Review

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The Role of Intermittent Fasting and Calorie Restriction in Preventing Neurodegenerative Diseases within the Context of Adult Neurogenesis

Yetişkin Nörogenezi Ekseninde Aralıklı Oruç ve Kalori Kısıtlamasının Nörodejeneratif Hastalıkları Önlemede Rolü

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ABSTRACT

Aging is considered the most important risk factor for neurodegenerative diseases such as Alzheimer's, Parkinson's and Huntington's diseases. Moreover, it is interpreted that irregular neurogenesis may also be one of the causes of neurodegenerative diseases. The brain-derived neurotrophic factor signal, a growth factor known to play an important role in the development and plasticity of the brain by promoting neurogenesis, synaptic plasticity and cell survival, decreases in the brain with aging and may be the cause of neurodegenerative diseases. Intermittent fasting or calorie restriction, a nutritional method, increases brain-derived neurotrophic factor expression in various regions of the human and rodent brain. This brings to mind the question of whether nutritional methods such as intermittent fasting and calorie restriction may play a role in preventing neurodegenerative diseases. Based on this, it has been investigated how these nutritional methods trigger adult hippocampal neurogenesis by signaling brain-derived neurotrophic factor and how they affect the brain's resistance to aging by causing changes in the hippocampus area of the brain that controls learning, memory and mood. Significant evidence obtained from human and animal studies reveals that brain-derived neurotrophic factor signaling plays a role in the beneficial effects of intermittent fasting and calorie restriction on brain aging and that this is important in terms of promising a functional result in preventing neurodegenerative diseases.

Keywords: Adult hippocampal neurogenesis, ıntermittent fasting, calorie restriction, neurodegenerative disorders

ÖZ

Yaşlanma, Alzheimer, Parkinson ve Huntington hastalıkları gibi nörodejeneratif hastalıkların en önemli risk faktörü olarak değerlendirilmektedir. Dahası düzensiz nörogenezin de nörodejeneratif hastalıkların sebeplerinden biri olabileceği yorumlanmaktadır. Nörogenezi, sinaptik plastisiteyi ve hücre sağ kalımını teşvik ederek beynin gelişiminde ve plastisitesinde önemli rol oynadığı bilinen bir büyüme faktörü olan beyin türevli nörotrofik faktör sinyalinin yaşlanma ile birlikte beyinde azaldığını ve nörodejenaratif hastalıkların sebebi olabileceğini ortaya koyan çalışmalar vardır. Bir beslenme metodu olan aralıklı oruç veya kalori kısıtlamasının insan ve kemirgen beyninin çeşitli bölgelerinde beyin türevli nörotrofik faktör ekspresyonunu arttırdığı bulgulanmıştır. Bu durum bize, yaşa bağlı azalma gösteren beyin türevli nörotrofik faktörün beslenme düzeni ile zenginleştirilebilecek bir nörotrofin olabileceğinin sinyalini vermektedir. Buradan hareketle söz konusu beslenme metotlarının beyin türevli nörotrofik faktörü sinyalleyerek yetişkin hipokampal nörogenezini tetiklemesi ve beynin öğrenme, hafıza ve ruh halini kontrol eden hipokampus alanında değişiklikler yaparak, yaşlanmaya karşı beynin direncini nasıl etkilediği araştırılmıştır. İnsan ve hayvan çalışmalarından elde edilen önemli kanıtlar, aralıklı oruç ve kalori kısıtlamasının beyin yaşlanması üzerindeki yararlı etkilerinde beyin türevli nörotrofik faktörün sinyallemesinin rol oynadığını ve bunun da nörodejeneratif hastalıkları önlemede fonksiyonel bir sonuç vaat etmesi açısından önemini ortaya koymaktadır.

Anahtar sözcükler: Yetişkin nörogenezi, aralıklı oruç, kalori kısıtlaması, nörodejeneratif hastalıklar

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Introduction

The brain's ability to change in response to various stimuli is one of its most notable characteristics. The brain is continuously evolving in the face of positive situations such as learning and adapting to environmental changes, or negative situations such as brain trauma and disease. In the human brain, billions of neurons can be produced whose interconnections are subject to plastic changes in order to ameliorate for the function lost in negative situations. However, the plasticity of the human brain is unable to spontaneously regenerate damaged or degenerated neurons. This may lead to irreversible dysfunctions (Wood 2011, Ansari et al. 2025). Neurodegeneration involves a gradual decline in neuronal integrity and connectivity, ultimately impairing essential brain functions (Toda et al. 2019). Neurodegenerative disorders are generally associated with neuronal death and can be characterized by the progressive loss of neuronal structure and function (Gilmore et al. 2008, Re et al. 2012, Shivani et al. 2018).

Advancing age significantly contributes to the risk of developing neurodegenerative conditions, with the elderly population being the most commonly affected by such diseases (Hou et al. 2018). Additionally, numerous studies suggest that impaired neurogenesis plays a pivotal role in the pathogenesis of these disorders. Neurogenesis, a fundamental process for maintaining synaptic communication, is also tightly linked to the development of axonal and dendritic structures. In the context of neurodegeneration, disturbances in adult hippocampal neurogenesis (AHN) may result in neuronal loss and a reduced capacity of neural stem cells (NSCs) to regenerate. As a result, the presumed function of newly generated neurons is compromised or entirely lost (Horgusluoglu et al. 2017, Toda et al. 2019).

