university of groningen / faculty of science and engineering

Peripheral Exercise-induced Factors as Boosters of Adult Hippocampal Neurogenesis in Healthy Aging and Alzheimer's Disease

By

Mark Trivanović

In association with prof. dr. Eddy van der Zee

Bachelor's Thesis

Faculty of Science and Engineering

University of Groningen

June, 2023

Table of Contents

Abstract

Levels of adult hippocampal neurogenesis (AHN) gradually decrease with age. However, Alzheimer's disease (AD) patients exhibit a significantly sharper drop in AHN levels compared to age-matched controls. Ameliorating AHN malfunction by promoting inherent AHN holds great potential for recovering or delaying learning and memory impairment from the disease. Physical activity, such as exercise, has emerged as a prominent, accessible, and cost-effective booster of AHN. Exercise leads to an upregulation of expression of factors from peripheral tissues, like liver and muscle, which are in turn transported to the brain via blood. Hence, this thesis focuses on the roles of exercise-induced factors in improving hippocampal function by promoting neurogenesis, increasing synaptic plasticity and cerebral blood flow. Particular spotlight is put on identifying the specific molecules involved in exercise-induced AHN amelioration. Administration of these factors to elderly people or AD patients unable to engage in physical activity due to preexisting conditions has the potential to mimic the positive effects of exercise, thus providing a safe alternative.

Introduction

The global population is aging rapidly. According to the United Nations, the number of people aged 60 or over is expected to double by 2050 [1]. This demographic shift will have significant social, economic, and healthcare implications. Consequently, healthy aging is crucial as it has the potential to improve the quality of life of older individuals, reduce healthcare costs, and support sustainable development. Prolonged lifespan also brings to the forefront the pressing issue of age-related cognitive decline and neurodegenerative disorders, such as Alzheimer's disease (AD). AD, the most prevalent form of dementia, is a progressive, irreversible disease that gradually impairs memory, thinking, behavior, and social skills. Alzheimer's is a growing global health concern, and it poses an enormous burden on society. There are estimated 50 million patients with dementia, costing more than a trillion US dollars annually. By 2050, the number of patients is estimated to increase almost threefold (~131 million), and the annual total costs of AD treatment are projected to reach $9.12 trillion [2]. Dementia is the fifth leading cause of death globally and AD is the fourth leading cause of disability-adjusted life-years (DALYs) lost in persons aged 75 years and older. A recent study derived a global estimate of 416 million persons in the AD continuum, far exceeding the commonly cited estimate of ≈50 million persons with dementia [3]. This constitutes 22% of the 1.9 billion people aged 50 and above worldwide [3]. A positive takeaway from this is that the vast majority of persons on the AD continuum do not have dementia but are in the predementia stages of the disease, providing a window of opportunity for prevention [3].

At present, with no single cause and with multiple risk factors, AD is one of the most complex challenges modern science is yet to solve. Despite relentless efforts and advancements in medical research, the lack of effective treatments remains a crucial issue. Alzheimer disease's characteristic brain pathology is clinically recognized by progressive cognitive impairments and pathophysiologically by the extracellular accumulation of β-amyloid (Aβ) peptides, formation of neurofibrillary tangles (NFTs) composed of highly phosphorylated tau proteins, neuronal loss, and neuroinflammation [4]. The most commonly used drugs in treating AD are cholinesterase inhibitors, N-methyl-D-aspartate (NMDA) receptor antagonists, and drugs that target amyloid-beta and tau proteins, inflammation, and brain cell growth and survival.

However, encouraging advancements in our understanding of the mechanism of the disease have recently occurred. In the late 2010s, a series of studies reported a sharp decline in adult hippocampal neurogenesis (AHN) levels among individuals with AD [5-9]. The revelation highlighted the detrimental impact of the disease on the regenerative capacity of the hippocampus, a region crucial for learning and memory. In turn, this ignited further studies aimed at unraveling the intricate relationship between neurogenesis and AD, with the ultimate goal of developing interventions that can restore neurogenesis and potentially enhance cognitive function in affected individuals. Thus, the prospect of ameliorating AHN in AD and dementia patients has begun to open up as a novel avenue in treating the disease.

Most notably, exercise and exercise-induced molecules have emerged as prominent, accessible, and cost-effective boosters of AHN. Studies have demonstrated that physical exercise, such as aerobic training, can enhance neurogenesis in the hippocampus, thus presenting a compelling new opportunity for intervention [10-12]. Exercise-induced molecules from peripheral tissues, like muscle and liver, have taken center stage as the mediators of the beneficial effects of exercise on AHN, and consequently cognitive function [13]. These findings have sparked considerable interest, and ongoing research is exploring the mechanisms by which these molecules exert their beneficial effects.

However, while exercise may be an effective way to promote brain health, it is not always feasible for all individuals, especially those with underlying health issues that make it challenging to engage in physical activity. Hence, exercise-induced factors responsible is critical, as it opens up new possibilities for developing treatments to improve brain health and cognitive function. Therefore, in the following sections, this thesis will focus on recent progress in identifying factors that transfer the positive effects of exercise on AHN and thus ameliorate cognitive decline observed in AD and milder forms of dementia.

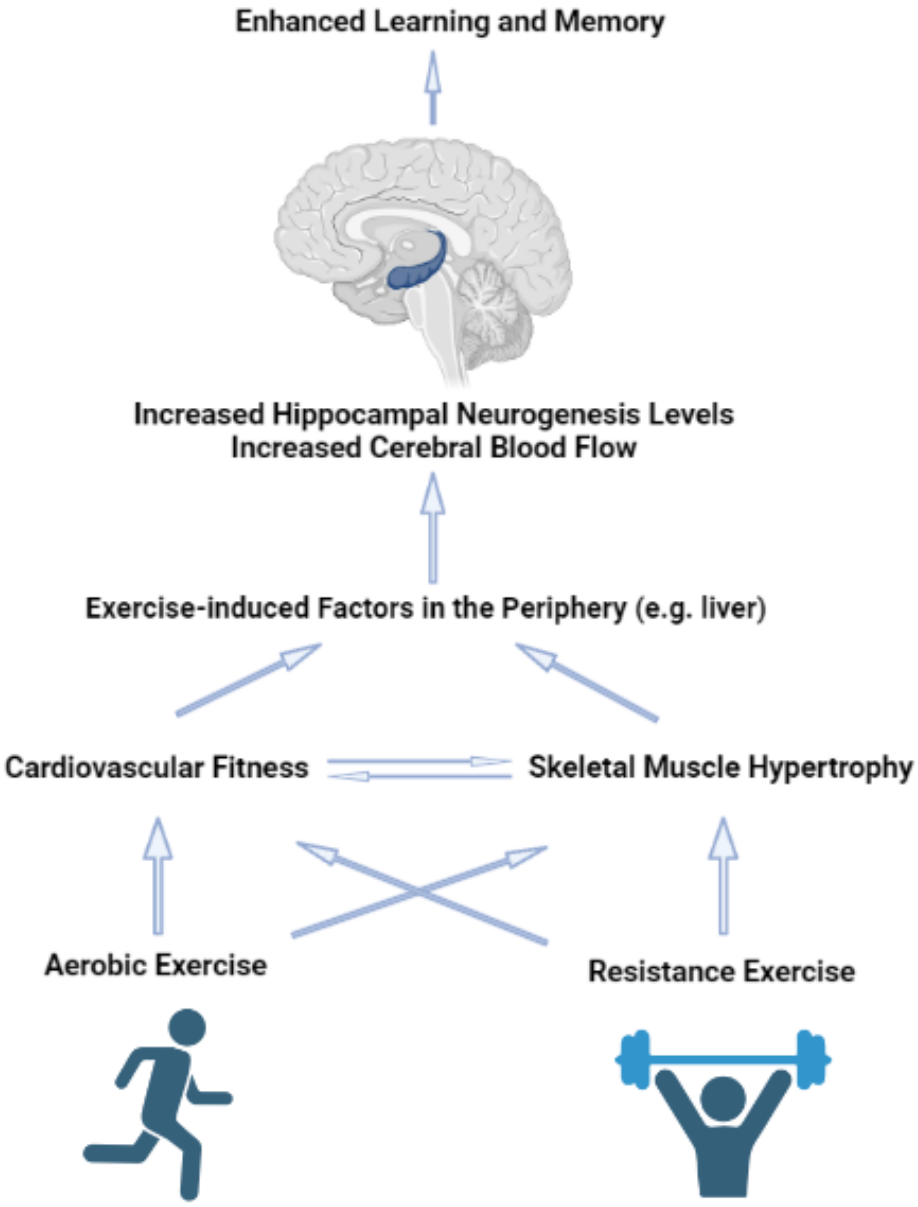

Fig. 1 – Beneficial effects of exercise on hippocampal neurogenesis and overall brain health are largely mediated by exercise-induced molecules from peripheral tissues such as the liver and muscle.

1. Hippocampal Neurogenesis – Overview

Hippocampal neurogenesis refers to the lifelong formation of new neurons in the hippocampus, a brain region important for learning and memory. The idea of brain plasticity was already present in the late 19th century [14]. However, for decades to come, a preexisting dogma that functional neurons are only generated during embryonic and perinatal stages in mammals hindered progress [15]. It took almost 70 years before Altman and Das serendipitously showed evidence for the birth of new dentate granule cells in the postnatal rat hippocampus [16]. The paper, now considered groundbreaking, was met with controversy and skepticism at the time. Subsequently, the first evidence for the functional incorporation of newly born neurons into neuronal circuitry came in songbirds in 1984 [17]. Thus, attributing a physiological role to the process of neurogenesis for the first time. The hypothesis that the addition of new neurons was related to improved physiological and cognitive processes gained momentum again and was embraced with enthusiasm by the field. In addition, the introduction of a novel lineage tracer, namely bromodeoxyuridine (BrdU), allowed for precise following of new neurons along their lineage [18]. Set in motion by these technological advancements and the ever-increasing general interest, significant progress has since been made in this field. A wide array of studies went on to overturn the dogma and elucidate the process of postnatal neurogenesis in both non-mammals and mammals.
Active adult neurogenesis appears to be restricted to two distinct brain regions, the subgranular zone (SGZ) of the dentate gyrus (DG) of the hippocampus [16] and the subventricular zone (SVZ) of the lateral ventricles [19,20]. For a full summary of the mechanism of hippocampal neurogenesis see the Afterword at the end of the thesis.

While there is limited information on SVZ neurogenesis, multifold and broad evidence confirms the existence of AHN in humans. Still, despite the overwhelming amount of evidence in other mammals, and conclusive results in humans, the concept of human AHN is still doubted. Since the discovery of human AHN by Erikkson and colleagues [21], the idea has been questioned [22,23] and supported [24,25]. This debate proved useful in clarifying standards and encouraging improvement. The conflicting results were attributed to technical limitations, such as the limited availability of adequately preserved human brain tissue samples and the inability to follow the process of AHN in vivo [26]. Erikkson et al. showed that several months after the incorporation of BrdU into the adult human DG, BrdU-positive cells coexpressed several neuronal markers and entered the neuronal lineage [21]. Although this seminal study was the first to demonstrate AHN in humans, it did not provide insight into the extent and dynamics of the process. Subsequent studies turned to quantifying the number of cells expressing the neuronal precursor (neuroblast) marker doublecortin (DCX) to estimate the extent of AHN in humans [27,28]. Finally, in 2013, Spalding et al. provided a detailed view of the hippocampal neurons turnover dynamics using nuclear-bomb-test-derived ^{14}C [29]. This innovative approach showed substantial neurogenesis throughout a lifetime, with a modest decline occurring during aging. It also allowed for a comparison to the previous work done in rodents and demonstrated that more hippocampal neurons are subject to exchange in humans than in rodents. These two paramount studies paved the way for the future.

