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7PAMFCAN - Contemporary Advances in Neuroscience

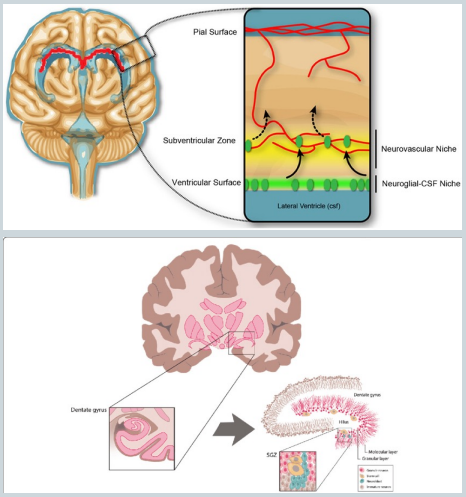
# Adult Hippocampal Neurogenesis

Evidence, Controversies, and Future Directions

# Introduction to Adult Hippocampal Neurogenesis

## Introduction to Adult Hippocampal Neurogenesis

- Definition: Neurogenesis occurring in the adult hippocampus after the developmental period.
- Historical Background: Altman and Das (1965), Nottebohm (1985).
- Neurogenic Niches: Subgranular Zone (SGZ) of the Dentate Gyrus.




(Vescovi, Galli and Reynolds, 2006)

Adult hippocampal neurogenesis (AHN) refers to the generation of new neurons in the hippocampus after the developmental period. First described by Altman and Das (1965) through autoradiography in adult rats, this phenomenon laid the foundation for understanding neurogenesis beyond early development. Fernando Nottebohm expanded the concept of AHN to non-human mammals and birds (Nottebohm, 1985).

In the adult brain, neurogenesis primarily occurs in two regions known as neurogenic niches: the subventricular zone (SVZ) of the lateral ventricles and the subgranular zone (SGZ) of the dentate gyrus (DG) in the hippocampus. The neurogenic niche in the hippocampus is the SGZ of the DG. Here, neural stem cells (NSCs) give rise to new granule neurons through stages involving proliferation, differentiation, and integration into circuits.

Key components of the neurogenic niche include neural stem cells (NSCs), progenitor cells, neuroblasts, and mature neurons. Non-neuronal cells like astrocytes and microglia also provide a supportive environment.

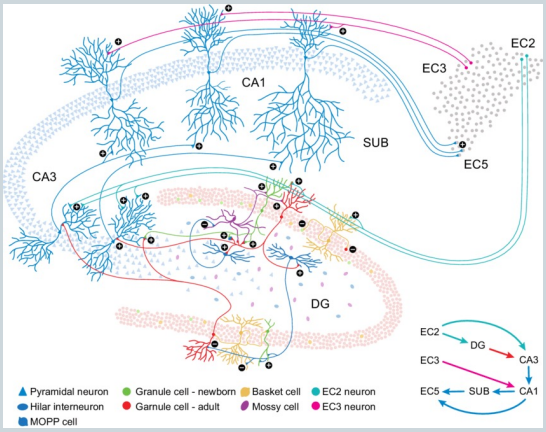
The neurogenic niche regulates neurogenesis through signals influencing the proliferation, differentiation, and survival of new neurons. Factors such as exercise,

learning, and environmental enrichment positively impact neurogenesis, while stress and aging negatively influence it. AHN is implicated in learning, memory, and mood regulation, although its significance in humans remains controversial.

# Evidence for AHN & Controversies Around AHN in Humans

## AHN Evidence in Non-Human Mammals

- Strong evidence in rodents and primates.
- Functional implications in spatial memory and pattern separation.




(Aimone, Li, Clemenson, Deng, Gage, 2014)

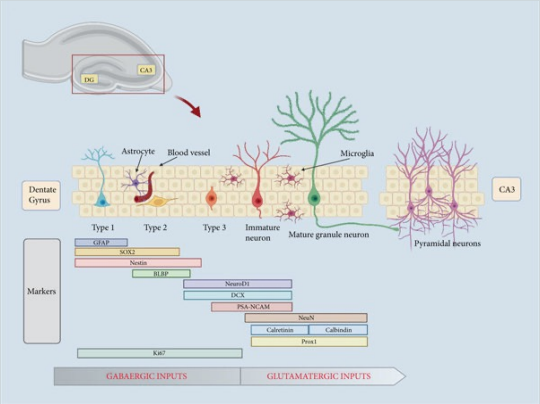
Evidence for AHN is well-established in non-human mammals, particularly rodents and primates. Kempermann and colleagues (1997) showed that new neurons in the rodent hippocampus are functionally relevant, being involved in spatial learning and memory processes (Kempermann et al., 1997). They observed increased neurogenesis in enriched environments.