Aging has been associated with a decline in brain-derived neurotrophic factor (BDNF) signaling in the brain (Hayashi et al. 2001). BDNF is expressed in the amygdala, hippocampus, entorhinal cortex—regions involved in short-term memory—as well as in thalamic, cortical, and striatal areas (Katoh-Semba et al. 1997, Leal et al. 2016). Intermittent fasting (IF), a dietary intervention, has been reported to increase BDNF expression (Li et al. 2020). Moreover, studies in rodent models indicate that both IF and caloric restriction (CR) can stimulate brain-derived neurotrophic factor (BDNF) pathways across several brain areas, notably in the hippocampus and the prefrontal cortex (Lee et al. 2002, Kaptan et al. 2015).

A possible explanation for the age-related decline in hippocampal volume is the gradual loss of neurons in this region as part of the aging trajectory. Supporting this view, researchers have noted that 25-month-old female mice exhibit markedly fewer NeuN-labeled neurons and non-neuronal cells in the hippocampus when compared to 7-month-old counterparts (Fu et al. 2015). Furthermore, it is evident that impaired continuous neurogenesis in the hippocampus, along with neuroinflammation, is one of the distinguishing features of certain neurodegenerative diseases (Sung et al. 2020).

This review article proposes that IF and CR may stimulate AHN via their regulatory effects on BDNF levels, thereby inducing molecular adaptations within the hippocampus that confer neuroprotection and promote healthy brain aging.

Aging and Neurodegenerative Diseases

As a complex and inescapable biological phenomenon, aging manifests through progressive alterations in physical form and physiological performance. It is characterized by the cumulative deterioration of multiple systems—biological, cognitive, and emotional—which collectively elevate susceptibility to illness and death, while also accelerating cognitive decline (Zhavoronkov et al. 2019). Like many other organs in the body, the brain is particularly vulnerable to age-related changes and functional decline. Among the various risk factors for neurodegeneration, the aging process itself exerts by far the greatest influence (Bondi et al. 2017, Wassouf et al. 2018). Moreover, accumulating evidence suggests that aging is associated with a decline in AHN (Go et al. 2018).

Although advances in healthcare have contributed to an increase in average life expectancy, no treatment has yet been developed to prevent aging. This contributes to the growing prevalence of age-related neurodegenerative diseases (Dorsey et al. 2013, Zahra et al. 2020). Neurodegenerative disorders represent

a diverse spectrum of central nervous system pathologies, encompassing conditions such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), among others (Toda et al. 2019). The etiology of neurodegenerative diseases is complex and associated with multiple factors, such as age, genetics, lifestyle, and environmental influences (Gilmore et al. 2008, Re et al. 2012). Despite differing clinical manifestations and pathological mechanisms, these disorders share key features, including progressive neuronal loss and both structural and functional impairments in the nervous system (Chi et al. 2018).

In order to understand age-related cognitive deterioration, it is important to focus on the hippocampus — a brain structure critically involved in memory formation, emotional regulation, and learning processes. Notably, this region retains the capacity for both functional and morphological plasticity, including sustained neurogenesis throughout adult life (Bettio 2017). A positive correlation has been observed between aging and the decline in BDNF signaling. In studies conducted on primates, levels of BDNF protein in dentate granule cells and hippocampal pyramidal neurons were found to decrease with age (Hayashi et al. 2001, Mendonça et al. 2025). Age-related loss in the number and/or activity of NSCs may underlie this decline in brain function. Age-related impairments in cognition have been linked to a variety of neurobiological alterations occurring in the hippocampus over time. These include heightened oxidative damage, persistent neuroinflammatory activity, disruptions in intracellular communication and gene transcription, as well as reductions in neurogenesis and synaptic adaptability (Bettio 2017). Therefore, interventions that reverse aging in NSCs could potentially extend cognitive healthspan. One compelling hypothesis suggests that the decline in brain function with age results from a time-dependent reduction in the number and/or activity of stem cells, and that delaying or reversing stem cell aging could extend both lifespan and healthspan in humans (Schultz and Sinclair 2016). Notably, age-related structural and functional impairments in the hippocampus have been shown to be mitigated through non-invasive strategies such as physical exercise, CR and environmental enrichment. Consequently, these strategies might offer promising avenues for mitigating age-associated neural impairments and preserving cognitive integrity by reducing vulnerability to neurodegenerative conditions linked to aging (Bettio 2017, Hou et al. 2019).

In light of existing evidence, it is plausible to suggest that preventing the age-related decline—or promoting the proliferation—of neural stem cells could serve as an effective preventive strategy against the onset of age-associated diseases. Additionally, such an approach may offer potential for reducing the incidence and severity of neurodegenerative disorders and their detrimental effects on daily functioning and overall well-being.

Alzheimer's Disease

Alzheimer's Disease (AD), the most prevalent form of dementia in older adults, is characterized by gradual degeneration of central nervous system structures. Individuals diagnosed with AD often present with shrinkage of the hippocampus, impaired memory functions, broader cognitive challenges, and a diminished sense of smell (Horgusluoglu et al. 2017). AD accounts for approximately 60–70% of dementia cases worldwide, making it the most prevalent neurodegenerative disorder. PD is the second most common neurodegenerative condition, affecting an estimated 8.5 million people globally. In contrast, HD is less prevalent, with around 2.7 million cases worldwide. According to recent epidemiological data, AD is the most frequent among these disorders, followed by PD and then HD (Medina et al. 2022). Clinically, AD initially presents with impairment in recent (short-term) memory, typically affecting memories closest to the present (Jack et al. 2018, McGregor and Nelson 2019). As the severity of the disease progresses, the aforementioned symptoms become more pronounced, and individuals with AD exhibit broader impairments, including deterioration in language, orientation, and executive functions, which ultimately leads to a decline in self-care abilities (Jack et al. 2018).