Nowadays, AHN has become one of the fundamental concepts of neurobiology, with Moreno-Jiménez and colleagues recently demonstrating the existence of AHN in the human DG throughout physiological and pathological aging up until the tenth decade of life [5]. Early-life neurogenesis appears robust and gradually declines with age. However, pathological conditions like mild cognitive impairment and AD are accompanied by a significantly sharp decline in AHN levels [5-9]. Association studies examining cognitive performance and the degree of decline in AHN suggest impaired AHN is directly related to cognitive dysfunction in patients [30]. The interest in quantifying AHN in AD patients dates back to the late 1990s, however, it was also hindered by the technological limitations of the time. Investigations into the extent

of AHN in postmortem tissues of AD patients yielded conflicting results (for a detailed review see [31]). The idea being that increased AHN in AD patients points to a self-repair mechanism in the brain where novel endogenous cells are recruited to replace damaged cells and promote recovery. Conversely, decreased AHN might exacerbate hippocampal function and contribute to cognitive dysfunction in AD. If the latter is true, ameliorating inherent AHN in AD patients could hold promise as a treatment to recover or delay learning and memory impairment from the disease.

Indeed, recent papers did show that AHN drops sharply in AD and mild cognitive impairment (MCI) patients compared to healthy-aged individuals [5,30]. This finding shifted the focus to examining whether impaired AHN contributes to cognitive dysfunction and/or other AD pathologies and whether ameliorating AHN could salvage or even improve cognition. Animal loss- and gain- of function studies, where AHN is either ablated or increased, have been the primary tool in examining the therapeutic potential of ameliorating AHN (for a full review see [31]). Notably, loss-of-function studies point to impaired AHN as one of the critical events in early AD pathogenesis that exacerbates cognitive dysfunction and mediates other symptoms. Conversely, gain-of-function studies show that increasing AHN betters cognitive functions even in the presence of stable Aβ pathologies.

The exact underlying molecular mechanisms of AHN impairment remain elusive. Previous studies indicate that the accumulation of Aβ plaques and/or hyperphosphorylated Tau protein leads to impaired AHN [32]. In addition, Terreros-Roncal et al. noted that neurogenic niche disturbances like reduced phagocytic capacity of microglia, astrogliosis, and altered microvasculature of the dentate gyrus lead to AHN impairments as well [33].

Taken together, these findings strongly entail the possibility that therapies targeting AHN may be useful in treating and preventing dementia and AD.

2.1 Exercise as an intervention for ameliorating hippocampal neurogenesis

The neuroscience of exercise is a fascinating intersection of physical activity and brain health, and a rapidly developing area of research. Physical activity can increase blood flow, promote the growth and survival of neurons, reduce inflammation and oxidative stress, improve mood and reduce stress, and promote the growth of new blood vessels. In addition, one key discovery was that the hippocampus exhibits extensive plasticity in response to exercise. The functional importance of newly formed neurons in the hippocampus depends on their control and regulation by a wide range of stimuli, encompassing both behavioral and biological factors [34]. Exercise has been demonstrated to have a particularly strong positive effect on AHN [10,11]. However, this effect was not observed in the SGZ, the other neurogenic niche [12,33]. The first discovery that running boosts neurogenesis in the DG of the rodent hippocampus and thereby enhances learning and memory came in 1999 [10,11]. Moreover, in a mice strain 129SvEv which exhibits high variation in individual voluntary running distances, research showed a positive correlation between the distance ran and the number of new cells born and their survival. However, the same year, Rhodes and colleagues showed a lack of association between running distance in hyperactive mice and the number of cells produced [36]. Thus showing hyperactivity may be associated with neurological deficits that affect brain function [36]. Subsequent studies have revealed hippocampal neurogenesis in response to exercise to be a robust phenomenon [37-39]. Kroonenberg and colleagues established that neurogenesis peaks after 3 days of running, but levels return to baseline after 32 days [40]. However, they also show that the number of immature neurons continues to increase after this time point [40]. Further evidence came from a study by Berg et al. at Johns Hopkins University, who used single-cell lineage tracing and population fate-mapping to report a "continuous" model in which a single precursor population continuously and exclusively contributes to dentate neurogenesis from early embryonic stages to adulthood. Thereby, sustained physical activity seems to keep precursor cell divisions at a level corresponding to a much younger age and

prevent the age-dependent decline in the precursor cell-based potential for adult hippocampal neurogenesis [40]. Moreover, the effects of exercise on HN are not only quantitative but also qualitative. In particular, enhanced mushroom spine density and decreased spine motility are observed during the development of new neurons, even though the total number of dendritic protrusions remains unchanged [41]. Finally, running increases long-term potentiation, an indicator of synaptic transmission and a neuronal correlate of learning and memory, in both voluntary running and forced exercise paradigms [42,43].

Taken together with studies reporting human AHN, these data point to a therapeutic potential of boosting AHN with exercise in humans. Moreover, several studies using an antibody for the immature neuron marker, DCX, have discovered potential neuronal progenitors expressed throughout human DG in response to exercise [5,24,44]. Indeed, long-term human studies consistently show that exercise reduces age-related cognitive decline and AD and dementia risk [45,46]. Despite this, the National Academies report in 2017 deemed evidence from human studies as inconclusive for preventing cognitive decline and insufficient to recommend exercise for reducing the risk of dementia [47]. Their resolution was based on the inconsistency of cognitive benefits in randomized controlled trials (RCTs), and the lack of correspondence between cognitive change, and changes in intervention-induced biomarkers of brain dysfunction [48,49]. Therefore, further exploration of the relationship between exercise and cognitive preservation in older adults could hold substantial societal and economic value, given the widely accessible and health-promoting nature of exercise.

Thus far, best understood was the close association between trophic factors and exercise benefits on the brain. Most notably, brain-derived neurotrophic factor (BDNF) plays an essential role in neurogenesis, cell proliferation and survival, synaptic plasticity, and neurite outgrowth. Knockdowns or deficits of BDNF or its receptor tyrosine receptor kinase B (TrkB) lead to impaired memory function [50]. BDNF acts on downstream targets cAMP-response element binding (CREB) protein, synapsin I, and synaptophysin, while simultaneously increasing its own messenger RNA (mRNA) and its receptor tyrosine kinase B (TrkB) [51]. In rodents, exercise upregulates hippocampal BDNF/TrkB mRNA and protein expression after both short (2–7 days) and long (1–8 months) periods across a range of intensities, exercise, and housing conditions ([52,53]; for review, see [54]). Blocking hippocampal BDNF or ablating the TrkB receptor prevents neurogenesis and impairs cognitive performance [55,56]. In humans, exercise-induced increase in levels of serum BDNF are associated with increased hippocampal volume [57]. Conversely, reduced serum BDNF levels are associated with age-related decline in hippocampal volume [58]. Non-neuronal cells, astrocytes, produce BDNF and express TrkB, thus supporting the development of new neurons [59]. Exercise upregulates the number of astrocytes, lengthens their cell processes, and increases cell body size, thereby likely mediating the exercise-induced changes in BDNF levels [60]. In addition, microglial number is downregulated by exercise [61]. However, complete ablation of microglia impairs HN [62]. Thereby indicating that an interplay of cytokines produced by microglia may be required to maintain the neurogenic process. Notably, the downregulation in microglial number contributes to halting inflammation-induced reduction in AHN [61]. Finally, exercise-induced BDNF levels appear to also be mediated by epigenetic changes. Exercise promotes histone H3 acetylation [63] and downregulates hippocampal histone deacetylases (HDAC) [64], which in turn upregulates BDNF gene expression [65].

Moreover, the blood-brain barrier (BBB), a highly specialized and selective barrier formed by brain endothelial cells (BECs), plays a crucial role in the passage of substances from the bloodstream into the brain. Blood plasma proteins abundantly cross from the periphery to the brain in healthy young adult mice via BECs [66]. However, this bulk uptake of blood plasma proteins is significantly reduced in aged mice due to a shift from a receptor-mediated to a less specific BEC transcytosis [66]. Type 1 cells of the adult DG reside

in a vascular niche and directly contact blood vessels [67]. Hence, blood plasma is likely a significant mode of communication between acute systemic changes in the periphery and the hippocampus.
Exercise improves cerebrovasculature. Improved vasculature results in enhanced perfusion, leading to the more efficient delivery of oxygen, nutrients, neurotrophins, and other substances that can support and enhance brain function. Exercise-mediated modulation in cerebral blood flow (CBF) has been observed in the hippocampus (as well as cortex and striatum) but not the other neurogenic niche, the olfactory bulb [68,69]. The exercise intensity and duration differentially modulate the increase in CBF [69-71]. Prolonged exercise improves CBF and cerebrovascular plasticity by promoting neovascularization and angiogenesis [72,73], and the effects persist in old animals [74]. Previous work has reported exercise-mediated improvement in increased vascular density and pericyte coverage of endothelial cells [74], as well as reduced vascular leakage [75].
Vascular endothelial growth factor (VEGF) likely plays a key role in mediating exercise-induced vascular plasticity, adult neurogenesis, and communication between peripheral tissues and the brain [38,76,77]. VEGF is a neurotrophin produced in multiple tissue types whose primary function is to stimulate the production of new blood vessels. Pharmacologically inhibiting VEGF precludes exercise-induced improvement in AHN [38], indicating that VEGF may be produced by a distant peripheral origin outside of the hippocampus [78]. The actual source of VEGF release remains elusive; however, muscle appears to be the best candidate considering 60-90% of peripheral VEGF is produced there [79]. Furthermore, Licht and colleagues have shown that even short-term exposure to VEGF attenuates age-related HN decline. Long-term exposure, on the other hand, has the potential to morphologically remodel NSCs, resembling a "juvenile" pattern of NSC and blood vessel engagements [80]. Therefore, the exercise-induced increase in VEGF is one of the factors contributing to long-term neurogenic enhancement.
In addition, changes in complement and coagulation cascades have recently also been implicated as the effects of exercise and in reducing neuroinflammation [81]. For example, In AD, the complement pathway is activated, and inhibiting the complement proteins C1q or C3 reduces neuroinflammation, the toxic effect of Aβ plaques, and attenuates synapse loss [59].

