Damianidou O, Boziki M, Konstantinidou N, et al. (2023) CNS Ageing in Health and Neurodegenerative Disorders. J Clin Med 12(6): 2255.

15. Navarro P, Yeo RW, Brunet A (2020) Aging and Rejuvenation of Neural Stem Cells and Their Niches. Cell Stem Cell 27(2): 202-223.

16. Kennedy MB (2013) Synaptic Signaling in Learning and Memory. Cold Spring Harb Perspect Biol 8(2): a016824.

17. Scott DN, Frank MJ (2023) Adaptive control of synaptic plasticity integrates micro-and macroscopic network function. Neuropsychopharmacology 48(1): 121-144.

18. Pozo K, Goda Y (2010) Unraveling mechanisms of homeostatic synaptic plasticity. Neuron 66(3): 337-351.

19. Kaminska A, Radoszkiewicz K, Rybkowska P, Wedzinska A, Sarnowska A (2022) Interaction of Neural Stem Cells (NSCs) and Mesenchymal Stem Cells (MSCs) as a Promising Approach in Brain Study and Nerve Regeneration. Cells 11(9): 1464.

20. Gutierrez-Fernandez M, Fuentes B, Rodriguez-Frutos B, Ramos-Cejudo J, Vallejo-Cremades MT, et al. (2012) Trophic factors and cell therapy to stimulate brain repair after ischaemic stroke. J Cell Mol Med 16(10): 2280-2290.

21. Miranda M, Morici JF, Zanoni MB, Bekinschtein P (2019) Brain-Derived Neurotrophic Factor: A Key Molecule for Memory in the Healthy and the Pathological Brain. Front Cell Neurosci 13: 363.

22. Dwyer ND, Chen B, Chou SJ, Hippenmeyer S, Nguyen L, et al. (2016) Neural Stem Cells to Cerebral Cortex: Emerging Mechanisms Regulating Progenitor Behavior and Productivity. J Neurosci 36(45): 11394-11401.

23. Bond AM, Ming GL, Song H (2021) Ontogeny of adult neural stem cells in the mammalian brain. Curr Top Dev Biol 142: 67-98.

24. Obernier K, Alvarez-Buylla A (2019) Neural stem cells: origin, heterogeneity and regulation in the adult mammalian brain. Development 146(4): dev156059.

25. Conover JC, Todd KL (2017) Development and aging of a brain neural stem cell niche. Exp Gerontol 94: 9-13.

26. Jiang X, Nardelli J (2016) Cellular and molecular introduction to brain development. Neurobiol Dis 92(Pt A): 3-17.

27. Molnsar Z, Clowry GJ, Sestan N, Alzu'bi A, Bakken T, et al. (2019) New insights into the development of the human cerebral cortex. J Anat 235(3): 432-451.

28. Hatanaka Y, Zhu Y, Torigoe M, Kita Y, Murakami F (2016) From migration to settlement: the pathways, migration modes and dynamics of neurons in the developing brain. Proc Jpn Acad Ser B Phys Biol Sci 92(1): 1-19.

29. Peregrina C, Del Toro D (2020) FLRTing Neurons in Cortical Migration during Cerebral Cortex Development. Front Cell Dev Biol 8: 578506.

30. Evsyukova I, Plestant C, Anton ES (2013) Integrative mechanisms of oriented neuronal migration in the developing brain. Annu Rev Cell Dev Biol 29: 299-353.

31. Kwan KY, Sestan N, Anton ES (2012) Transcriptional co-regulation of neuronal migration and laminar identity in the neocortex. Development 139(9):1535-1546.

32. Bond AM, Ming GL, Song H (2021) Ontogeny of adult

neural stem cells in the mammalian brain. Curr Top Dev Biol 142: 67-98.

33. Ma DK, Bonaguidi MA, Ming GL, Song H (2009) Adult neural stem cells in the mammalian central nervous system. Cell Res 19(6): 672-682.

34. Toda T, Parylak SL, Linker SB, Gage FH (2019) The role of adult hippocampal neurogenesis in brain health and disease. Mol Psychiatry 24(1): 67-87.

35. Poulose SM, Miller MG, Scott T, Shukitt-Hale B (2017) Nutritional Factors Affecting Adult Neurogenesis and Cognitive Function. Adv Nutr 8(6): 804-811.

36. Kumar A, Pareek V, Faiq MA, Ghosh SK, Kumari C (2019) Adult Neurogenesis In Humans: A Review Of Basic Concepts, History, Current Research, And Clinical Implications. Innov Clin Neurosci 16(5-6): 30-37.