One of the key pathological hallmarks of AD, a long-term progressive brain disorder, is the build-up of amyloid-beta (Aβ) plaques outside neurons and the formation of tau protein tangles within them (Shefa et al. 2019). Exposure of synapses to Aβ plaques leads to dysfunction and irreversible damage, and synapses

are considered key sites in the initiation of the neurodegenerative process (Murphy et al. 2014). As AD progresses, plaques and tangles tend to form earlier in the entorhinal cortex, hippocampus, and olfactory bulb compared to the neocortex (Culig et al. 2022). The hippocampus, which is responsible for learning, memory, and executive functions, is the most affected brain region in AD; therefore, impairments in these cognitive domains are among the most prominent clinical features (Holtzman et al. 2011, Holger 2013).

The hippocampus plays a vital role in regulating memory functions, emotional responses, and how the brain reacts to stress (Brown 1999). According to Tobin et al. (2019), AD is associated with a gradual decrease in both the quantity and maturation of newly generated neurons in this brain region, a decline that may contribute to worsening cognitive symptoms. Consequently, AHN has been proposed as a promising biomarker for neurodegenerative conditions like AD, and is now increasingly recognized as part of the disease's pathological framework (Lazarov et al. 2010). Additionally, the neurotrophic factor BDNF is also recognized as a key marker in AD. Studies have shown that BDNF expression in hippocampal tissue samples from AD patients is reduced compared to age-matched controls (Mattson et al. 2004). Research conducted in both AD mouse models and human patients has demonstrated decreased brain BDNF mRNA levels, as well as reductions in BDNF concentrations in the cerebrospinal fluid (Franzmeier et al. 2021). It has been proposed that the reduction in BDNF detected in the brains of AD cadavers may contribute to the cognitive impairments observed in the disease (Peng et al. 2005). Autopsy studies have further revealed that hippocampal BDNF levels are diminished in individuals with AD dementia or mild cognitive impairment (Franzmeier et al. 2021). Postmortem studies on AD patients have shown decreased numbers of BDNF-immunopositive neurons and reduced immunostaining intensity within neuronal cell bodies in both the hippocampus and temporal cortex (Connor et al. 1997). In a longitudinal study on aging and dementia, individuals with AD-related dementia exhibited lower BDNF mRNA levels compared to non-demented counterparts. This BDNF reduction is associated with synaptic loss in the hippocampus, manifesting as cognitive dysfunction (Michalski et al. 2015). These observations prompt an important consideration: might variations in BDNF levels influence the extent to which AD's pathology affects neural function? Preclinical experiments conducted on transgenic mouse models of AD suggest that enhancing BDNF expression—whether through gene delivery or other methods—can alleviate memory deficits in the hippocampus and counteract the detrimental effects of amyloid plaques and tau tangles. Collectively, these findings highlight the potential neuroprotective function of BDNF in the context of AD (Franzmeier et al. 2021).

Parkinson's Disease

Parkinson's Disease (PD), the second most common neurodegenerative disorder, arises from a complex interplay of genetic, epigenetic, and environmental influences. Among these, aging stands out as the primary risk factor. It primarily affects males over the age of 60, with incidence rates increasing progressively with age (Levi and Michaelson 2007, McGregor and Nelson 2019, Qi et al. 2021).

The pathophysiology of PD is mainly associated with the progressive loss of dopaminergic neurons in the nigrostriatal pathway (Pandey et al. 2018, Tolosa et al. 2021). One of the central contributors to neuronal degeneration in PD is the misfolding and intracellular buildup of α-synuclein, which aggregates into Lewy bodies. These protein accumulations initiate multiple toxic pathways within dopaminergic neurons, ultimately leading to their functional decline and death (Pandey et al. 2018, Leão et al. 2015, Villegas et al. 2014). Lewy bodies accumulate particularly in dopaminergic neurons of the substantia nigra pars compacta, ultimately causing a marked reduction in dopamine levels. This dopamine depletion plays a central role in the emergence of the core motor symptoms of PD, such as rigidity, bradykinesia, and tremor (Vidyadhara et al. 2019).

Recently, reduced expression of BDNF has emerged as a noteworthy pathophysiological mechanism in PD (Alomari et al. 2018, Wang et al. 2019). Increasing BDNF levels in the brain has been shown to modulate monoaminergic systems and alleviate motor dysfunctions (Campêlo et al. 2017). These findings underscore the potential role of BDNF in understanding PD pathophysiology and as a therapeutic target.

PD presents with a range of symptoms, encompassing both motor dysfunctions and non-motor disturbances. Motor symptoms include movement difficulties (such as slowness and gait abnormalities),

postural instability, muscular rigidity, and tremors in the limbs and face (Church 2021). Non-motor symptoms encompass sleep disturbances, olfactory dysfunction, visual impairments, cognitive decline and psychiatric symptoms (Obeso et al. 2017). Currently, there is no curative treatment for PD, and existing therapies are limited to symptom management and slowing disease progression (Raza and Anjum 2019).

Decreased levels of AHN have been observed in various animal models of PD (Le Grand et al. 2015, Lim et al. 2018). Moreover, the accumulation of α-synuclein in neurogenic regions of the hippocampus interferes with the neurogenesis process (Horgusluoglu et al. 2017).