2.2 Exerkines and Hippocampal Neurogenesis

Due to its paramount role in our perception and sense of self, the brain is frequently considered isolated from the body, emphasizing its profound significance in shaping our identity and experiences. However, this is far from true. Recent improvements in proteomic approaches and single-cell RNA-sequencing technologies have begun to elucidate the intertissue communication between the periphery and the brain. Heterochronic parabiosis studies, in which a young and an aged animal's circulatory systems are surgically connected, have been particularly instrumental in shedding light on this topic. Heterochronic parabiosis studies have previously shown that young blood-borne factors mediate the rejuvenation of aged muscle, liver, heart, pancreas, bone, spinal cord, and brain, leading to increased life and healthspan. The effects on the brain include increased hippocampal and subventricular zone neurogenesis, synaptic plasticity and synaptic density, vascular density and cerebral blood flow, and attenuation of cellular senescence markers within the forebrain. Furthermore, heterochronic bone marrow transplantation from young to aged animals increased synaptic density, attenuated microglial activation, and enhanced hippocampus-dependent cognitive function in aged mice. Thereby showing that along with the cell-intrinsic mechanisms, the systemic environment also plays a vital role in brain health (for a full review see [82]).
Similarly, systemic and lifestyle interventions such as exercise and caloric restriction have shown wide-ranging rejuvenating effects on the brain due to interactions with the circulatory system [83,84]. Recent work has begun to decode individual components in exercising blood plasma and decipher their influence on AHN. Several peripheral organs and their respective metabolic energy metabolism pathways have been related to eliciting and coordinating the adaptive responses to exercise in the brain. Systemic factors

released from the periphery in response to exercise are collectively termed "exerkines". Peripheral organs involved and their respective exerkines are muscle (myokines), liver (hepatokines), and adipose tissue (adipokines). However, adipose tissue remains an understudied area and will therefore be excluded from this thesis (for a review see [85]). The mechanism via which these factors influence hippocampal neurotrophin and neurogenesis levels and memory function remains to be completely illuminated.

Consequently, these findings challenge the prevailing notion that brain aging is an irreversible process. The arising hypothesis states that the molecular players that mediate the beneficial effects of exercise on the brain serve the dual purpose of an energy fuel and modulators that affect hippocampal gene expression. Hence, this chapter will provide an overview of the main peripheral blood factors involved in transferring the positive effects of exercise to the hippocampal neurogenesis, thus ameliorating cognitive decline in health and disease.
Notably, while previous research discovered a series of muscle-derived myokines, recently, the focus shifted to the liver. The liver is the essential hub for numerous physiological and metabolic processes. As a novel series of exercise-induced hepatokines have been identified, the interest in the function of the liver as a major secretory organ is rapidly growing [13]. Furthermore, awareness is growing that liver dysfunction is an early event in AD, and its role as a potential therapeutic target for AD appears prospective [86].

2.3 Muscle and myokines

The idea that skeletal muscle releases cytokines that might be linked to neural plasticity came from the observations that patients with myopathies suffer significant cognitive deficits [87-89]. Subsequently, Kobilo and colleagues examined a potential link between endurance exercise and cognitive function, namely hippocampus-mediated spatial memory [90]. Treating L6 mice with an AMPK (muscle "master regulator") agonist AICAR led to significant improvements in spatial memory, which were precluded by muscle-specific AMPK a2-subunit deficiency [90], thereby establishing the link between muscle and hippocampal cognition. In the following study, Moon and colleagues identified a novel myokine, cathepsin B (Ctsb), as the mediator of exercise-induced hippocampal plasticity [91]. Ctsb is a lysosomal thiol proteinase that has up to that point been studied exclusively in relation to pathological processes in the brain. Alzheimer's disease (AD) mouse model studies yielded contradictory results [92,93]. However, applying Ctsb to adult hippocampal progenitor cell cultures induced the expression of BDNF and DCX, thereby confirming the neurogenic role of Ctsb [91]. In addition, Moon and colleagues reported impaired spatial memory in Ctsb knockout mice, thus affirming its role in hippocampal function [91].
Furthermore, peroxisome proliferator-activated receptor g coactivator (PGC-1a) is a transcriptional coactivator activated in exercising muscle, and its activation leads to the production of fibronectin type III domain containing 5 (FNDC5), a membrane protein, which is cleaved and secreted as irisin. Irisin is involved in regulating metabolism, promoting the browning of white adipose tissue, and thermogenesis. In the body, FNDC5 is mainly expressed in the brain, including the hippocampus [94]. Interestingly, after thirty days of voluntary exercise, the increase in FNDC5 mRNA was localized in the quadriceps and hippocampus but not the rest of the brain. Importantly, an increase in FNDC5 expression in neurons and peripheral up-regulation of FNDC5 resulted in increases in hippocampal BDNF gene expression [95]. Moreover, an exercise-induced increase in plasma was also demonstrated in humans [96]. 12 weeks of high-intensity aerobic training increased FNDC5 expression in various areas of the brain, hippocampus included [95]. However, some questions remained open. No conclusive data existed on whether the cleaved and secreted part of FNDC5, irisin, or the full-length membrane-bound form FNDC5, was the active moiety, as well as whether muscle-derived or hippocampus-derived irisin is responsible for the cognitive benefits with exercise. Luckily, decisive results came from a study by Islam et al. in 2021 [97]. Mice with a genetic ablation

of FNDC5/Irisin exhibit impaired cognitive function in exercise, aging, and AD. By using an AAV8 vector that only forces expression of irisin but not the parent protein FNDC5, the group showed that irisin is the active moiety and that it can restore cognitive function. Furthermore, peripheral administration of irisin led to elevated central levels of irisin and successfully rescued the cognitive decline in two different mouse models of AD—even after the significant disease progression [97]. To examine the direct effects on AHN, the group used F5KO mice, in which exercise does not increase dendritic complexity, spines size, and number, and an altered transcriptome and neuronal activation [97]. This abnormal AHN is accompanied by impaired pattern separation, which can be rescued by irisin application into the DG, strongly suggesting that dysregulated adult-born neurons are, at least in part, responsible for the defect in cognitive function caused by genetic ablation of Fndc5/irisin. Notably, whether muscle-derived or hippocampus-derived irisin is responsible for the cognitive benefits of exercise remains unknown.

Additionally, the metabolite lactate from exercising muscle reportedly crosses the blood-brain barrier (BBB), enhances BDNF expression and, in turn, promotes learning and memory [98]. Lactate levels have previously been shown to be upregulated in the hippocampus following exercise [99]. The present study identified lactate as a novel endogenous metabolite that links exercise to hippocampal BDNF expression and cognition. Lactate activates the NAD+-dependent histone deacetylase SIRT1, which in turn engages the previously identified hippocampal PGC1a/FNDC5(Irisin) pathway to induce BDNF expression [98]. Lactate activates SIRT1 by altering the NAD+/NADH ratio of neurons, and SIRT1 deacetylates the transcriptional coactivator PGC1a thus promoting its activity [98].

2.4 Liver and Hepatokines

The liver is the largest gland in the body, and it expresses and releases a large number of proteins into the blood. Liver-derived hepatokines mainly regulate glucose and lipid homeostasis [100]. Certain hepatokines have also been identified as mediators of the beneficial effects of exercise on cognitive function. Exercise-induced hepatokines directly boost AHN, ameliorate age-related cognitive dysfunction, and reduce inflammation. Thus, making it tempting to speculate that exercise prompts the liver to induce changes that benefit the brain.

One of the first hepatokines, and exerkines in general, shown to be involved in exercise-induced enhancement of cognitive function was IGF-1. Radiolabeling IGF-1 demonstrated that it crosses BBB via receptor-mediated transport [101]. In rats, IGF-1 administration via a ventricular osmotic minipump ameliorates the age-related cognitive decline in hippocampal tasks [102], and peripheral administration of IGF selectively increases AHN [102]. In humans, acute brief exercise increases plasma levels of IGF-1 in an intensity-dependent manner [103]. Therefore, increased uptake of circulating IGF-I by brain cells after physical exercise is involved in the effects of exercise on AHN [104]. In addition, blocking the IGF-1 receptor in the hippocampus abolished exercise-induced increases in BDNF levels and worsened cognitive performance. However, despite the promising results, a meta-analysis of 115 human studies showed that approx. 50% found no difference in the levels of IGF-1 in response to exercise, rendering it impossible to draw firm conclusions [105]. To make matters worse, depletion of IGF-1 appears to be protective in mouse models of AD. Hence, further research is warranted to determine the role of IGF-1 as a systemic link between exercise and cognition.

Furthermore, b-hydroxybutyrate (BHA), one of three ketone bodies derived from acetyl-CoA, serves as an alternative energy source for the brain, particularly during glucose scarcity [106]. Following exercise, BHA levels in the brain are increased, and in turn increase BDNF expression through HDAC2/HDAC3 inhibition and histone H3 acetylation in the hippocampus [107]. While this provides a physical link between exercise and increased BDNF levels, the study lacks behavioral analyses to draw conclusions about cognitive function.

Fortunately, recent studies have identified a multitude of other exercise-induced hepatokines, thereby strongly pointing to a possible liver-to-brain axis. Given the observation that systemic administration of blood plasma derived from mice that exercised ameliorates age-related impairments in AHN and cognitive function in the aged hippocampus, Horowitz and colleagues set out to identify the exact factors responsible [108]. The group identified glycosylphosphatidylinositol (GPI)–specific phospholipase D1 (GPLD-1) as an exercise-induced hepatokine sufficient to rescue hippocampal function in aged mice. Exercise elevates blood levels of GPLD-1 in both aged mice and healthy elderly humans [108]. This study did not, however, relate increased GPLD-1 levels to improved hippocampal function in humans. Moreover, overexpression of GPLD-1 mRNA in the liver, by using hydrodynamic tail vein injection (HDTVI)–mediated in vivo transfection, recapitulated the benefit of exercise on AHN and cognitive function. The underlying mechanism via which GPLD-1 confers these benefits is likely the result of changes in the coagulation and complement system cascade [108]. In addition, Li and colleagues found that GPLD-1 levels are elevated in long-lived mouse strains, as well as in response to lifespan-extending drugs [109]. Hence, GPLD-1 holds promise for ameliorating age-related decline in neurogenesis and cognition.

Given this observation, a study by De Miguel and colleagues further investigated whether blood plasma from exercising mice contains factors that can benefit not only the old, but also the young, healthy brain [81]. Indeed, administering plasma from exercising mice led to a significant increase in total proliferating cells, DCX+ neuroblasts, and surviving cells in sedentary mice [81]. Mass Spectrometry (MS) identified 235 unique proteins, of which 23 were downregulated and 26 were upregulated in the plasma of running mice [81]. Biological pathway analysis pointed to activation of the complement system's alternative pathways, suggesting that the clotting cascade is overall inhibited in exercising animals [81]. Immunodepleting 4 top differentially expressed proteins from exercising plasma identified a novel exerkine, clusterin (CLU or apolipoprotein J (ApoJ)) [81]. CLU acts as an inhibitor of apoptosis, inflammation, and complement activation [110]. CLU targets hippocampal BECs and binds to its receptor, LDL-like receptor 8 (LRP8), on BECs. CLU broadly reduces interferon signaling and dampens inflammation. In addition, CLU is also expressed in astrocytes, but the levels do not change following exercise. Hence, the main systemic source of CLU is most likely the liver. Consistently with the findings in mice, CLU plasma levels are increased after 6 months of exercise in patients with mild cognitive impairment. This similar anti-inflammatory gene expression profile further implicates the complement and coagulation cascades in exercise-mediated effects [81].