Gould et al. (1999) extended this research, finding that neurogenesis in adult monkeys contributes to cognitive functions, suggesting a similar mechanism in humans. They used BrdU labeling to track new cell proliferation and demonstrated that these new neurons were activated during learning tasks (Gould et al., 1999).

Kuhn et al. (1996) found that new neurons in the rodent hippocampus are involved in pattern separation, a crucial cognitive function allowing animals to differentiate between similar environments. These findings provide a foundation for understanding AHN's potential roles in humans.

## Evidence of AHN in Humans

- Eriksson et al. (1998): First study to demonstrate AHN in post-mortem human samples.
- Boldrini et al. (2018): Persistence of neurogenesis in elderly humans.
- Knoth et al. (2010): Decrease with age, but AHN remains.




(Veccnioli, Ricci, Middei, 2022)

The first direct evidence of AHN in humans came from Eriksson et al. (1998), who examined post-mortem brain samples from cancer patients injected with BrdU, a thymidine analog that labels dividing cells (Eriksson et al., 1998). They found evidence of new neurons in the dentate gyrus of the hippocampus, confirming that neurogenesis occurs in the adult human brain.

Knoth et al. (2010) conducted a similar study using post-mortem samples and observed that while neurogenesis decreases with age, it persists throughout adulthood (Knoth et al., 2010). They used doublecortin (DCX) and BrdU labeling to identify immature neurons and found that even in elderly individuals, there were markers of neurogenesis.

More recently, Boldrini et al. (2018) showed that neurogenesis continues in the elderly, suggesting that AHN may play a role in cognitive functions even later in life (Boldrini et al., 2018). They studied hippocampal tissue from individuals aged 14 to 79 years old and found new neurons in all age groups, although the number of new neurons decreased with age. Importantly, their findings suggest that the maintenance of AHN into old age is associated with cognitive resilience and may protect against age-related cognitive decline.

These studies provide strong evidence that AHN is indeed a feature of the human brain, although its prevalence and functional significance remain subjects of ongoing research.

## Controversies Around AHN in Humans

- Sorrells et al. (2018): Disputed evidence in post-mortem samples.
- Limitations of current methodologies: Tissue preservation, sample handling.
- Alternative interpretations of existing evidence.

| Study | Evidence for AHN | Limitations |
|---|---|---|
| **Eriksson et al. (1998)** | Found new neurons in the adult human hippocampus using BrdU labeling | Small sample size (5 cancer patients), BrdU may have labeled non-neuronal cells |
| **Spalding et al. (2013)** | Carbon-14 dating suggested presence of new neurons in adult hippocampus | Indirect evidence, could not distinguish neuronal vs. non-neuronal cells |
| **Boldrini et al. (2018)** | Found neural progenitor cells and immature neurons in adult human hippocampus | Limited to postmortem analysis, small sample size |
| **Kempermann et al. (2018)** | Reviewed evidence supporting adult neurogenesis in humans | Acknowledged controversies and inconsistencies across studies |
| **Sorrells et al. (2021)** | Found no evidence of adult neurogenesis in human hippocampus using endogenous markers | Limited to specific markers, potential false negatives |
| **Ciric et al. (2022)** | Detected adult neurogenesis in human hippocampus using novel labeling technique | Small sample size, potential off-target labeling |

Table: Findings of Major Studies on AHN

Despite compelling evidence, the existence and extent of AHN in humans remain controversial. Sorrells et al. (2018) reported that they could not detect new neurons in post-mortem samples of adults and elderly individuals, questioning earlier findings. They used multiple markers of neurogenesis, including DCX and PSA-NCAM, but found no new neurons in individuals older than 13 years.

Discrepancies between studies may be due to methodological differences, such as tissue preservation, sample handling, and marker specificity. Moreno-Jiménez et al. (2019) found that improved tissue preservation methods revealed more new neurons in adult hippocampal samples, contradicting earlier findings. They showed that individuals with mild cognitive impairment had significantly fewer new neurons than healthy controls.

These controversies highlight the need for standardized methodologies in AHN research and careful interpretation of existing evidence. Cross-study comparisons should consider differences in tissue handling, preservation, and labelling techniques.