Huntington's Disease

Huntington's Disease (HD) is a progressive and ultimately fatal neurodegenerative condition resulting from mutations in the huntingtin (HTT) gene. The altered protein interferes with several cellular pathways, contributing to neuronal impairment and eventual cell death (Khalil et al. 2015). A hallmark of HD is the progressive cognitive impairment and severe motor dysfunction resulting from neuronal loss in the cortex, striatum, and hippocampus (Culig et al. 2022). Although striatal degeneration is a hallmark of HD, neuronal loss has also been reported in other brain areas, such as the hippocampus (Gil-Mohapel et al. 2011).

Individuals genetically predisposed to develop HD can be identified through predictive genetic testing even before the clinical onset of the disease. This enables researchers to study the neurodegenerative process prior to the manifestation of overt symptoms (Garcia-Gorro et al. 2019). In genetic rodent models of HD, a dramatic and consistently observed decline in the generation of new neurons within the hippocampus has been detected before the appearance of motor symptoms (Kandasamy et al. 2010). These outcomes indicate that a decline in AHN and the cellular processes supporting it may contribute to HD pathogenesis (MacMillan et al. 2011).

In mutant HD mice, a reduction in NeuroD1—a key regulator of proliferation, differentiation, and maturation of neural progenitor cells—was observed in the neural progenitor zone of the dentate gyrus. Additionally, the expression of doublecortin and calretinin in newly generated neurons was found to be impaired. These results indicate that protein alterations in HD pathology may disrupt AHN and contribute to cognitive dysfunction (Horgusluoglu et al. 2017).

BDNF-based studies have demonstrated that BDNF levels are reduced in HD patients as well as in transgenic and knockout HD mouse models (Ferrer et al. 2000). Given that BDNF has been shown to promote AHN (Benraiss et al. 2001), the reduction in BDNF may also serve as a potential biomarker for HD.

In addition to the neurodegenerative diseases discussed above, numerous other forms of neurodegenerative disorders exist. These conditions place a significant burden on patients and their caregivers. This situation highlights the growing need for novel and effective therapeutic approaches, especially given the current lack of curative treatments for neurodegenerative disorders (Gorelick 2011).

Hippocampus and Adult Hippocampal Neurogenesis

The identification of neurogenesis occurring in the adult mammalian brain was first reported by Joseph Altman and Gopal Das during the 1960s (Culig et al. 2022). It is now widely accepted that neurogenesis primarily takes place in two distinct brain regions: the subgranular zone (SGZ) of the dentate gyrus within the hippocampus, and the subventricular zone (SVZ) lining the lateral ventricles (Hagg 2009). The dentate gyrus is comprised of several layers, including the granule cell layer, SGZ, hilus, and molecular layer, with the SGZ positioned at the boundary between the granule cell layer and the hilus. In adult mammals, neurogenesis mainly continues in the SVZ and SGZ, where progenitor cells originating in the SVZ migrate via the rostral migratory stream to the olfactory bulb to mature and incorporate into neural circuits. Meanwhile, granule neurons from the dentate gyrus extend their projections to pyramidal neurons located in the CA3 hippocampal region (Hsieh 2012).

A unique feature of the hippocampus—particularly the dentate gyrus—is its sustained capacity to generate new functional neurons throughout postnatal life. The process of AHN is supported by the presence of

NSCs capable of self-renewal and differentiation into mature neurons. This process is regulated by both intrinsic signaling pathways that govern proliferative activity and neuronal differentiation, and by the local microenvironment known as the neurogenic niche (Mu et al. 2010). Neurogenesis refers to the generation of new neurons from NSCs and neural progenitor cells through four major stages: proliferation, differentiation, migration, and survival (Hsieh 2012). A distinct feature of adult neurogenesis is its modulation by a wide range of factors including genetic, transcriptional, and epigenetic regulators, as well as environmental stimuli and pathological states (Mu et al. 2010). Because the orientation, migration, and integration of newly born neurons into pre-existing circuits depend on intricate signaling within the neurogenic niche, AHN is a tightly regulated and highly dynamic process (Mu et al. 2010).

AHN is closely linked to processes such as learning, memory formation, and the regulation of stress responses. It also holds significant importance in the pathology of neurodegenerative and psychiatric conditions. Being dependent on age, AHN is notably affected by brain development stages both before and after birth, underscoring its relevance in neuroscience research (Ortega-Martínez 2015). Neurogenesis is essential for synaptic transmission and is closely related to axonal and dendritic development. Impaired AHN in neurodegenerative diseases contributes to neuronal loss and reduced regenerative capacity of NSCs, ultimately compromising or abolishing the intended function of newly formed neurons (Horgusluoglu et al. 2017). The hippocampus is fundamentally involved in forming episodic and spatial memories and has been linked to the pathology of several neurodegenerative disorders (Horgusluoglu et al. 2017). Figure 1 illustrates the key stages of adult hippocampal neurogenesis.