Another primarily liver-derived protein, selenoprotein P (SEPP1), has been shown to mediate exercise-induced enhancement of AHN [111]. A comparison of the proteomic screen on the blood plasma from sedentary and exercising mice yielded 68 proteins as significantly upregulated by exercise [111]. Of which, 25 were selenoproteins, however, SEPP1 is the most important for maintaining selenium levels in the brain. Exercise increases the systemic level of SEPP1, which transports selenium from the systemic environment to NPCs of the DG by binding to the LRP8 receptor on BECs [111]. In the DG, selenium activates quiescent hippocampal NPCs and recruits them into the neurogenic trajectory. Mouse models where either SEPP1 or LRP8 are knocked out exhibit no improvements in AHN, thus showing that both are necessary [111]. Moreover, exercise-induced enhancement in AHN and reversal of age-related cognitive decline can be mimicked by dietary selenium supplementation. Thus, suggesting potential therapeutic relevance for selenium in ameliorating age-related cognitive decline and injury [111].

Factor	Induced by	Effect on hippocampus	Translation to human research	Peripheral source	References
BDNF	*Acute exercise*	*↑neurogenesis* *↑cell proliferation and survival* *↑synaptic plasticity, and neurite outgrowth*	*↑Hippocampus-dependent cognition* *↓Age-related cognitive decline*	*Muscle, heart, liver, platelets, adipose tissue*	*50-65*
VEGF	*Acute exercise*	*↑angiogenesis and CBF* *↑Hippocampal neurogenesis* *↑Synaptic plasticity*	*↑Hippocampus-dependent cognition* *↓Age-related cognitive decline*	*Muscle and other tissues*	*38, 76-80*
CTSB	*Exercise training*	*In vitro: ↑ neurotrophin and DCX expression but not proliferation or survival of NPCs*	*↑Hippocampus-dependent cognition in well-trained adults*	*Muscle*	*91-93*
Irisin	*Aerobic exercise training*	*↑ BDNF and markers of synaptic plasticity* *AD mouse model:* *↑ Synaptic plasticity* *↓ Glial activation*	*↑Hippocampus-dependent cognition in plasma of aerobic exercise-trained adults*	*Muscle*	*94-97*
Lactate	*Acute exercise*	*↑ VEGF* *↑angiogenesis* *↑ Hippocampal BDNF*	*↑Hippocampus-dependent cognition*	*Muscle*	*98,99*
IGF-1	*Acute exercise*	*↑ BDNF and synaptic plasticity* *↑ Neurogenesis*	*↑hippocampus-dependent cognition in aged mice*	*Liver and other tissues*	*101-105*
β-hydroxybutyrate	*Acute exercise*	*↑ CBF* *↑BDNF* *↓Systemic inflammation and ROS*	*↑Hippocampus-dependent cognition*	*Liver*	*106,107*
GPLD-1	*Exercise training*	*↑Hippocampal neurogenesis*	*↑Hippocampus-dependent cognition in older individuals*	*Liver*	*108-109*
Clusterin (ApoJ)	*Exercise training*	*↑ BDNF and markers of synaptic plasticity* *↓ Inflammation*	*↑Hippocampus-dependent cognition in mild cognitive impairment*	*Liver*	*81,110*
SEPP1/selenium	*Acute exercise*	*↑Hippocampal neurogenesis*	*↑Hippocampus-dependent cognition*	*Liver (SEPP1), diet (selenium)*	*111*

Table 1 – List of exercise-induced factors from different peripheral tissues, and their effect on hippocampal state as well as potential translational value for human research.

Discussion and Conclusion

In conclusion, this thesis has explored the relationship between peripheral exerkines and hippocampal neurogenesis, focusing on their potential implications for the treatment of Alzheimer's disease and dementia. The findings highlight the potential of exercise-induced molecules from the liver and muscle to boost hippocampal neurogenesis. Enhanced AHN, in turn, leads to offsetting the cognitive impairment observed in AD and milder forms of dementia. By elucidating the mechanisms underlying this phenomenon, the research paves the way for developing novel therapeutic interventions to promote neurogenesis and thus mitigate cognitive decline in AD.

Moreover, many elderly individuals face limitations that prevent them from engaging in physical activity. Identifying the specific molecules involved in the exercise-induced AHN amelioration allows for mimicking the positive effects of exercise, providing an alternative for those unable to engage in physical activity. Such molecular players could serve as promising therapeutic agents to enhance cognitive function, promote neuroplasticity, and potentially slow down the progression of age-related cognitive decline, ultimately improving the quality of life for elderly individuals affected by these conditions.

Despite many questions regarding 'how' exercise benefits the brain remaining unanswered, the field of evolutionary neuroscience has postulated a hypothesis as to 'why' [112]. Around 2 million years ago, a notable shift in human evolution occurred, characterized by a transition from comparatively lower aerobic physical activity to increased activity levels [113]. The transition was prompted by a changing climate that compelled our predecessors to move away from densely forested environments towards more open habitats [113,114]. This change necessitated hunting and foraging for foods scattered across varying distances. Consequently, it potentially demanded enhanced spatial navigation, memory, and attention skills. The connection between the cognitive requirements of foraging and exercise may have exerted a significant evolutionary force that led to exercise-induced neurogenesis. It may have also influenced the changes in cortical connectivity by promoting synaptogenesis and myelination. Thus, cognitive demands of novelty and exploration may be the key link between physical activity and AHN. That is not to say exercise alone is insufficient to induce physiological changes in the AHN, however, there appears to be an increased effect on neuronal survival when physical and cognitive challenges are combined. In support, studies where the cognitive task is thematically linked to the exercise session have shown promising results [115-117]. For instance, Anderson-Hanley et al. reported that three months of exercise on a stationary bike in a virtual environment significantly improved executive functions and increased BDNF levels compared to controls exercising on a stationary bike with no cognitive stimulation [115].

Finally, elucidating the precise signaling pathways and interactions of peripheral exerkines with the hippocampus and other brain regions will provide invaluable insights into their neurogenic potential and therapeutic implications. Investigations into the molecular cascades triggered by peripheral exerkines can aid in uncovering potential synergistic effects with existing therapeutic strategies for Alzheimer's and dementia. Additionally, exploring the temporal dynamics, dosage effects, and long-term consequences of these molecules on neurogenesis and cognitive function is crucial for developing safe and effective interventions. Therefore, continued research efforts are warranted to unlock the full therapeutic potential of these exercise-induced molecules and translate them into targeted interventions that can benefit individuals suffering from neurodegenerative disorders.

Reference List

1. United Nations Department of Economic and Social Affairs. (2019). World population ageing 2019. Retrieved from https://www.un.org/en/development/desa/population/publications/pdf/ageing/WorldPopulationAgeing2019-Report.pdf
2. Jia, J., Wei, C., Chen, S., Li, F., Tang, Y., Qin, W., Zhao, L., Jin, H., Xu, H., Wang, F., Zhou, A., Zuo, X., Wu, L., Han, Y., Han, Y., Huang, L., Wang, Q., Li, D., Chu, C., Shi, L., … Gauthier, S. (2018). The cost of Alzheimer's disease in China and re-estimation of costs worldwide. Alzheimer's & dementia : the journal of the Alzheimer's Association, 14(4), 483–491. https://doi.org/10.1016/j.jalz.2017.12.006
3. Gustavsson, A, Norton, N, Fast, T, et al. Global estimates on the number of persons across the Alzheimer's disease continuum. Alzheimer's Dement. 2023; 19: 658– 670. https://doi.org/10.1002/alz.12694
4. Tanzi, R. E., & Bertram, L. (2005). Twenty years of the Alzheimer's disease amyloid hypothesis: a genetic perspective. Cell, 120(4), 545–555. https://doi.org/10.1016/j.cell.2005.02.008
5. Moreno-Jiménez, E. P., Flor-García, M., Terreros-Roncal, J., Rábano, A., Cafini, F., Pallas-Bazarra, N., Ávila, J., & Llorens-Martín, M. (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. https://doi.org/10.1038/s41591-019-0375-9
6. Choi, S. H., & Tanzi, R. E. (2019). Is Alzheimer's Disease a Neurogenesis Disorder?. Cell stem cell, 25(1), 7–8. https://doi.org/10.1016/j.stem.2019.06.001
7. Lemprière S. (2019). Birth of hippocampal neurons declines in Alzheimer disease. Nature reviews. Neurology, 15(5), 245. https://doi.org/10.1038/s41582-019-0182-4
8. Tobin, M. K., Musaraca, K., Disouky, A., Shetti, A., Bheri, A., Honer, W. G., Kim, N., Dawe, R. J., Bennett, D. A., Arfanakis, K., & Lazarov, O. (2019). Human Hippocampal Neurogenesis Persists in Aged Adults and Alzheimer's Disease Patients. Cell stem cell, 24(6), 974–982.e3. https://doi.org/10.1016/j.stem.2019.05.003
9. Zhou, Y., Su, Y., Li, S., Kennedy, B. C., Zhang, D. Y., Bond, A. M., Sun, Y., Jacob, F., Lu, L., Hu, P., Viaene, A. N., Helbig, I., Kessler, S. K., Lucas, T., Salinas, R. D., Gu, X., Chen, H. I., Wu, H., Kleinman, J. E., … Song, H. (2022). Molecular landscapes of human hippocampal immature neurons across lifespan. Nature, 607, 527–533. https://doi.org/10.1038/ s41586-022-04912-w
10. g, 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. https://doi.org/10.1038/6368
11. van Praag, H., Christie, B. R., Sejnowski, T. J., & Gage, F. H. (1999). Running enhances neurogenesis, learning, and long-term potentiation in mice. Proceedings of the National Academy of Sciences of the United States of America, 96(23), 13427–13431. https://doi.org/10.1073/pnas.96.23.13427
12. - Brown, J., Cooper-Kuhn, C. M., Kempermann, G., Van Praag, H., Winkler, J., Gage, F. H., & Kuhn, H. G. (2003). Enriched environment and physical activity stimulate hippocampal but not olfactory bulb neurogenesis. The European journal of neuroscience, 17(10), 2042–2046. https://doi.org/10.1046/j.1460-9568.2003.02647.x
13. Bieri, G., Schroer, A. B., & Villeda, S. A. (2023). Blood-to-brain communication in aging and rejuvenation. Nature neuroscience, 26(3), 379–393. https://doi.org/10.1038/s41593-022-01238-8