37. Bergmann O, Spalding KL, Frisén J (2015) Adult Neurogenesis in Humans. Cold Spring Harb Perspect Biol 7(7): a018994.

38. Jurkowski MP, Bettio L, Woo EK, Patten A, Yau SY, et al. (2020) Beyond the Hippocampus and the SVZ: Adult Neurogenesis Throughout the Brain. Front Cell Neurosci 14: 576444.

39. Deng W, Aimone JB, Gage FH (2010) New neurons and new memories: how does adult hippocampal neurogenesis affect learning and memory? Nat Rev Neurosci 11(5): 339-350.

40. Babcock KR, Page JS, Fallon JR, Webb AE (2010) Adult Hippocampal Neurogenesis in Aging and Alzheimer's Disease. Stem Cell Reports 16(4): 681-693.

41. Duque A, Arellano JI, Rakic P (2022) An assessment of the existence of adult neurogenesis in humans and value of its rodent models for neuropsychiatric diseases. Mol Psychiatry 27(1): 377-382.

42. Culig L, Chu X, Bohr VA (2022) Neurogenesis in aging and age-related neurodegenerative diseases. Ageing Res Rev 78: 101636.

43. Geigenmuller JN, Tari AR, Wisloff U, Walker TL (2024) The relationship between adult hippocampal neurogenesis and cognitive impairment in Alzheimer's disease. Alzheimers Dement 20(10): 7369-7383.

44. Aimone JB, Li Y, Lee SW, Clemenson GD, Deng W, et al. (2014) Regulation and function of adult neurogenesis: from genes to cognition. Physiol Rev 94(4):991-1026.

45. Sada A, Tumbar T (2013) New insights into mechanisms of stem cell daughter fate determination in regenerative tissues. Int Rev Cell Mol Biol 300:1-50.

46. Zhang H, Wang ZZ (2008) Mechanisms that mediate stem cell self-renewal and differentiation. J Cell Biochem 103(3): 709-718.

47. Dreiwi H, Feliciangeli F, Castro M, Lythe G, Molina-París C, et al. (2024) Stochastic journeys of cell progenies through compartments and the role of self-renewal, symmetric and asymmetric division. Sci Rep 14(1): 16287.

48. Gómez-Oliva R, Martínez-Ortega S, Atienza-Navarro I, Domínguez-García S, Bernal-Utrera C, et al. (2023) Rescue of neurogenesis and age-associated cognitive decline in SAMP8 mouse: Role of transforming growth factor-alpha. Aging Cell 22(6): e13829.

49. Ibrayeva A, Bay M, Pu E, Jörg DJ, Peng L, et al. (2021) Early stem cell aging in the mature brain. Cell Stem Cell 28(5): 955-966.

50. Conover JC, Shook BA (2011) Aging of the subventricular zone neural stem cell niche. Aging Dis 2(1): 49-63.

51. Terzi MY, Izmirli M, Gogebakan B (2016) The cell fate: senescence or quiescence. Mol Biol Rep 43(11): 1213-1220.

52. Cho IJ, Lui PP, Obajdin J, Riccio F, Stroukov W, et al. (2019) Mechanisms, Hallmarks, and Implications of Stem Cell Quiescence. Stem Cell Reports 12(6): 1190-1200.

53. Cheung TH, Rando TA (2013) Molecular regulation of stem cell quiescence. Nat Rev Mol Cell Biol 14(6): 329-340.

54. Shahriyari L, Komarova NL (2013) Symmetric vs. asymmetric stem cell divisions: an adaptation against cancer? PLoS One 8(10): e76195.

55. Gómez-López S, Lerner RG, Petritsch C (2014) Asymmetric cell division of stem and progenitor cells during homeostasis and cancer. Cell Mol Life Sci 71(4): 575-597.

56. Obernier K, Cebrian-Silla A, Thomson M, Parraguez JI, Anderson R, et al. (2018) Adult Neurogenesis is Sustained by Symmetric Self-Renewal and Differentiation. Cell Stem Cell 22(2): 221-234.

57. Lazutkin A, Podgorny O, Enikolopov G (2019) Modes of division and differentiation of neural stem cells. Behav Brain Res 374: 112118.

58. Anand KS, Dhikav V (2012) Hippocampus in health and

disease: An overview. Ann Indian Acad Neurol 15(4): 239-246.

59. Rubin RD, Watson PD, Duff MC, Cohen NJ (2014) The role of the hippocampus in flexible cognition and social behavior. Front Hum Neurosci 8: 742.

60. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G (2013) The hallmarks of aging. Cell 153(6): 1194-217.