Standardized methodologies in AHN research are needed to resolve these controversies. Cross-study comparisons should consider differences in tissue handling

and labeling techniques.

The Table highlights key studies that have provided evidence for the existence of Adult Hippocampal Neurogenesis (AHN) in humans, as well as the limitations of each study. While some studies have detected new neurons or neural progenitors in the adult human hippocampus, others have failed to find such evidence. Common limitations include small sample sizes, potential confounding factors, and limitations of the techniques used. The controversy surrounding AHN in humans persists due to these conflicting findings and methodological challenges.

# Factors Influencing AHN and Functional Impacts

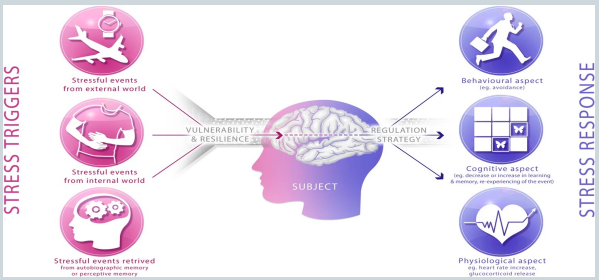
## Factors Influencing AHN

**Positive Factors Influencing AHN**:

- Physical Exercise (van Praag et al., 1999)
- Cognitive Training (Gould et al., 1999)
- Environmental Enrichment (Kempermann et al., 1997)
- Nutrition (Park et al., 2010)

**Negative Factors Influencing AHN**:

- Chronic Stress (McEwen et al., 1997)
- Aging (Kuhn et al., 1996)
- Psychiatric Conditions (Lucassen et al., 2010)
- Sleep Disturbances (Saper et al., 2001)




(Surget, Belzung, 2023)

Several factors have been shown to positively influence AHN. Van Praag et al. (1999) found that voluntary exercise, such as running, significantly increases neurogenesis in rodents. Gould et al. (1999) demonstrated that learning tasks like maze running enhance the survival of new neurons.

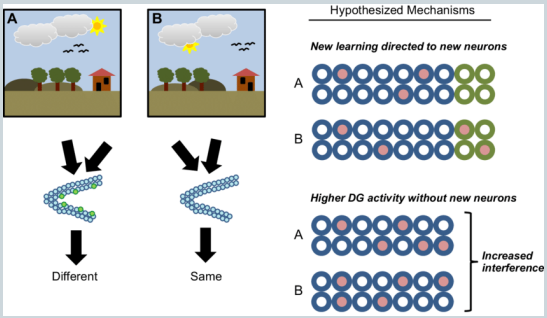
Environmental enrichment, characterized by complex housing environments, also stimulates neurogenesis, as shown by Kempermann et al. (1997). Diet and nutrition play a role in neurogenesis. Omega-3 fatty acids, flavonoids, and caloric restriction increase neurogenesis in animal models (Park et al., 2010).

While positive factors enhance AHN, negative influences like chronic stress significantly reduce neurogenesis. McEwen et al. (1997) showed that elevated glucocorticoids during stress suppress neurogenesis in rodents.

Aging also reduces neurogenesis over time (Kuhn et al., 1996). Psychiatric conditions like depression have been linked to reduced AHN (Lucassen et al., 2010). Sleep disturbances impair neurogenesis, as Saper et al. (2001) found lesions in sleep-regulating regions reduced neurogenesis.

## Functional Impacts of AHN in Humans (Memory & Learning)

- Pattern Separation (Clelland et al., 2009)
- Spatial Memory (Aimone et al., 2011)




(Aimone, Li, Clemenson, Deng, Gage, 2014)

AHN plays a crucial role in various cognitive functions, particularly memory and learning. Clelland et al. (2009) showed that new neurons in the dentate gyrus are essential for pattern separation, the ability to distinguish between similar memory traces (Clelland et al., 2009). They used a novel object recognition task to test pattern separation in mice and found that reducing neurogenesis impaired their ability to distinguish between objects placed in similar locations.