14. Kempermann, G., Song, H. and Gage, F.H. (2023), Adult neurogenesis in the hippocampus. Hippocampus, 33: 269-270. https://doi-org.proxy-ub.rug.nl/10.1002/hipo.23525
15. Ming, G. L., & Song, H. (2005). Adult neurogenesis in the mammalian central nervous system. Annual review of neuroscience, 28, 223–250. https://doi.org/10.1146/annurev.neuro.28.051804.101459
16. Altman, J., & Das, G. D. (1965). Autoradiographic and histological evidence of postnatal hippocampal neurogenesis in rats. The Journal of comparative neurology, 124(3), 319–335. https://doi.org/10.1002/cne.901240303
17. Paton, J. A., & Nottebohm, F. N. (1984). Neurons generated in the adult brain are recruited into functional circuits. Science (New York, N.Y.), 225(4666), 1046–1048. https://doi.org/10.1126/science.6474166
18. 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. The Journal of neuroscience: the official journal of the Society for Neuroscience, 16(6), 2027–2033. https://doi.org/10.1523/JNEUROSCI.16-06-02027.1996
19. Lois, C., & Alvarez-Buylla, A. (1994). Long-distance neuronal migration in the adult mammalian brain. Science (New York, N.Y.), 264(5162), 1145–1148. https://doi.org/10.1126/science.8178174
20. Lois, C., García-Verdugo, J. M., & Alvarez-Buylla, A. (1996). Chain migration of neuronal precursors. Science (New York, N.Y.), 271(5251), 978–981. https://doi.org/10.1126/science.271.5251.978
21. 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. https://doi.org/10.1038/3305
22. Cipriani, S., Ferrer, I., Aronica, E., Kovacs, G. G., Verney, C., Nardelli, J., Khung, S., Delezoide, A. L., Milenkovic, I., Rasika, S., Manivet, P., Benifla, J. L., Deriot, N., Gressens, P., & Adle-Biassette, H. (2018). Hippocampal Radial Glial Subtypes and Their Neurogenic Potential in Human Fetuses and Healthy and Alzheimer's Disease Adults. Cerebral cortex (New York, N.Y. : 1991), 28(7), 2458–2478. https://doi.org/10.1093/cercor/bhy096
23. Sorrells, S. F., Paredes, M. F., Cebrian-Silla, A., Sandoval, K., Qi, D., Kelley, K. W., James, D., Mayer, S., Chang, J., Auguste, K. I., Chang, E. F., Gutierrez, A. J., Kriegstein, A. R., Mathern, G. W., Oldham, M. C., Huang, E. J., Garcia-Verdugo, J. M., Yang, Z., & Alvarez-Buylla, A. (2018). Human hippocampal neurogenesis drops sharply in children to undetectable levels in adults. Nature, 555(7696), 377–381. https://doi.org/10.1038/nature25975
24. Boldrini, M., Fulmore, C. A., Tartt, A. N., Simeon, L. R., Pavlova, I., Poposka, V., Rosoklija, G. B., Stankov, A., Arango, V., Dwork, A. J., Hen, R., & Mann, J. J. (2018). Human Hippocampal Neurogenesis Persists throughout Aging. Cell stem cell, 22(4), 589–599.e5. https://doi.org/10.1016/j.stem.2018.03.015
25. Knoth, R., Singec, I., Ditter, M., Pantazis, G., Capetian, P., Meyer, R. P., Horvat, V., Volk, B., & Kempermann, G. (2010). Murine features of neurogenesis in the human hippocampus across the lifespan from 0 to 100 years. PloS one, 5(1), e8809. https://doi.org/10.1371/journal.pone.0008809
26. Kempermann, G., Gage, F. H., Aigner, L., Song, H., Curtis, M. A., Thuret, S., Kuhn, H. G., Jessberger, S., Frankland, P. W., Cameron, H. A., Gould, E., Hen, R., Abrous, D. N., Toni, N., Schinder, A. F., Zhao, X., Lucassen, P. J., & Frisén, J. (2018). Human Adult Neurogenesis: Evidence and Remaining Questions. Cell stem cell, 23(1), 25–30. https://doi.org/10.1016/j.stem.2018.04.004

27. Knoth, R., Singec, I., Ditter, M., Pantazis, G., Capetian, P., Meyer, R. P., Horvat, V., Volk, B., & Kempermann, G. (2010). Murine features of neurogenesis in the human hippocampus across the lifespan from 0 to 100 years. PloS one, 5(1), e8809. https://doi.org/10.1371/journal.pone.0008809
28. Wang, C., Liu, F., Liu, Y. Y., Zhao, C. H., You, Y., Wang, L., Zhang, J., Wei, B., Ma, T., Zhang, Q., Zhang, Y., Chen, R., Song, H., & Yang, Z. (2011). Identification and characterization of neuroblasts in the subventricular zone and rostral migratory stream of the adult human brain. Cell research, 21(11), 1534–1550. https://doi.org/10.1038/cr.2011.83
29. Spalding, K. L., Bergmann, O., Alkass, K., Bernard, S., Salehpour, M., Huttner, H. B., Boström, E., Westerlund, I., Vial, C., Buchholz, B. A., Possnert, G., Mash, D. C., Druid, H., & Frisén, J. (2013). Dynamics of hippocampal neurogenesis in adult humans. Cell, 153(6), 1219–1227. https://doi.org/10.1016/j.cell.2013.05.002
30. Tobin, M. K., Musaraca, K., Disouky, A., Shetti, A., Bheri, A., Honer, W. G., Kim, N., Dawe, R. J., Bennett, D. A., Arfanakis, K., & Lazarov, O. (2019). Human Hippocampal Neurogenesis Persists in Aged Adults and Alzheimer's Disease Patients. Cell stem cell, 24(6), 974–982.e3. https://doi.org/10.1016/j.stem.2019.05.003
31. Choi, S. H., & Tanzi, R. E. (2023). Adult neurogenesis in Alzheimer's disease. Hippocampus, 33(4), 307– 321. https://doi.org/10.1002/hipo.23504
32. Farioli-Vecchioli, S., Ricci, V., & Middei, S. (2022). Adult hippocampal neurogenesis in Alzheimer's disease: An overview of human and animal studies with implications for therapeutic perspectives aimed at memory recovery. Neural Plasticity, 2022, 9959044. https://doi.org/10. 1155/2022/9959044
33. Terreros-Roncal, J., Moreno-Jimenez, E. P., Flor-Garcia, M., RodriguezMoreno, C. B., Trinchero, M. F., Cafini, F., Rabano, A., & LlorensMartin, M. (2021). Impact of neurodegenerative diseases on human adult hippocampal neurogenesis. Science, 374, 1106–1113. https:// doi.org/10.1126/science.abl5163
34. Eisinger, B. E., & Zhao, X. (2018). Identifying molecular mediators of environmentally enhanced neurogenesis. Cell and tissue research, 371(1), 7–21. https://doi.org/10.1007/s00441-017-2718-5
35. - Leiter, O., Seidemann, S., Overall, R. W., Ramasz, B., Rund, N., Schallenberg, S., Grinenko, T., Wielockx, B., Kempermann, G., & Walker, T. L. (2019). Exercise-Induced Activated Platelets Increase Adult Hippocampal Precursor Proliferation and Promote Neuronal Differentiation. Stem cell reports, 12(4), 667–679. https://doi.org/10.1016/j.stemcr.2019.02.009
36. Rhodes, J. S., Hosack, G. R., Girard, I., Kelley, A. E., Mitchell, G. S., & Garland, T., Jr (2001). Differential sensitivity to acute administration of cocaine, GBR 12909, and fluoxetine in mice selectively bred for hyperactive wheel-running behavior. Psychopharmacology, 158(2), 120–131. https://doi.org/10.1007/s002130100857
37. Trejo, J. L., Carro, E., & Torres-Aleman, I. (2001). Circulating insulin-like growth factor I mediates exercise-induced increases in the number of new neurons in the adult hippocampus. The Journal of neuroscience : the official journal of the Society for Neuroscience, 21(5), 1628–1634. https://doi.org/10.1523/JNEUROSCI.21-05-01628.2001
38. Fabel, K., Fabel, K., Tam, B., Kaufer, D., Baiker, A., Simmons, N., Kuo, C. J., & Palmer, T. D. (2003). VEGF is necessary for exercise-induced adult hippocampal neurogenesis. The European journal of neuroscience, 18(10), 2803–2812. https://doi.org/10.1111/j.1460-9568.2003.03041.x
39. Kitamura, T., Mishina, M., & Sugiyama, H. (2003). Enhancement of neurogenesis by running wheel exercises is suppressed in mice lacking NMDA receptor epsilon 1 subunit. Neuroscience research, 47(1), 55–63. https://doi.org/10.1016/s0168-0102(03)00171-8

40. Kronenberg, G., Bick-Sander, A., Bunk, E., Wolf, C., Ehninger, D., & Kempermann, G. (2006). Physical exercise prevents age-related decline in precursor cell activity in the mouse dentate gyrus. Neurobiology of aging, 27(10), 1505–1513. https://doi.org/10.1016/j.neurobiolaging.2005.09.016
41. Zhao, C., Teng, E. M., Summers, R. G., Jr, Ming, G. L., & Gage, F. H. (2006). Distinct morphological stages of dentate granule neuron maturation in the adult mouse hippocampus. The Journal of neuroscience : the official journal of the Society for Neuroscience, 26(1), 3–11. https://doi.org/10.1523/JNEUROSCI.3648-05.2006
42. Farmer, J., Zhao, X., van Praag, H., Wodtke, K., Gage, F. H., & Christie, B. R. (2004). Effects of voluntary exercise on synaptic plasticity and gene expression in the dentate gyrus of adult male Sprague-Dawley rats in vivo. Neuroscience, 124(1), 71–79. https://doi.org/10.1016/j.neuroscience.2003.09.029
43. O'Callaghan, R. M., Ohle, R., & Kelly, A. M. (2007). The effects of forced exercise on hippocampal plasticity in the rat: A comparison of LTP, spatial- and non-spatial learning. Behavioural brain research, 176(2), 362–366. https://doi.org/10.1016/j.bbr.2006.10.018
44. Lourenco MV, Frozza RL, de Freitas GB, Zhang H, Kincheski GC, Ribeiro FC, Goncalves RA, Clarke JR, Beckman D, Staniszewski A, Berman H, Guerra LA, Forny-Germano L, Meier S, Wilcock DM, de Souza JM, Alves-Leon S, Prado VF, Prado MAM, Abisambra JF, Tovar-Moll F, Mattos P, Arancio O, Ferreira ST, De Felice FG. Exercise-linked FNDC5/irisin rescues synaptic plasticity and memory defects in Alzheimer's models. Nat Med. 2019;25:165–75. https://doi.org/10.1038/s41591-018-0275-4.
45. Beydoun, M. A., Beydoun, H. A., Gamaldo, A. A., Teel, A., Zonderman, A. B., & Wang, Y. (2014). Epidemiologic studies of modifiable factors associated with cognition and dementia: systematic review and meta-analysis. BMC public health, 14, 643. https://doi.org/10.1186/1471-2458-14-643
46. Blondell, S. J., Hammersley-Mather, R., & Veerman, J. L. (2014). Does physical activity prevent cognitive decline and dementia?: A systematic review and meta-analysis of longitudinal studies. BMC public health, 14, 510. https://doi.org/10.1186/1471-2458-14-510
47. National Academies of Sciences, Engineering, and Medicine, Health and Medicine Division, Board on Health Sciences Policy, Committee on Preventing Dementia and Cognitive Impairment, Downey, A., Stroud, C., Landis, S., & Leshner, A. I. (Eds.). (2017). Preventing Cognitive Decline and Dementia: A Way Forward. National Academies Press (US).
48. Sink, K. M., Espeland, M. A., Castro, C. M., Church, T., Cohen, R., Dodson, J. A., Guralnik, J., Hendrie, H. C., Jennings, J., Katula, J., Lopez, O. L., McDermott, M. M., Pahor, M., Reid, K. F., Rushing, J., Verghese, J., Rapp, S., Williamson, J. D., & LIFE Study Investigators (2015). Effect of a 24-Month Physical Activity Intervention vs Health Education on Cognitive Outcomes in Sedentary Older Adults: The LIFE Randomized Trial. JAMA, 314(8), 781–790. https://doi.org/10.1001/jama.2015.9617
49. Barnes, D. E., Santos-Modesitt, W., Poelke, G., Kramer, A. F., Castro, C., Middleton, L. E., & Yaffe, K. (2013). The Mental Activity and eXercise (MAX) trial: a randomized controlled trial to enhance cognitive function in older adults. JAMA internal medicine, 173(9), 797–804. https://doi.org/10.1001/jamainternmed.2013.189
50. Heldt, S. A., Stanek, L., Chhatwal, J. P., & Ressler, K. J. (2007). Hippocampus-specific deletion of BDNF in adult mice impairs spatial memory and extinction of aversive memories. Molecular psychiatry, 12(7), 656–670. https://doi.org/10.1038/sj.mp.4001957
51. Vaynman, S., Ying, Z., & Gomez-Pinilla, F. (2003). Interplay between brain-derived neurotrophic factor and signal transduction modulators in the regulation of the effects of exercise on synaptic-plasticity. Neuroscience, 122(3), 647–657. https://doi.org/10.1016/j.neuroscience.2003.08.001