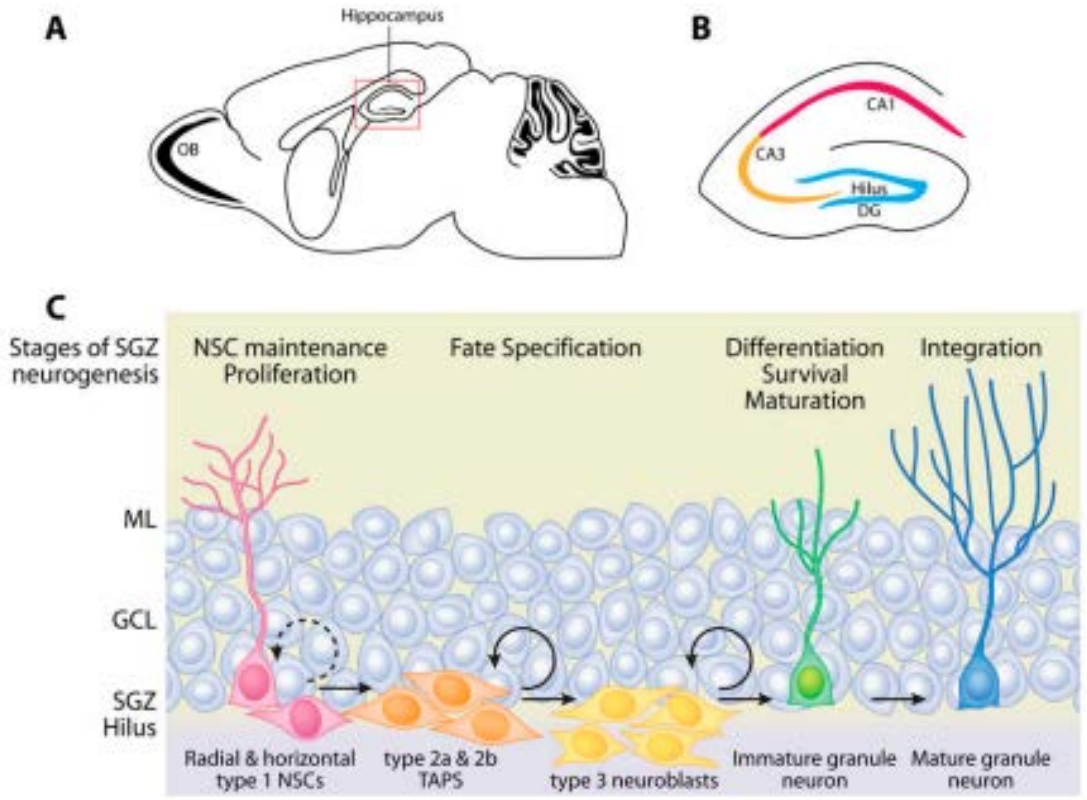

Figure 1. Adult neurogenesis in the subgranular zone (SGZ) of the dentate gyrus within the hippocampus

(A) Sagittal view of the rodent brain with a boxed area summarizing the hippocampal formation. (B) Schematic representation of the hippocampus, including CA1, CA3, dentate gyrus (DG), and hilus regions. (C) The SGZ niche consists of radial and horizontal type 1 neural stem cells (pink), early-stage type 2a and type 2b progenitor cells (orange), late-stage type 3 progenitor cells (yellow), immature granule neurons (green), and mature granule neurons (blue) (Hsieh 2012).

The hippocampus is known to play a critical role in maintaining cognitive function, particularly in learning and memory storage (Luo et al. 2017). Evidence has demonstrated a relationship between AHN and cognitive function in rodents (Anacker and Hen 2017). Following genetic disruption of hippocampal neurogenesis, deficits in spatial memory and electrophysiological properties within the dentate gyrus have been confirmed (Massa et al. 2011). Functionally, the absence or partial impairment of AHN has been associated with significant declines in learning abilities, as well as increased behaviors related to depression and anxiety. These findings clearly indicate that AHN is essential for both cognitive and emotional regulation (Revest et al. 2009).

In the adult brain, the hippocampus remains a prominent site of ongoing neurogenesis, supporting both cognitive and emotional processes. This dynamic activity is shaped by a wide range of internal and external influences, among which nutritional factors are particularly significant. Brain-derived neurotrophic factor (BDNF), a key molecule within the neurotrophin family, plays an essential role across the lifespan by regulating neuronal growth, synaptic remodeling, and neurogenesis. A substantial body of research has confirmed that BDNF is closely associated with neurogenesis, regulating neuronal proliferation, apoptosis, and synapse formation in the hippocampus. These properties make BDNF essential for hippocampus-dependent memory and learning processes (Franzmeier et al. 2021, Xie et al. 2025).

BDNF is expressed in the amygdala, hippocampus, entorhinal cortex (regions involved in short-term memory), as well as in thalamic, striatal, and cortical areas (Katoh-Semba et al. 1997, Leal et al. 2016). Decreased BDNF levels in these brain regions have been associated with disrupted neurogenesis and impaired development of neuronal circuits, which may accelerate processes of neurodegeneration and promote neuroinflammatory responses (Miranda et al. 2019, Miao et al. 2020, Zhang et al. 2023, Nieto et al. 2023).

Intermittent Fasting and Caloric Restriction

IF is a dietary regimen characterized by recurring cycles of eating and fasting, where individuals abstain from food intake for a certain period of time (Erbaba et al. 2021). More specifically, IF refers to a modified eating pattern that alternates between prolonged periods (e.g., 16–24 hours) of minimal or no caloric intake and periods of refeeding (Mattson et al. 2017). In summary, IF represents a metabolic cycle between fasting phases, in which the metabolic switch is turned on, and feeding phases, where it is turned off (Li et al. 2020).