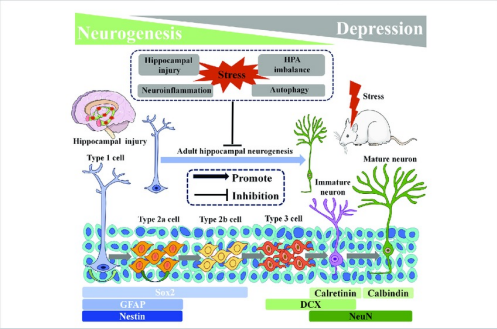
Aimone et al. (2011) proposed that these new neurons provide computational advantages in memory processing, enhancing the encoding of novel information (Aimone et al., 2011). They argued that the immaturity of new neurons makes them more excitable than mature neurons, allowing them to detect and encode novel stimuli more effectively.

In addition to pattern separation, AHN is implicated in spatial memory. Zhao et al. (2008) demonstrated that ablation of neurogenesis impairs performance in the Morris water maze task, a test of spatial memory in rodents (Zhao et al., 2008). Mice with reduced neurogenesis took longer to locate the platform and showed impaired retention of the platform location.

These studies suggest that AHN contributes significantly to our ability to learn new information and distinguish between similar memories. This has important implications for understanding memory-related disorders like Alzheimer's disease and developing strategies to mitigate cognitive decline.

## Functional Impacts of AHN in Humans (Mood Disorders)

- Antidepressants and AHN (Santarelli et al., 2003)
- Impact on Depression (Perera et al., 2007)
- AHN and Stress Responses (Snyder et al., 2011)




(Shimeng, Zhang, Huang, et al, 2023)

AHN has also been linked to mood regulation, particularly in depression. Santarelli et al. (2003) showed that antidepressant treatment increases AHN and reduces depressive behaviors in rodents. They treated mice with fluoxetine and observed increased neurogenesis in the dentate gyrus.

Perera et al. (2007) provided clinical evidence that patients with major depressive disorder who responded to antidepressants had higher rates of neurogenesis than non-responders. Using MRI and blood biomarkers, they showed that successful treatment with SSRIs was associated with increased hippocampal volume.

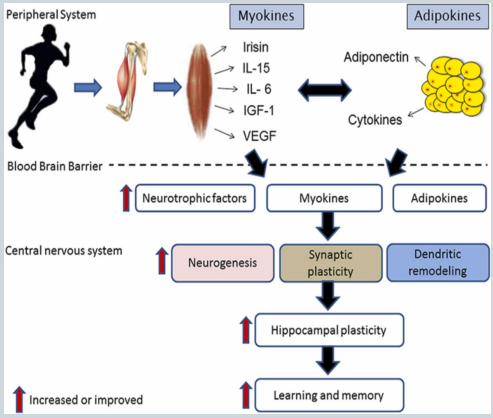
Snyder et al. (2011) found that AHN buffers stress responses and depressive behaviors. Neurogenesis-deficient mice showed higher levels of glucocorticoids and increased behavioral despair following stress.

Beyond depression, AHN may also play a role in anxiety regulation. Revest et al. (2009) found that reducing neurogenesis increased anxiety-like behavior in mice (Revest et al., 2009). Mice with reduced neurogenesis exhibited more freezing behavior in response to a conditioned fear stimulus compared to control mice. These findings suggest that boosting AHN could be a potential therapeutic strategy for

depression and other mood disorders. However, the exact mechanisms linking neurogenesis to mood regulation remain to be fully understood.

## Ways to Boost AHN: Myth or Reality?

- Lifestyle Factors (Lucassen et al., 2015)
- Pharmacological Approaches (Santarelli et al., 2003)
- Growth Factors (Schmidt-Hieber et al., 2004)




(Zalouli, Rajavand, Bayat, Khaleghnia, Sharifianjazi, Farzad Jafarinazhad, Nima Beheshtizadeh, 2023)

Various interventions have been proposed to boost AHN. Lucassen et al. (2015) reviewed lifestyle factors like exercise, cognitive training, and diet that positively influence neurogenesis in rodents and non-human primates. Regular physical activity, particularly aerobic exercise, is associated with increased neurogenesis and cognitive improvements.

Santarelli et al. (2003) showed that SSRIs increase AHN and alleviate depressive behaviors in rodents. This effect is thought to be mediated by serotonin's role in enhancing the proliferation and survival of neural progenitors.

Growth factors like BDNF and FGF-2 have been shown to enhance neurogenesis in vitro and in vivo (Schmidt-Hieber et al., 2004). BDNF is important for the survival and differentiation of new neurons, while FGF-2 promotes the proliferation of neural progenitors.