52. Neeper, S. A., Gómez-Pinilla, F., Choi, J., & Cotman, C. (1995). Exercise and brain neurotrophins. Nature, 373(6510), 109. https://doi.org/10.1038/373109a0
53. Freitas, D. A., Rocha-Vieira, E., Soares, B. A., Nonato, L. F., Fonseca, S. R., Martins, J. B., Mendonça, V. A., Lacerda, A. C., Massensini, A. R., Poortamns, J. R., Meeusen, R., & Leite, H. R. (2018). High intensity interval training modulates hippocampal oxidative stress, BDNF and inflammatory mediators in rats. Physiology & behavior, 184, 6–11. https://doi.org/10.1016/j.physbeh.2017.10.027
54. Voss, M. W., Vivar, C., Kramer, A. F., & van Praag, H. (2013). Bridging animal and human models of exercise-induced brain plasticity. Trends in cognitive sciences, 17(10), 525–544. https://doi.org/10.1016/j.tics.2013.08.001
55. Vaynman, S., Ying, Z., & Gomez-Pinilla, F. (2004). Hippocampal BDNF mediates the efficacy of exercise on synaptic plasticity and cognition. The European journal of neuroscience, 20(10), 2580–2590. https://doi.org/10.1111/j.1460-9568.2004.03720.x
56. Li, Y., Luikart, B. W., Birnbaum, S., Chen, J., Kwon, C. H., Kernie, S. G., Bassel-Duby, R., & Parada, L. F. (2008). TrkB regulates hippocampal neurogenesis and governs sensitivity to antidepressive treatment. Neuron, 59(3), 399–412. https://doi.org/10.1016/j.neuron.2008.06.023
57. Erickson, K. I., Voss, M. W., Prakash, R. S., Basak, C., Szabo, A., Chaddock, L., Kim, J. S., Heo, S., Alves, H., White, S. M., Wojcicki, T. R., Mailey, E., Vieira, V. J., Martin, S. A., Pence, B. D., Woods, J. A., McAuley, E., & Kramer, A. F. (2011). Exercise training increases size of hippocampus and improves memory. Proceedings of the National Academy of Sciences of the United States of America, 108(7), 3017–3022. https://doi.org/10.1073/pnas.1015950108
58. Erickson, K. I., Prakash, R. S., Voss, M. W., Chaddock, L., Heo, S., McLaren, M., Pence, B. D., Martin, S. A., Vieira, V. J., Woods, J. A., McAuley, E., & Kramer, A. F. (2010). Brain-derived neurotrophic factor is associated with age-related decline in hippocampal volume. The Journal of neuroscience : the official journal of the Society for Neuroscience, 30(15), 5368–5375. https://doi.org/10.1523/JNEUROSCI.6251-09.2010
59. Miklic, S., Juric, D. M., & Carman-Krzan, M. (2004). Differences in the regulation of BDNF and NGF synthesis in cultured neonatal rat astrocytes. International journal of developmental neuroscience : the official journal of the International Society for Developmental Neuroscience, 22(3), 119–130. https://doi.org/10.1016/j.ijdevneu.2004.03.001
60. Saur, L., Baptista, P. P., de Senna, P. N., Paim, M. F., do Nascimento, P., Ilha, J., Bagatini, P. B., Achaval, M., & Xavier, L. L. (2014). Physical exercise increases GFAP expression and induces morphological changes in hippocampal astrocytes. Brain structure & function, 219(1), 293–302. https://doi.org/10.1007/s00429-012-0500-8
61. Gebara, E., Sultan, S., Kocher-Braissant, J., & Toni, N. (2013). Adult hippocampal neurogenesis inversely correlates with microglia in conditions of voluntary running and aging. Frontiers in neuroscience, 7, 145. https://doi.org/10.3389/fnins.2013.00145
62. Vukovic, J., Colditz, M. J., Blackmore, D. G., Ruitenberg, M. J., & Bartlett, P. F. (2012). Microglia modulate hippocampal neural precursor activity in response to exercise and aging. The Journal of neuroscience : the official journal of the Society for Neuroscience, 32(19), 6435–6443. https://doi.org/10.1523/JNEUROSCI.5925-11.2012
63. Ieraci, A., Mallei, A., Musazzi, L., & Popoli, M. (2015). Physical exercise and acute restraint stress differentially modulate hippocampal brain-derived neurotrophic factor transcripts and epigenetic mechanisms in mice. Hippocampus, 25(11), 1380–1392. https://doi.org/10.1002/hipo.22458
64. Abel, J. L., & Rissman, E. F. (2013). Running-induced epigenetic and gene expression changes in the adolescent brain. International journal of developmental neuroscience : the official journal

of the International Society for Developmental Neuroscience, 31(6), 382–390. https://doi.org/10.1016/j.ijdevneu.2012.11.002
65. Intlekofer, K. A., & Cotman, C. W. (2013). Exercise counteracts declining hippocampal function in aging and Alzheimer's disease. Neurobiology of disease, 57, 47–55. https://doi.org/10.1016/j.nbd.2012.06.011
66. Yang, A. C., Stevens, M. Y., Chen, M. B., Lee, D. P., Stähli, D., Gate, D., Contrepois, K., Chen, W., Iram, T., Zhang, L., Vest, R. T., Chaney, A., Lehallier, B., Olsson, N., du Bois, H., Hsieh, R., Cropper, H. C., Berdnik, D., Li, L., Wang, E. Y., … Wyss-Coray, T. (2020). Physiological blood-brain transport is impaired with age by a shift in transcytosis. Nature, 583(7816), 425–430. https://doi.org/10.1038/s41586-020-2453-z
67. Hong, S., Beja-Glasser, V. F., Nfonoyim, B. M., Frouin, A., Li, S., Ramakrishnan, S., Merry, K. M., Shi, Q., Rosenthal, A., Barres, B. A., Lemere, C. A., Selkoe, D. J., & Stevens, B. (2016). Complement and microglia mediate early synapse loss in Alzheimer mouse models. Science (New York, N.Y.), 352(6286), 712–716. https://doi.org/10.1126/science.aad8373
68. Nishijima, T., Okamoto, M., Matsui, T., Kita, I., & Soya, H. (2012). Hippocampal functional hyperemia mediated by NMDA receptor/NO signaling in rats during mild exercise. Journal of applied physiology (Bethesda, Md. : 1985), 112(1), 197–203. https://doi.org/10.1152/japplphysiol.00763.2011
69. Nishijima, T., Torres-Aleman, I., & Soya, H. (2016). Exercise and cerebrovascular plasticity. Progress in brain research, 225, 243–268. https://doi.org/10.1016/bs.pbr.2016.03.010
70. Nishijima, T., & Soya, H. (2006). Evidence of functional hyperemia in the rat hippocampus during mild treadmill running. Neuroscience research, 54(3), 186–191. https://doi.org/10.1016/j.neures.2005.11.005
71. Nakajima, K., Uchida, S., Suzuki, A., Hotta, H., & Aikawa, Y. (2003). The effect of walking on regional blood flow and acetylcholine in the hippocampus in conscious rats. Autonomic neuroscience : basic & clinical, 103(1-2), 83–92. https://doi.org/10.1016/s1566-0702(02)00263-1
72. Gertz, K., Priller, J., Kronenberg, G., Fink, K. B., Winter, B., Schröck, H., Ji, S., Milosevic, M., Harms, C., Böhm, M., Dirnagl, U., Laufs, U., & Endres, M. (2006). Physical activity improves long-term stroke outcome via endothelial nitric oxide synthase-dependent augmentation of neovascularization and cerebral blood flow. Circulation research, 99(10), 1132–1140. https://doi.org/10.1161/01.RES.0000250175.14861.77
73. Barnes J. N. (2015). Exercise, cognitive function, and aging. Advances in physiology education, 39(2), 55–62. https://doi.org/10.1152/advan.00101.2014
74. Ding, Y. H., Li, J., Zhou, Y., Rafols, J. A., Clark, J. C., & Ding, Y. (2006). Cerebral angiogenesis and expression of angiogenic factors in aging rats after exercise. Current neurovascular research, 3(1), 15–23. https://doi.org/10.2174/156720206775541787
75. Soto, I., Graham, L. C., Richter, H. J., Simeone, S. N., Radell, J. E., Grabowska, W., Funkhouser, W. K., Howell, M. C., & Howell, G. R. (2015). APOE Stabilization by Exercise Prevents Aging Neurovascular Dysfunction and Complement Induction. PLoS biology, 13(10), e1002279. https://doi.org/10.1371/journal.pbio.1002279
76. Cotman, C. W., Berchtold, N. C., & Christie, L. A. (2007). Exercise builds brain health: key roles of growth factor cascades and inflammation. Trends in neurosciences, 30(9), 464–472. https://doi.org/10.1016/j.tins.2007.06.011
77. Udo, H., Yoshida, Y., Kino, T., Ohnuki, K., Mizunoya, W., Mukuda, T., & Sugiyama, H. (2008). Enhanced adult neurogenesis and angiogenesis and altered affective behaviors in mice overexpressing vascular endothelial growth factor 120. The Journal of neuroscience : the official