CR, on the other hand, refers to the limitation of energy intake through food. For instance, it typically means consuming about 1,800–2,200 kcal/day for men and 1,600–2,000 kcal/day for women (Mattson 2019). Another widely accepted definition describes CR as a reduction in total calorie intake by 20–40% while maintaining adequate nutritional intake (Trepanowski et al. 2011). The term is sometimes used interchangeably with "dietary restriction," which can involve limiting specific macro- or micronutrients such as proteins, carbohydrates, or amino acids without necessarily reducing total energy intake (Selman 2014).

In recent years, IF has emerged as a promising non-pharmacological, dietary intervention to optimize brain function and enhance resilience against various types of brain injury (Mattson et al. 2017, De Cabo and Mattson 2019). IF is non-invasive, cost-effective, applicable in a wide range of settings, and suitable for integration with other chronic disease interventions (Sibille et al. 2016). At the cellular level, IF has been shown to enhance cellular function by reducing inflammation and oxidative stress while boosting cellular metabolism. Improvements in sensory and motor function, learning, and memory have been observed (Longo and Mattson, 2014). Moreover, the neuroprotective effects of IF have been associated with the preservation of learning and memory abilities (Mattson and Wan, 2005). Neurobiologically, IF enhances synaptic plasticity and may promote the production of new neurons from neural stem cells (Mattson et al. 2003).

Caloric restriction is also known to positively influence learning and memory functions (Culig et al. 2022). Chronic CR has been found to enhance cognitive performance in rodents (Kuhla et al. 2013, Wahl et al.

2018). Mice subjected to CR demonstrated a 52% increase in adult-born neurons in the rostral dentate gyrus compared to ad libitum-fed controls (Hornsby et al. 2016). In healthy humans, a randomized clinical trial with a 25% reduction in caloric intake over two years reported improved working memory, enhanced processing speed, and longer attention span. These improvements are thought to be mediated through enhanced hippocampal neurogenesis and synaptic plasticity. Additionally, an interventional study in elderly individuals showed that three months of CR (a 30% reduction in caloric intake) had beneficial effects on memory performance (Culig et al. 2022).

Both IF and CR are beneficial in mitigating the epigenetic changes induced by aging, a key factor in the development of neurodegeneration (Mayor 2023). Emerging anti-aging strategies include autophagy enhancement, clearance of senescent cells, plasma transfusion from young blood, IF, promotion of adult neurogenesis, antioxidant intake, physical exercise, and stem cell therapies (Shetty et al. 2018). IF and CR offer numerous health benefits, such as extending lifespan, delaying the onset of age-related diseases, preventing or postponing age-associated cognitive decline, enhancing visual cortex plasticity, and improving cognitive function (Martin et al. 2006, Spolidoro et al. 2011, Fusco and Pani 2013). These interventions have also been shown to reverse age-related decline in neurogenic activity in glial cells of the dentate gyrus in aged rodents, significantly improving their survival (Bondolfi et al. 2004).

In clinical practice, compulsory CR may become particularly relevant in the context of bariatric surgery or specific neurological disease models, where metabolic and psychiatric side effects can be critical. Therefore, assessing the psychiatric impact of CR could contribute to a more comprehensive understanding of the pathophysiology of neurodegenerative diseases. Studies in patients who have undergone bariatric surgery have reported associations between changes in dietary habits and psychiatric conditions such as depression, anxiety, and eating disorders (Sevinçer et al. 2014, Bayrak et al. 2020). Such evaluations would allow consideration of CR not only from a neurobiological perspective but also in terms of its behavioral and psychosocial effects.

The Impact of Intermittent Fasting and Caloric Restriction on Neurodegenerative Diseases

Data from animal and epidemiological studies suggest that IF and CR may support healthy brain aging. Substantial evidence from animal models indicates that BDNF signaling plays a key role in the beneficial effects of IF and CR on brain aging. When rats or mice are fed on an IF regimen, BDNF levels increase and signaling is enhanced in various brain regions, including the hippocampus, striatum, and cerebral cortex (Duan et al. 2001, Lee et al. 2002, Setel et al. 2022). Moreover, considering that reduced BDNF levels have been linked to neurodegenerative diseases (Shetty et al. 2018), it becomes evident that dietary patterns have a significant impact on brain health.

BDNF is a key neurotrophin involved in neural development and plasticity, primarily through its roles in supporting neurogenesis, synaptic remodeling, and neuronal survival. During the developmental stages of the cerebral cortex and hippocampus, BDNF regulates the differentiation of NSCs into mature neurons and promotes the persistence of these newly generated cells within neural circuits (Lee et al. 2002, Barnabé-Heider and Miller 2003, Cheng et al. 2003). At the synaptic level, BDNF facilitates long-term potentiation (LTP)—a fundamental process underpinning learning and memory—by enhancing synaptic efficacy (Mattson et al. 2003). Beyond its direct neurogenic actions, BDNF expression in the brain is modulated by both nutritional and behavioral influences, which have also been shown to support neuronal plasticity and offer protection against age-related neuronal decline. Evidence from rodent models indicates that the positive effect of dietary restriction on hippocampal neurogenesis is substantially diminished in BDNF heterozygous knockout mice (Lee et al. 2002). Furthermore, blocking BDNF signaling via antibody infusion into the lateral ventricles eliminates the neuroprotective benefits of dietary restriction against excitotoxic damage in hippocampal neurons (Duan et al. 2001). These findings demonstrate that BDNF signaling plays a pivotal role in mediating neurogenesis. In an AD transgenic mouse model, 30% caloric restriction over a four-month period resulted in prominent changes in disease pathophysiology. Specifically, increased expression of genes supporting neurogenesis and synaptic plasticity in the hippocampus was observed,

along with a reduction in the expression of inflammation-related genes. These changes suggest that CR may slow disease progression by enhancing hippocampal neurogenesis (Murphy et al. 2014).