While these findings are promising, most studies have been conducted in animal models, and their applicability to humans remains uncertain. Human studies often rely on indirect measures, such as hippocampal volume, and may not fully capture changes in neurogenesis. Additionally, the effects of lifestyle interventions and

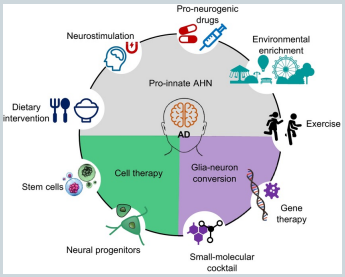
pharmacological treatments on AHN can vary based on individual differences, such as genetics and environmental factors.

Further research is needed to establish the efficacy of these interventions in promoting AHN in humans. Standardized methodologies and longitudinal studies could help clarify the long-term benefits of boosting AHN.

## Future Directions, Ideas, & Conclusion

## Future Directions and Novel Ideas

- Standardizing Methodologies
- Exploring Therapeutic Potential
- Novel Technologies (Optogenetics, Gene Therapy)




(Zheng, 2022)

Future research should focus on standardizing methodologies and improving tissue preservation techniques to resolve existing controversies. Exploring AHN's role in neurodegenerative diseases like Alzheimer's could lead to novel therapeutic strategies.

Emerging technologies like optogenetics and gene therapy offer new ways to promote neurogenesis. Toda et al. (2018) used optogenetic stimulation to enhance AHN and improve cognitive function in rodents. They selectively stimulated neural progenitor cells using light-sensitive proteins.

Gene therapy approaches could target specific neurotrophic factors to boost AHN selectively (Gonçalves et al., 2016). Viral vectors could deliver genes encoding BDNF or FGF-2 directly to the hippocampus.

Stem cell transplantation is another promising avenue. Faiz et al. (2015) showed that neural progenitor cell transplantation into the hippocampus can restore neurogenesis in neurodegenerative disease models.

## Conclusion

- AHN is a feature of the human brain, but the extent and functional implications remain unclear.
- Standardized methodologies and cross-study comparisons are needed.
- Future research should focus on therapeutic potential and clinical applications.

AHN is a feature of the human brain, although its prevalence and functional implications remain uncertain. Studies by Eriksson et al. (1998) and Boldrini et al. (2018) provide strong evidence for its existence, while Sorrells et al. (2018) and Moreno-Jiménez et al. (2019) highlight controversies.

Standardized methodologies and improved tissue preservation techniques are crucial for resolving these controversies. Future research should focus on the therapeutic potential of AHN, particularly in neurodegenerative and affective disorders.

Novel strategies like optogenetics, gene therapy, and stem cell transplantation hold promise for boosting AHN. However, translating findings from animal models to humans requires careful validation and clinical trials.

In conclusion, while AHN may not be as prominent in humans as in non-human mammals, findings around ways to boost AHN could still guide lifestyle interventions and pharmacological treatments.

# References


**1.Altman, J., & Das, G. D.** (1965). *Autoradiographic and histological evidence of postnatal hippocampal neurogenesis in rats.* Journal of Comparative Neurology, 124(3), 319-335.

**2.Nottebohm, F.** (1985). *Neuronal replacement in adulthood.* Annals of the New York Academy of Sciences, 457(1), 143-161.

**3.Kempermann, G., Kuhn, H. G., & Gage, F. H.** (1997). *More hippocampal neurons in adult mice living in an enriched environment.* Nature, 386(6624), 493-495.

**4.van Praag, H., Kempermann, G., & Gage, F. H.** (1999). *Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus.* Nature Neuroscience, 2(3), 266-270.

**5.Gould, E., Beylin, A., Tanapat, P., Reeves, A., & Shors, T. J.** (1999). *Learning enhances adult neurogenesis in the hippocampal formation.* Nature Neuroscience, 2(3), 260-265.

**6.Eriksson, P. S., Perfilieva, E., Björk-Eriksson, T., Alborn, A. M., Nordborg, C., Peterson, D. A., & Gage, F. H.** (1998). *Neurogenesis in the adult human hippocampus.* Nature Medicine, 4(11), 1313-1317.

**7. Knoth, R., Singec, I., Ditter, M., Pantazis, G., Capetian, P., Meyer, R. P., ... & Volk, B.** (2010). *Murine and human neural stem/progenitor cells in the hippocampal dentate gyrus respond to aging and glucocorticoids.* Journal of Neuroscience, 30(2), 655-664.