journal of the Society for Neuroscience, 28(53), 14522–14536. https://doi.org/10.1523/JNEUROSCI.3673-08.2008
78. Kannangara, T. S., & Vani, M. A. (2017). The muscles' grip on neurogenesis: contributions of skeletal muscle-derived vascular endothelial growth factor to running-induced stem cell proliferation. The Journal of physiology, 595(22), 6821–6822. https://doi.org/10.1113/JP275251
79. Rich, B., Scadeng, M., Yamaguchi, M., Wagner, P. D., & Breen, E. C. (2017). Skeletal myofiber vascular endothelial growth factor is required for the exercise training-induced increase in dentate gyrus neuronal precursor cells. The Journal of physiology, 595(17), 5931–5943. https://doi.org/10.1113/JP273994
80. Licht, T., Rothe, G., Kreisel, T., Wolf, B., Benny, O., Rooney, A. G., Ffrench-Constant, C., Enikolopov, G., & Keshet, E. (2016). VEGF preconditioning leads to stem cell remodeling and attenuates age-related decay of adult hippocampal neurogenesis. Proceedings of the National Academy of Sciences of the United States of America, 113(48), E7828–E7836. https://doi.org/10.1073/pnas.1609592113
81. De Miguel, Z., Khoury, N., Betley, M. J., Lehallier, B., Willoughby, D., Olsson, N., Yang, A. C., Hahn, O., Lu, N., Vest, R. T., Bonanno, L. N., Yerra, L., Zhang, L., Saw, N. L., Fairchild, J. K., Lee, D., Zhang, H., McAlpine, P. L., Contrepois, K., Shamloo, M., … Wyss-Coray, T. (2021). Exercise plasma boosts memory and dampens brain inflammation via clusterin. Nature, 600(7889), 494–499. https://doi.org/10.1038/s41586-021-04183-x
82. DeCarolis, N. A., Kirby, E. D., Wyss-Coray, T., & Palmer, T. D. (2015). The Role of the Microenvironmental Niche in Declining Stem-Cell Functions Associated with Biological Aging. Cold Spring Harbor perspectives in medicine, 5(12), a025874. https://doi.org/10.1101/cshperspect.a025874
83. van Praag, H., Shubert, T., Zhao, C., & Gage, F. H. (2005). Exercise enhances learning and hippocampal neurogenesis in aged mice. The Journal of neuroscience : the official journal of the Society for Neuroscience, 25(38), 8680–8685. https://doi.org/10.1523/JNEUROSCI.1731-05.2005
84. Witte, A. V., Fobker, M., Gellner, R., Knecht, S., & Flöel, A. (2009). Caloric restriction improves memory in elderly humans. Proceedings of the National Academy of Sciences of the United States of America, 106(4), 1255–1260. https://doi.org/10.1073/pnas.0808587106
85. Cooper, C., Moon, H. Y., & van Praag, H. (2018). On the Run for Hippocampal Plasticity. Cold Spring Harbor perspectives in medicine, 8(4), a029736. https://doi.org/10.1101/cshperspect.a029736
86. Huang, Z., Lin, H. W. K., Zhang, Q., & Zong, X. (2022). Targeting Alzheimer's Disease: The Critical Crosstalk between the Liver and Brain. Nutrients, 14(20), 4298. https://doi.org/10.3390/nu14204298
87. Black F. W. (1973). Intellectual ability as related to age and stage of disease in muscular dystrophy: a brief note. The Journal of psychology, 84(2d Half), 333–334. https://doi.org/10.1080/00223980.1973.9923848
88. Hinton, V. J., De Vivo, D. C., Nereo, N. E., Goldstein, E., & Stern, Y. (2000). Poor verbal working memory across intellectual level in boys with Duchenne dystrophy. Neurology, 54(11), 2127–2132. https://doi.org/10.1212/wnl.54.11.2127
89. Anderson, J. L., Head, S. I., Rae, C., & Morley, J. W. (2002). Brain function in Duchenne muscular dystrophy. Brain : a journal of neurology, 125(Pt 1), 4–13. https://doi.org/10.1093/brain/awf012
90. Kobilo, T., Guerrieri, D., Zhang, Y., Collica, S. C., Becker, K. G., & van Praag, H. (2014). AMPK agonist AICAR improves cognition and motor coordination in young and aged mice. Learning & memory (Cold Spring Harbor, N.Y.), 21(2), 119–126. https://doi.org/10.1101/lm.033332.113
91. Moon, H. Y., Becke, A., Berron, D., Becker, B., Sah, N., Benoni, G., Janke, E., Lubejko, S. T., Greig, N. H., Mattison, J. A., Duzel, E., & van Praag, H. (2016). Running-Induced Systemic Cathepsin B

Secretion Is Associated with Memory Function. Cell metabolism, 24(2), 332–340. https://doi.org/10.1016/j.cmet.2016.05.025
92. Hook, V. Y., Kindy, M., & Hook, G. (2008). Inhibitors of cathepsin B improve memory and reduce beta-amyloid in transgenic Alzheimer disease mice expressing the wild-type, but not the Swedish mutant, beta-secretase site of the amyloid precursor protein. The Journal of biological chemistry, 283(12), 7745–7753. https://doi.org/10.1074/jbc.M708362200
93. Embury, C. M., Dyavarshetty, B., Lu, Y., Wiederin, J. L., Ciborowski, P., Gendelman, H. E., & Kiyota, T. (2017). Cathepsin B Improves ß-Amyloidosis and Learning and Memory in Models of Alzheimer's Disease. Journal of neuroimmune pharmacology : the official journal of the Society on NeuroImmune Pharmacology, 12(2), 340–352. https://doi.org/10.1007/s11481-016-9721-6
94. Teufel, A., Malik, N., Mukhopadhyay, M., & Westphal, H. (2002). Frcp1 and Frcp2, two novel fibronectin type III repeat containing genes. Gene, 297(1-2), 79–83. https://doi.org/10.1016/s0378-1119(02)00828-4
95. Wrann, C. D., White, J. P., Salogiannnis, J., Laznik-Bogoslavski, D., Wu, J., Ma, D., Lin, J. D., Greenberg, M. E., & Spiegelman, B. M. (2013). Exercise induces hippocampal BDNF through a PGC-1α/FNDC5 pathway. Cell metabolism, 18(5), 649–659. https://doi.org/10.1016/j.cmet.2013.09.008
96. Jedrychowski, M. P., Wrann, C. D., Paulo, J. A., Gerber, K. K., Szpyt, J., Robinson, M. M., Nair, K. S., Gygi, S. P., & Spiegelman, B. M. (2015). Detection and Quantitation of Circulating Human Irisin by Tandem Mass Spectrometry. Cell metabolism, 22(4), 734–740. https://doi.org/10.1016/j.cmet.2015.08.001
97. Islam, M. R., Valaris, S., Young, M. F., Haley, E. B., Luo, R., Bond, S. F., Mazuera, S., Kitchen, R. R., Caldarone, B. J., Bettio, L. E. B., Christie, B. R., Schmider, A. B., Soberman, R. J., Besnard, A., Jedrychowski, M. P., Kim, H., Tu, H., Kim, E., Choi, S. H., Tanzi, R. E., … Wrann, C. D. (2021). Exercise hormone irisin is a critical regulator of cognitive function. Nature metabolism, 3(8), 1058–1070. https://doi.org/10.1038/s42255-021-00438-z
98. El Hayek, L., Khalifeh, M., Zibara, V., Abi Assaad, R., Emmanuel, N., Karnib, N., El-Ghandour, R., Nasrallah, P., Bilen, M., Ibrahim, P., Younes, J., Abou Haidar, E., Barmo, N., Jabre, V., Stephan, J. S., & Sleiman, S. F. (2019). Lactate Mediates the Effects of Exercise on Learning and Memory through SIRT1-Dependent Activation of Hippocampal Brain-Derived Neurotrophic Factor (BDNF). The Journal of neuroscience : the official journal of the Society for Neuroscience, 39(13), 2369–2382. https://doi.org/10.1523/JNEUROSCI.1661-18.2019
99. Sleiman, S. F., Henry, J., Al-Haddad, R., El Hayek, L., Abou Haidar, E., Stringer, T., Ulja, D., Karuppagounder, S. S., Holson, E. B., Ratan, R. R., Ninan, I., & Chao, M. V. (2016). Exercise promotes the expression of brain derived neurotrophic factor (BDNF) through the action of the ketone body β-hydroxybutyrate. eLife, 5, e15092. https://doi.org/10.7554/eLife.15092
100. Stefan, N., & Häring, H. U. (2013). The role of hepatokines in metabolism. Nature reviews. Endocrinology, 9(3), 144–152. https://doi.org/10.1038/nrendo.2012.258
101. Reinhardt, R. R., & Bondy, C. A. (1994). Insulin-like growth factors cross the blood-brain barrier. Endocrinology, 135(5), 1753–1761. https://doi.org/10.1210/endo.135.5.7525251
102. Markowska, A. L., Mooney, M., & Sonntag, W. E. (1998). Insulin-like growth factor-1 ameliorates age-related behavioral deficits. Neuroscience, 87(3), 559–569. https://doi.org/10.1016/s0306-4522(98)00143-2
103. Schwarz, A. J., Brasel, J. A., Hintz, R. L., Mohan, S., & Cooper, D. M. (1996). Acute effect of brief low- and high-intensity exercise on circulating insulin-like growth factor (IGF) I, II, and IGF-binding

protein-3 and its proteolysis in young healthy men. The Journal of clinical endocrinology and metabolism, 81(10), 3492–3497. https://doi.org/10.1210/jcem.81.10.8855791

104. Carro, E., Nuñez, A., Busiguina, S., & Torres-Aleman, I. (2000). Circulating insulin-like growth factor I mediates effects of exercise on the brain. The Journal of neuroscience : the official journal of the Society for Neuroscience, 20(8), 2926–2933. https://doi.org/10.1523/JNEUROSCI.20-08-02926.2000
105. Orenstein, M.R., & Friedenreich, C.M. (2004). Review of Physical Activity and the IGF Family, Journal of Physical Activity and Health, 1(4), 291-320. Retrieved May 25, 2023, from https://doi.org/10.1123/jpah.1.4.291
106. - Laffel L. (1999). Ketone bodies: a review of physiology, pathophysiology and application of monitoring to diabetes. Diabetes/metabolism research and reviews, 15(6), 412–426. https://doi.org/10.1002/(sici)1520-7560(199911/12)15:6<412::aid-dmrr72>3.0.co;2-8
107. Sleiman, S. F., Henry, J., Al-Haddad, R., El Hayek, L., Abou Haidar, E., Stringer, T., Ulja, D., Karuppagounder, S. S., Holson, E. B., Ratan, R. R., Ninan, I., & Chao, M. V. (2016). Exercise promotes the expression of brain derived neurotrophic factor (BDNF) through the action of the ketone body β-hydroxybutyrate. eLife, 5, e15092. https://doi.org/10.7554/eLife.15092
108. Horowitz, A. M., Fan, X., Bieri, G., Smith, L. K., Sanchez-Diaz, C. I., Schroer, A. B., Gontier, G., Casaletto, K. B., Kramer, J. H., Williams, K. E., & Villeda, S. A. (2020). Blood factors transfer beneficial effects of exercise on neurogenesis and cognition to the aged brain. Science (New York, N.Y.), 369(6500), 167–173. https://doi.org/10.1126/science.aaw2622
109. Li, X., Shi, X., McPherson, M., Hager, M., Garcia, G. G., & Miller, R. A. (2022). Cap-independent translation of GPLD1 enhances markers of brain health in long-lived mutant and drug-treated mice. Aging cell, 21(9), e13685. https://doi.org/10.1111/acel.13685
110. Schwarz, M., Spath, L., Lux, C. A., Paprotka, K., Torzewski, M., Dersch, K., Koch-Brandt, C., Husmann, M., & Bhakdi, S. (2008). Potential protective role of apoprotein J (clusterin) in atherogenesis: binding to enzymatically modified low-density lipoprotein reduces fatty acid-mediated cytotoxicity. Thrombosis and haemostasis, 100(1), 110–118. https://doi.org/10.1160/TH07-12-0737
111. O. Leiter, Z. Zhuo, R. Rust, J.M. Wasielewska, L. Gronnert, S. Kowal, R.W. Overall, V.S. Adusumilli, D.G. Blackmore, A. Southon, et al. Selenium mediates exercise-induced adult neurogenesis and reverses learning deficits induced by hippocampal injury and aging Cell Metabol., 34 (2022), pp. 408-423, 10.1016/j.cmet.2022.01.005
112. Raichlen, D. A., & Alexander, G. E. (2017). Adaptive Capacity: An Evolutionary Neuroscience Model Linking Exercise, Cognition, and Brain Health. Trends in neurosciences, 40(7), 408–421. https://doi.org/10.1016/j.tins.2017.05.001
113. Bramble, D. M., & Lieberman, D. E. (2004). Endurance running and the evolution of Homo. Nature, 432(7015), 345–352. https://doi.org/10.1038/nature03052
114. Cashdan, E., & Gaulin, S. J. (2016). Why Go There? Evolution of Mobility and Spatial Cognition in Women and Men : An Introduction to the Special Issue. Human nature (Hawthorne, N.Y.), 27(1), 1–15. https://doi.org/10.1007/s12110-015-9253-4
115. Anderson-Hanley, C., Arciero, P. J., Brickman, A. M., Nimon, J. P., Okuma, N., Westen, S. C., Merz, M. E., Pence, B. D., Woods, J. A., Kramer, A. F., & Zimmerman, E. A. (2012). Exergaming and older adult cognition: a cluster randomized clinical trial. American journal of preventive medicine, 42(2), 109–119. https://doi.org/10.1016/j.amepre.2011.10.016