Furthermore, IF has been shown to improve impaired motor function in PD (Duan and Mattson 1999) and HD (Duan et al. 2003, Andika et al. 2021). In HD mouse models, CR can normalize BDNF levels and delay disease progression. This intervention promotes neuronal plasticity and protects neurons from oxidative and metabolic damage (Mattson 2003). Diet—its total intake, frequency, and composition—is a major environmental factor that influences brain plasticity, including AHN (Zainuddin and Thuret 2012). In addition to IF's previously demonstrated effects on lifespan extension (McCay et al. 1935) and preservation of neuronal integrity (Halagappa et al. 2007, Arumugam et al. 2010), it has also been shown to induce the expression of neurogenesis markers in the adult hippocampus and increase neurotrophic levels that promote neuronal proliferation (Duan et al. 2001, Kristina et al. 2014). One of the hypothesized mechanisms through which CR exerts its positive effects on cognitive aging involves its influence on adult neurogenesis. Experimental studies in young adult rats have demonstrated that CR can stimulate the generation of new neurons in the adult brain (Lee et al. 2000, Hornsby et al. 2016). In human research, findings from a study on obese adults suggest that CR may affect memory performance by modulating neurogenic activity (Kim et al. 2020). Additionally, evidence from mouse models indicates that CR promotes NSC proliferation in early life stages and mitigates age-associated declines in neurogenesis within the SVZ, which is linked to enhanced olfactory memory (Apple et al. 2019).

The formation of neurotrophic factors is another important adaptive and neuroprotective response to CR (Rothman et al. 2012). During IF, when the metabolic switch is active, glucose and insulin levels decrease, while BDNF expression increases (Wei et al. 2020). Given that adult neurogenesis is influenced by dietary factors (Poulose et al. 2017), a positive relationship has recently been proposed between food restriction and hippocampus-dependent cognition (Hu et al. 2017, Andika et al. 2021). In support of the link between IF and hippocampal neurogenesis (Baik et al. 2020), a study involving brain injury showed that one month of IF enhanced post-injury hippocampal neurogenesis and improved cognitive performance (Cao et al. 2022). This finding is particularly significant as it suggests that dietary patterns may not only preserve and enhance existing function but also have the potential to reverse impairment. IF increases the resistance of hippocampal neurons to excitotoxic stress, indicating various neuroprotective effects of IF (Anson et al. 2003). Therefore, stimulating neurogenesis through nutritional interventions to alleviate neurodegenerative diseases represents a promising therapeutic perspective (Melgar-Locatelli et al. 2023).

The literature on the relationship between IF and BDNF is predominantly based on animal models. In contrast, human studies have primarily focused on the beneficial effects of CR on cognitive functions. For instance, clinical trials have demonstrated that CR improves cognitive performance parameters such as working memory, episodic memory, and attention. These effects are believed to stem from CR's ability to increase BDNF levels, thereby supporting synaptic plasticity and promoting neurogenesis (Witte et al. 2009, Mattson et al. 2017). Table 1 below summarizes the findings of studies examining the relationships among AHN, IF, CR, and neurodegenerative diseases. These findings support the core hypotheses proposed in our study.

Table 1. Findings on the relationships between adult hippocampal neurogenesis, intermittent fasting, calorie restriction, and neurodegenerative diseases

Author (Year)	Sample	Method	Findings
Anacker and Hen (2017)	Review of human and animal model studies	Analysis of experimental and clinical studies on the effect of AHN on learning, memory, and cognition	Highlighted that AHN increases cognitive flexibility in learning and memory processes.
Bondolfi et al. (2004)	C57BL/6 mice in different age groups	Neurogenesis analysis in the dentate gyrus	While neurogenesis in the dentate gyrus significantly declined with age, CR notably increased the formation of new neurons in aged (24-month-old) mice and enhanced neuronal differentiation in the CR group.