61. Tenchov R, Sasso JM, Wang X, Zhou QA (2024) Aging Hallmarks and Progression and Age-Related Diseases: A Landscape View of Research Advancement. ACS Chem Neurosci 15(1): 1-30.

62. Baechle JJ, Chen N, Makhijani P, Winer S, Furman D, et al. (2023) Chronic inflammation and the hallmarks of aging. Mol Metab 74: 101755.

63. Burkhalter MD, Rudolph KL, Sperka T (2015) Genome instability of ageing stem cells--Induction and defence mechanisms. Ageing Research Reviews 23(Part A): 29-36.

64. Guo J, Huang X, Dou L, Yan M, Shen T, et al. (2022) Aging and aging-related diseases: from molecular mechanisms to interventions and treatments. Signal Transduction and Targeted Therapy 7(1): 391.

65. Cadet J, Davies KJA (2017) Oxidative DNA damage & repair: An introduction. Free Radical Biology and Medicine 107: 2-12.

66. Chen JH, Hales CN, Ozanne SE (2007) DNA damage, cellular senescence and organismal ageing: causal or correlative? Nucleic Acids Research 35(22): 7417-7428.

67. Zocher S, Toda T (2023) Epigenetic aging in adult neurogenesis. Hippocampus 33(4): 347-359.

68. Shi J, Wang Z, Wang Z, Shao G, Li X (2024) Epigenetic regulation in adult neural stem cells. Front Cell Dev Biol 12: 1331074.

69. Ferrón SR, Marqués-Torrejón MA, Mira H, Flores I, Taylor K, et al. (2009) Telomere shortening in neural stem cells disrupts neuronal differentiation and neuritogenesis. J Neurosci 29(46): 14394-14407.

70. Lupatov AY, Yarygin KN (2022) Telomeres and Telomerase in the Control of Stem Cells. Biomedicines 10(10): 2335.

71. Victorelli S, Passos JF (2017) Telomeres and Cell Senescence - Size Matters Not. eBioMedicine 21: 14-20.

72. Lupatov AY, Yarygin KN (2022) Telomeres and Telomerase in the Control of Stem Cells. Biomedicines 10(10): 2335.

73. Wang K, Liu H, Hu Q, Wang L, Liu J, et al. (2022) Epigenetic regulation of aging: implications for interventions of aging and diseases. Signal Transduct Target Ther 7(1): 374.

74. Przybilla J, Rohlf T, Loeffler M, Galle J (2014) Understanding epigenetic changes in aging stem cells--a computational model approach. Aging Cell 13(2): 320-328.

75. Morimoto RI, Cuervo AM (2014) Proteostasis and the aging proteome in health and disease. J Gerontol A Biol Sci Med Sci 69 (Suppl 1): S33-S38.

76. Jin H, Komita M, Aoe T (2018) Decreased Protein Quality Control Promotes the Cognitive Dysfunction Associated With Aging and Environmental Insults. Front Neurosci 1(12): 753.

77. Higuchi-Sanabria R, Frankino PA, Paul JW, Tronnes SU, Dillin A (2018) A Futile Battle? Protein Quality Control and the Stress of Aging. Developmental Cell 44(2): 139-163.

78. Somasundaram I, Jain SM, Blot-Chabaud M, Pathak S, Banerjee A, et al. (2024) Mitochondrial dysfunction and its association with age-related disorders. Front Physiol 2(15): 1384966.

79. Payne BAI, Chinnery PF (2015) Mitochondrial dysfunction in aging: Much progress but many unresolved questions. Biochimica et Biophysica Acta (BBA) – Bioenergetics 1847(11): 1347-1353.

80. Wan Y, Finkel T (2020) The mitochondria regulation of stem cell aging. Mech Ageing Dev 191: 111334.

81. Negredo PN, Yeo RW, Brunet A (2020) Aging and Rejuvenation of Neural Stem Cells and Their Niches. Cell Stem Cell. 27(2): 202-223.

82. Shafqat A, Khan S, Omer MH, Niaz M, Albalkhi I, et al. (2023) Cellular senescence in brain aging and cognitive decline. Front Aging Neurosci 15: 1281581.

83. Chinta SJ, Woods G, Rane A, Demaria M, Campisi J, et al. (2015) Cellular senescence and the aging brain. Experimental Gerontology 68: 3-7.

84. Plakkot B, Agostino AD, Subramanian M (2023) Implications of Hypothalamic Neural Stem Cells on Aging and Obesity-Associated Cardiovascular Diseases. Cells. 12(5): 769.