116. Barcelos, N., Shah, N., Cohen, K., Hogan, M. J., Mulkerrin, E., Arciero, P. J., Cohen, B. D., Kramer, A. F., & Anderson-Hanley, C. (2015). Aerobic and Cognitive Exercise (ACE) Pilot Study for Older Adults: Executive Function Improves with Cognitive Challenge While Exergaming. Journal of the International Neuropsychological Society : JINS, 21(10), 768–779. https://doi.org/10.1017/S1355617715001083
117. Eggenberger, P., Schumacher, V., Angst, M., Theill, N., & de Bruin, E. D. (2015). Does multicomponent physical exercise with simultaneous cognitive training boost cognitive performance in older adults? A 6-month randomized controlled trial with a 1-year follow-up. Clinical interventions in aging, 10, 1335–1349. https://doi.org/10.2147/CIA.S87732
118. Boldrini, M., Fulmore, C. A., Tartt, A. N., Simeon, L. R., Pavlova, I., Poposka, V., Rosoklija, G. B., Stankov, A., Arango, V., Dwork, A. J., Hen, R., & Mann, J. J. (2018). Human Hippocampal Neurogenesis Persists throughout Aging. Cell stem cell, 22(4), 589–599.e5. https://doi.org/10.1016/j.stem.2018.03.015
119. Eisch, A. J., & Petrik, D. (2012). Depression and hippocampal neurogenesis: a road to remission?. Science (New York, N.Y.), 338(6103), 72–75. https://doi.org/10.1126/science.1222941
120. Revest, J. M., Dupret, D., Koehl, M., Funk-Reiter, C., Grosjean, N., Piazza, P. V., & Abrous, D. N. (2009). Adult hippocampal neurogenesis is involved in anxiety-related behaviors. Molecular psychiatry, 14(10), 959–967. https://doi.org/10.1038/mp.2009.15
121. Moreno-Jiménez, E. P., Flor-García, M., Terreros-Roncal, J., Rábano, A., Cafini, F., Pallas-Bazarra, N., Ávila, J., & Llorens-Martín, M. (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. https://doi.org/10.1038/s41591-019-0375-9
122. Winner, B., Desplats, P., Hagl, C., Klucken, J., Aigner, R., Ploetz, S., Laemke, J., Karl, A., Aigner, L., Masliah, E., Buerger, E., & Winkler, J. (2009). Dopamine receptor activation promotes adult neurogenesis in an acute Parkinson model. Experimental neurology, 219(2), 543–552.
123. Bonaguidi, M. A., Wheeler, M. A., Shapiro, J. S., Stadel, R. P., Sun, G. J., Ming, G. L., & Song, H. (2011). In vivo clonal analysis reveals self-renewing and multipotent adult neural stem cell characteristics. Cell, 145(7), 1142–1155. https://doi.org/10.1016/j.cell.2011.05.024
124. Kempermann, G., Song, H., & Gage, F. H. (2015). Neurogenesis in the Adult Hippocampus. Cold Spring Harbor perspectives in biology, 7(9), a018812. https://doi.org/10.1101/cshperspect.a018812
125. Suh H, Consiglio A, Ray J, Sawai T, D'Amour KA, Gage FH: In vivo fate analysis reveals the multipotent and self-renewal capacities of Sox2+ neural stem cells in the adult hippocampus. Cell Stem Cell 2007, 1:515-528
126. Cameron, H. A., & McKay, R. D. (2001). Adult neurogenesis produces a large pool of new granule cells in the dentate gyrus. The Journal of comparative neurology, 435(4), 406–417. https://doi.org/10.1002/cne.1040
127. van Praag H, Schinder AF, Christie BR, Toni N, Palmer TD, Gage FH. Functional neurogenesis in the adult hippocampus. Nature. 2002 Feb 28;415(6875):1030-4. doi: 10.1038/4151030a. PMID: 11875571; PMCID: PMC9284568.
128. Zheng J. (2022). Hippocampal neurogenesis and pro-neurogenic therapies for Alzheimer's disease. Animal models and experimental medicine, 5(1), 3–14. https://doi.org/10.1002/ame2.12212

Afterword – the Mechanism of Hippocampal Neurogenesis

While both neurogenic regions have been significant research areas, SGZ neurogenesis has received more attention. The hippocampus, the area where SGZ neurogenesis occurs, is well-known for its role in learning and memory, including spatial learning and memory, contextual fear conditioning, and pattern separation. For this reason, postnatal SGZ neurogenesis will be referred to as adult hippocampal neurogenesis (AHN) in the remainder of this thesis. By contrast, the function of SVZ neurogenesis in the olfactory system is less well understood, and it is unclear how it contributes to brain function and behavior. Furthermore, AHN has been more extensively studied in humans due to the accessibility of the hippocampus to imaging techniques such as magnetic resonance imaging (MRI). Finally, AHN has been implicated in a variety of neurological and psychiatric disorders, including depression [118,119], anxiety [120], and Alzheimer's disease [121], among others. Therefore, understanding AHN has significant and far-reaching implications for the development of new treatments for these disorders. Although there is growing evidence that SVZ neurogenesis may also be implicated in certain diseases, such as Parkinson's disease, its relevance to a broader range of neurological and psychiatric disorders remains to be fully elucidated [122]. For the aforementioned reasons, this thesis will exclusively focus on hippocampal neurogenesis.

The process of hippocampal neurogenesis begins with the proliferation of self-renewing and multipotent adult neural stem cells (NSCs) in the SGZ of the hippocampus. Two different populations of NSCs have been identified [123]. Type 1 neural progenitor cells (NPCs) are a population of radial glia-like cells that express the glial fibrillary acidic protein (GFAP), nestin, and Sox2 and act as quiescent NSCs [124]. These cells can self-renew and differentiate into both neurons and glial cells. They are characterized by their elongated cell bodies and radial processes that extend throughout the granule cell layer and into the entire molecular layer of the hippocampus [124].
Type 2 cells, also known as amplifying neural progenitors, are more restricted in their differentiation potential and can only differentiate into neurons. They are derived from type 1 cells and have a more rounded cell body and shorter processes than type 1 cells [124]. Type 2 cells express Sox2 and Nestin but not GFAP. They generate DCX+ neuroblasts that predominantly differentiate into local glutamatergic dentate granule cells (DGCs) [123].
Moreover, a subset of type 2 Sox2+ cells appears to play a role in amplifying the number of progenitor cells, which contributes to the overall rate of hippocampal neurogenesis, thereby pointing to a possible reciprocal lineage relationship between type 1 and type 2 cells in the SGZ [125].
As these progenitor cells differentiate into neurons, they migrate to their final destination within the hippocampus and integrate into the existing neural circuitry. About 50% of approximately 9,000 cells generated in the SGZ daily in young adult rats survive [126]. Once integrated, new neurons form new connections with other neurons, strengthening and modifying existing circuits. This process of neuroplasticity is thought to be one of the mechanisms behind learning and memory [127].

Therefore, hippocampal neurogenesis depends on the maintenance of "stemness" and commitment to differentiation, survival, and integration of new neurons. This is tightly regulated and tuned by intricate molecular mechanisms, including cell-intrinsic factors, systemic factors, the "niche" and systemic circulation. In addition, it can be modulated by various physiological, pathological, and pharmacological stimuli. Despite the recent surge in research on NSCs, our current understanding of the exact molecular effects on HN is relatively limited. In part because of technical challenges.

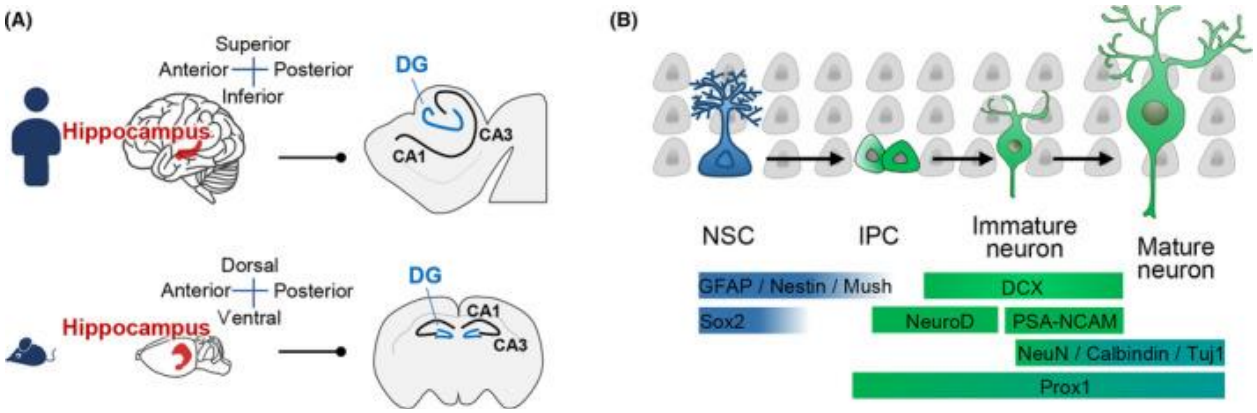

Fig. 2 - Adult hippocampus neurogenesis. (A) Illustration of the anterior-posterior (ventral-dorsal) axis of the hippocampus. (B) Different biomarkers of AHN during different stages [128]