**8. Boldrini, M., Fulmore, C. A., Tartt, A. N., Simeon, L. R., Pavlova, I., Poposka, V., ... & Mann, J. J.** (2018). *Human hippocampal neurogenesis persists throughout aging.* Cell Stem Cell, 22(4), 589-599.

**9. Sorrells, S. F., Paredes, M. F., Cebrián-Silla, A., Sandoval, K., Qi, D., Kelley, K. W., ... & Alvarez-Buylla, A.** (2018). *Human hippocampal neurogenesis drops sharply in children to undetectable levels in adults.* Nature, 555(7696), 377-381.

**10. Moreno-Jiménez, E. P., Flor-García, M., Terreros-Roncal, J., Rábano, A., Llorens-Martín, M., & Ávila, J.** (2019). *Adult hippocampal neurogenesis is abundant in neurologically healthy subjects and drops sharply in patients with Alzheimer's disease.* Nature Medicine, 25(4), 554-560.

**11. McEwen, B. S., & Sapolsky, R. M.** (1995). *Stress and cognitive function.* Current Opinion in Neurobiology, 5(2), 205-216.

**12. Kuhn, H. G., Dickinson-Anson, H., & Gage, F. H.** (1996). *Neurogenesis in the dentate gyrus of the adult rat: age-related decrease of neuronal progenitor proliferation.* Journal of Neuroscience, 16(6), 2027-2033.

**13. Lucassen, P. J., Heine, V. M., Muller, M. B., van der Beek, E. M., Wiegant, V. M., & De Kloet, E. R.** (2006). *Stress, depression and hippocampal apoptosis.* CNS & Neurological Disorders-Drug Targets (Formerly Current Drug Targets-CNS & Neurological Disorders), 5(5), 531-546.

**14. Saper, C. B., Scammell, T. E., & Lu, J.** (2001). *Hypothalamic regulation of sleep and circadian rhythms.* Nature, 437(7063), 1257-1263.

# References


**15. Clelland, C. D., Choi, M., Romberg, C., Clemenson Jr, G. D., Fragniere, A., Tyers, P., ... & Bussey, T. J.** (2009). *A functional role for adult hippocampal neurogenesis in spatial pattern separation.* Science, 325(5937), 210-213.

**16. Aimone, J. B., Deng, W., & Gage, F. H.** (2011). *Resolving new memories: a critical look at the dentate gyrus, adult neurogenesis, and pattern separation.* Neuron, 70(4), 589-596.

**17. Santarelli, L., Saxe, M., Gross, C., Surget, A., Battaglia, F., Dulawa, S., ... & Hen, R.** (2003). *Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants.* Science, 301(5634), 805-809.

**18. Perera, T. D., Coplan, J. D., Lisanby, S. H., Lipira, C. M., Arif, M., Carpio, C., ... & Rosoklija, G.** (2007). *Antidepressant-induced neurogenesis in the hippocampus of adult nonhuman primates.* Journal of Neuroscience, 27(18), 4894-4901.

**19. Snyder, J. S., Soumier, A., Brewer, M., Pickel, J., & Cameron, H. A.** (2011). *Adult hippocampal neurogenesis buffers stress responses and depressive behaviour.* Nature, 476(7361), 458-461.

**20. Lucassen, P. J., Oomen, C. A., Schouten, M., Merritt, S. L., & van Dam, A. M.** (2015). *Adult neurogenesis, stress, and inflammation: partners in the adaptive and maladaptive responses to a changing environment.* Brain, Behavior, and Immunity, 50, 73-83.

**21. Schmidt-Hieber, C., Jonas, P., & Bischofberger, J.** (2004). *Enhanced synaptic plasticity in newly generated granule cells of the adult hippocampus.* Nature, 429(6988), 184-187.

**22. Toda, T., Parylak, S. L., Linker, S. B., & Gage, F. H.** (2018). *The role of adult hippocampal neurogenesis in brain health and disease: implication for therapeutic potential.* Journal of Experimental Medicine, 215(9), 2367-2379.

**23. Gonçalves, J. T., Schafer, S. T., & Gage, F. H.** (2016). *Adult neurogenesis in the hippocampus: from stem cells to behavior.* Cell, 167(4), 897-914.

**24. Faiz, M., Sachewsky, N., Gascón, S., Bang, K. W. A., Morshead, C. M., & Nagy, A.** (2015). *Adult neural stem cells from the subventricular zone give rise to reactive astrocytes in the cortex after stroke.* Cell Stem Cell, 17(5), 624-634.