85. Allen NC, Reyes NS, Lee JY, Peng T (2022) Intersection of Inflammation and Senescence in the Aging Lung Stem Cell Niche. Front Cell Dev Biol 10: 932723.

86. Li X, Li C, Zhang W, Wang Y, Qian P, et al. (2023) Inflammation and aging: signaling pathways and intervention therapies. Signal Transduction and Targeted Therapy 8(1): 239.

87. Finnegan R, Becker S (2015) Neurogenesis paradoxically decreases both pattern separation and memory interference. Front Syst Neurosci 9: 136.

88. Andrea SC, David VE, Larry SZ, Michael C (2012) The impact of inflammation on cognitive function in older adults: implications for healthcare practice and research. Journal of Neuroscience Nursing 44(4): 206-217.

89. Jin R, Chan AKY, Wu J, Lee TMC (2022) Relationships between Inflammation and Age-Related Neurocognitive Changes. Int J Mol Sci 23(20): 12573.

90. Wang WY, Tan MS, Yu JT, Tan L (2015) Role of pro-inflammatory cytokines released from microglia in Alzheimer's disease. Ann Transl Med. 3(10): 136.

91. Cai Y, Liu J, Wang B, Sun M, Yang H (2022) Microglia in the Neuroinflammatory Pathogenesis of Alzheimer's Disease and Related Therapeutic Targets. Front Immunol 13: 856376.

92. Gao C, Jiang J, Tan Y, Chen S (2023) Microglia in neurodegenerative diseases: mechanism and potential therapeutic targets. Signal Transduct Target Ther 8(1): 359.

93. Wu A, Zhang J (2023) Neuroinflammation, memory, and depression: new approaches to hippocampal neurogenesis. J Neuroinflammation 20(1): 283.

94. Matanzo A, Llorens M, Hernandez F, Avila J (2013) Role of neuroinflammation in adult neurogenesis and Alzheimer disease: therapeutic approaches. Mediators Inflamm 2013: 260925.

95. Taupin P (2008) Adult neurogenesis, neuroinflammation and therapeutic potential of adult neural stem cells. Int J Med Sci 5(3): 127-132.

96. Reddy OC, Werf YD (2020) The Sleeping Brain: Harnessing the Power of the Glymphatic System through Lifestyle Choices. Brain Sci 10(11): 868.

97. Voumvourakis KI, Sideri E, Papadimitropoulos GN, Tsantzali I, Hewlett P, et al. (2023) The Dynamic Relationship between the Glymphatic System, Aging, Memory, and Sleep. Biomedicines 11(8): 2092.

98. Herrero A, Baril AA, Plante C, Jodoin M, Sanchez E, et al. (2023) The Putative Role of Neuroinflammation in the Interaction between Traumatic Brain Injuries, Sleep, Pain and Other Neuropsychiatric Outcomes: A State-of-the-Art Review. J Clin Med 12(5): 1793.

99. Bishir M, Bhat A, Essa MM, Ekpo O, Ihunwo AO, et al. (2020) Sleep Deprivation and Neurological Disorders. Biomed Res Int 2020: 5764017.

100. Desai D, Momin A, Hirpara P, Jha H, Thaker R, et al. (2024) Exploring the Role of Circadian Rhythms in Sleep and Recovery: A Review Article. Cureus 16(6): e61568.

101. Alnawwar MA, Alraddadi MI, Algethmi RA, Salem GA, Salem MA, et al. (2023) The Effect of Physical Activity on Sleep Quality and Sleep Disorder: A Systematic Review. Cureus 15(8): e43595.

102. Vogel AD, Upadhya R, Shetty AK (2018) Neural stem cell derived extracellular vesicles: Attributes and prospects for treating neurodegenerative disorders. eBioMedicine 38: 273-282.

103. Velikic G, Maric DM, Maric DL, Supic G, Puletic M, et al. (2024) Harnessing the Stem Cell Niche in Regenerative Medicine: Innovative Avenue to Combat Neurodegenerative Diseases. Int J Mol Sci 25(2): 993.

104. Wang J, Chen S, Pan C, Li G, Tang Z (2022) Application of Small Molecules in the Central Nervous System Direct Neuronal Reprogramming. Front Bioeng Biotechnol 10: 799152.

105. Andrade C, Radhakrishnan R (2009) The prevention and treatment of cognitive decline and dementia: An overview of recent research on experimental treatments. Indian Journal of Psychiatry 51(1): 12-25.

106. Frisoni GB, Altomare D, Ribaldi F, Villain N, Brayne C, et al. (2023) Dementia prevention in memory clinics: recommendations from the European task force for brain health services. The Lancet Regional Health Europe 26: 100576.