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Author (Year)	Sample	Method	Findings
Cao et al. (2022)	Traumatic brain-injured mice	Evaluation of IF and hippocampal neurogenesis	IF increased NPY levels, leading to a rise in BrdU+ and DCX+ cell counts, indicating enhanced neurogenesis.
Culig et al. (2022)	Review study	Analysis of neurogenesis in aging and neurodegenerative diseases	Observed a marked decline in neurogenesis with aging and more severe hippocampal neurogenesis impairment in AD and PD. Suggested that nutritional interventions such as CR may protect and support declining AHN.
Duan et al. (2001)	3–6-month-old male C57BL/6J mice	Impact of CR and ad libitum feeding via BDNF	CR has been shown to elevate BDNF expression in the hippocampus while simultaneously decreasing indicators of apoptosis and oxidative damage.
Fu et al. (2015)	Aged and young mouse brain and spinal cord tissues	Cell composition analysis; comparison of age-related changes	Detected age-related cellular composition changes in the brain and spinal cord.
Hayashi et al. (2001)	Adult and aged macaque monkeys	Histological analysis of BDNF-immunoreactive structures	Found a significant reduction in BDNF immunoreactivity in the soma and dendrites of hippocampal neurons with aging. Decreases were observed in all subfields except the CA2 region.
Horgusluoglu et al. (2017)	Systems biology-based review study	Analysis of the links between adult neurogenesis and neurodegenerative diseases	It has been proposed that adult neurogenesis may play a significant role in the pathophysiology of neurodegenerative disorders.
Hornsby et al. (2016)	8-week-old male mice, 3 days of 60% CR	Assessment of short-term CR and Ghsr relation; evaluation of DCX+ immature neurons	CR significantly increased BrdU+ and DCX+ cell counts in the dentate gyrus of Ghsr+/+ mice, but not in Ghsr–/– mice.
Kandasamy et al. (2010)	HD animal model	Analysis of TGF-β levels and stem cell activity	In HD mouse models, a reduction in hippocampal neurogenesis was detected prior to motor symptoms. Increased TGF-β signaling was associated with stem cell quiescence.
Kaptan et al. (2015)	Adolescent female Sprague-Dawley rats under CR	Analysis of BDNF level, NeuN expression, and cell proliferation in the dentate gyrus	CR during adolescence improved spatial learning and memory in adulthood, increased BDNF levels, and upregulated neurogenesis markers in the hippocampus and prefrontal cortex.
Kuhla et al. (2013)	Aged C57BL/6 mice	CR and hippocampal gene expression analysis	In aged mice, CR has been shown to upregulate hippocampal genes involved in neurogenesis and synaptic remodeling, while simultaneously suppressing the expression of genes linked to inflammation and microglial activation.
Lazic et al. (2006)	R6/1 transgenic HD model mice	Evaluation of effects of environmental enrichment	Environmental enrichment increased neurogenesis and improved motor function in HD model.
Le Grand et al. (2015)	PD models	Analysis of neural stem cell dynamics related to neurogenesis	Highlighted disruption in neurogenesis and stem cell dynamics in Parkinson's disease.
Lee et al. (2000)	3-month-old male Sprague-Dawley rats under 40% CR	CR; measurement of neurogenesis in the dentate gyrus	CR increased BDNF expression and the number of new neural cells in the dentate gyrus.
Lee et al. (2002)	Adult mice (wild-type and BDNF heterozygous knockout)	3 months: ad libitum feeding vs. CR; evaluation of neurogenesis	BDNF is essential for basal neurogenesis and CR-induced neurogenesis was reduced in BDNF+/- mice.
Lim et al. (2018)	PD model mice	Evaluation of hippocampal neurogenesis	Significant reduction in hippocampal neurogenesis in the Parkinson's model.

Table 1. Findings on the relationships between adult hippocampal neurogenesis, intermittent fasting, calorie restriction, and neurodegenerative diseases

Author (Year)	Sample	Method	Findings
Mattson (2003)	Review of animal and human studies	Review of effects of diets like CR and IF on genes and brain functions	CR reduced oxidative stress, increased BDNF, enhanced synaptic plasticity and learning in both animals and humans.
Mendonça et al. (2025)	Aged mice model of Parkinson's disease	BDNF levels in dorsal striatum and cognitive areas	Aging caused reduced BDNF levels in dorsal striatum and cognitive areas, associated with impaired memory.
Murphy et al. (2014)	Literature review of animal and human studies	Effects of CR and IF on brain plasticity, neurogenesis, and inflammation	CR promoted expression of genes supporting neurogenesis and synaptic plasticity and reduced inflammation-related gene expression in the hippocampus.
Setel et al. (2022)	Adult male mice subjected to CR and herbal treatment	Neurogenesis and apoptosis markers in the hippocampus	CR alone showed modest effect, but combination with Astragalus membranaceus significantly increased neurogenesis and decreased apoptosis markers.
Wahl et al. (2018)	Male C57BL/6J mice; lifelong exposure to different dietary patterns	Analysis of low-protein and high-carbohydrate diets	CR was more effective in delaying brain aging compared to high carbohydrate diet.

Conclusion

Animal studies have demonstrated that numerous dietary patterns and components can increase hippocampal neurogenesis levels in adults while also enhancing synaptic function. It is also known that IF or CR can stimulate AHN. Therefore, aiming to alleviate neurodegenerative diseases by stimulating neurogenesis through nutritional interventions is a promising approach. Building on evidence that adult neurogenesis is modulated by dietary factors, recent studies have highlighted a positive association between dietary restriction and cognitive functions dependent on the hippocampus. Particularly noteworthy are findings demonstrating that IF can enhance hippocampal neurogenesis following neural injury and improve cognitive outcomes. These results suggest that dietary interventions not only help maintain and strengthen existing brain functions but may also contribute to the recovery of compromised neural capacities. Furthermore, the increased resilience of hippocampal neurons to excitotoxic stress under IF indicates its broader neuroprotective potential. Such cellular and molecular adaptations are likely to account for the observed enhancements in cognitive performance and emotional regulation in animal models subjected to IF and other dietary regimens across various neurological disease models.

Aging, being a major risk factor for neurodegeneration and the development of the most common neurodegenerative diseases, is associated with a decline in BDNF signaling as well as age-related loss and/or decline in NSC numbers and/or activity, leading to impaired brain function. These findings suggest that interventions that delay or reverse stem cell aging could extend human lifespan and healthspan. The multiple health benefits of CR and IF—including extending human lifespan, delaying the onset of age-related diseases, preventing or slowing age-related brain dysfunction, and improving cognitive function—along with the role of BDNF signaling in their beneficial effects on healthy brain aging, and the increase and enhancement of BDNF levels and signaling in various brain regions including the hippocampus, cerebral cortex, and striatum in rodents under IF cycles, position IF and CR dietary routines as promising candidates for functional outcomes in preventing neurodegenerative diseases, which is the key question we seek to answer.

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