

Review

Intermittent Fasting and Brain Health: Efficacy and Potential Mechanisms of Action

Nikita Francis ^{1, 2, *}

1. George & Anne Ryan Institute for Neuroscience, University of Rhode Island, 130 Flagg Road, Kingston, RI, 02881, US; E-Mail: Nikita_francis@uri.edu
2. Department of Psychology, Stony Brook University, 100 Nicolls Rd, Stony Brook, NY, 11794, US

* **Correspondence:** Nikita Francis; E-Mail: Nikita_francis@uri.edu

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Abstract

Despite continuous efforts to combat neurodegenerative diseases, researchers have been unable to find an intervention that reverses degeneration and/or improves cognition in dementia or healthy aging. Therefore, it is considerably important to identify lifestyle factors that could potentially aid in healthy brain aging and prevent or delay neurodegenerative diseases. The emerging interest in the ancient practice of fasting has inclined researchers to study the physiological and behavioral effects of this practice. Fasting is implicated in the promotion of longevity and prevention of obesity, diabetes, cancers, heart diseases, and neurodegeneration. The current review examines the health benefits of intermittent fasting on the brain. Four of the plausible mediational mechanisms by which intermittent fasting could provide benefits are discussed. These include lowering of insulin resistance and improving metabolic regulation, increasing autophagy, reducing neuroinflammation, and increasing the brain-derived neurotrophic factor. Most of the studies examined yielded positive results. Thus, based on the research findings, intermittent fasting seems to be a promising approach for promoting healthy brain aging and preventing neurodegenerative



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diseases. Nevertheless, the current understanding is limited, and long-term effects of intermittent fasting should be investigated both clinically and by using animal models.

Keywords

Intermittent fasting; time-restricted feeding; alternate day fasting; brain health; healthy aging; modifiable lifestyle factors; neuroinflammation; autophagy; BDNF; insulin resistance; Alzheimer's disease

1. Introduction

Over the past few decades, brain diseases associated with aging, such as neurodegenerative diseases, have become relatively common and are among the leading causes of death [1]. Decades of research could not identify a “pharmaceutical cure”, thus, initiating the search for modifiable lifestyle factors. Moreover, greater insight into the lifestyle factors and their effects on aging and neurodegeneration has shown promising outcomes. Many scientists agree that modern lifestyle factors, such as poor diet and lack of exercise, play a role in the accelerated brain aging and associated pathologies that are observed in modern society [2, 3].

The Western diet has been largely associated with declining health and the incidence of chronic diseases [4]. Hypercaloric diet and metabolic diseases adversely affect the brain, as well as aggravate the pathology and symptoms associated with neurodegenerative diseases [5, 6]. Therefore, dietary restriction is one of the modifiable lifestyle factors that are protective in healthy brain aging. Researchers have already established the positive benefits of caloric restriction, which refers to 20–30% lesser calorie consumption than one's standard calorie level on longevity and brain health in rodents [7]. In a 20-year longitudinal study conducted in rhesus monkeys, the investigators found that the survival rate was significantly increased in the caloric restriction group compared to the control group [8, 9]. Caloric restriction was observed to reduce the incidence of cardiovascular diseases and cancer-like symptoms (abnormal tissue growth) by 50%. Additionally, age-associated diseases (e.g., arthritis) and brain atrophy were significantly reduced in the caloric restriction group when compared to the control group. Moreover, studies that utilized a 3-month caloric restriction intervention in healthy-overweight elderly individuals found a significant improvement in verbal memory scores that were positively correlated with fasting insulin levels [10]. The studies in humans and animals have shown consistent positive benefits of caloric restriction on longevity and brain health [11-13]. The current review assessed the current state of knowledge about intermittent fasting, a dietary regimen that has recently gained attention for its possible health benefits.

2. Methods

A comprehensive search of peer-reviewed published studies and review articles was conducted in Google Scholar and PubMed with the search terms: fasting, intermittent fasting, intermittent energy restriction, time-restricted feeding, alternate-day fasting, and modified fasting. The studies were included based on the following criteria: 1) controlled studies using a minimum of 16 h of

fasting regimen, except for one observational religious fasting study with fewer hours (14–15 h) of fasting; 2) adult subjects of both genders.

3. Types of Intermittent Fasting

Despite the recent popularization, various forms of fasting have been practiced by humans since ancient times. Fasting is an ancient tradition that is useful in spiritual healing [12]. With the advancements across science over the course of the decades, we now have a better understanding of the physiological process of fasting and its potential health benefits. A basic definition of intermittent fasting is the pattern of eating in which the time spent in eating is restricted rather than the amount of food. There are various forms of intermittent fasting regimens (see Figure 1). One form is known as time-restricted feeding, where eating is restricted for certain hours in a day, such as fasting for 16 h with a feeding window of 8 h. This pattern can be altered for a shorter feeding window based on one’s lifestyle/preference. Other forms include alternate day fasting, which consists of a day of feeding, followed by a day of fasting [14]. Generally, intermittent fasting encompasses fasting from 16-48 h with little or no energy intake [15]. However, a daily time-restricted fasting window of 12 or 14 h has also been reported in the literature. Although this method of fasting is more prevalent in the weight management regimen, scientists have found these fasting regimens to have many more health benefits than weight loss alone. This method of feeding has been associated with increased lifespan and healthy brain aging through various physiological reactions which are initiated by fasting [16, 17].

Fasting regimen	Basic definition	Commonly practiced	Example from studies using specific regimen
Time-restricted feeding (TRF)	This form of intermittent fasting involves caloric intake during a certain feeding window in a day and fasting outside of that feeding window.	16/8 method: Fasting for 16 hours and caloric consumption during the rest of the 8 hours in a day.	Hatori et al. (2012) used a TRF regimen. Experimental mice had access to food for 8 hours a day while control mice had access to food ad libitum. [30]
Alternate-day fasting (ADF)	This form of intermittent fasting involves fasting every other day or on certain days of the week. Ad libitum caloric intake is followed on non-fasting days.	5/2 method: Fasting for 2 nonconsecutive days in a week and ad libitum caloric consumption for 5 days in the week.	Anson et al. (2003) used an ADF regimen where intermittent fasting experimental mice had access to food every other day. [27]
Modified alternate-day fasting	This form of intermittent fasting is similar to alternate day fasting, except it involves a severe caloric restriction on fasting days that meets only 15-25% of one’s caloric needs. Ad libitum caloric intake is followed on non-fasting days.	5/2 method: Caloric consumption of about 300-500 calories on 2 nonconsecutive days in a week and ad libitum caloric consumption for 5 days in a week.	Johnson et al. (2007) used a modified ADF regimen that involved 10 subjects consuming calories ad libitum every other day and consuming about 320-380 calories on the next day. [79]
Other types of fasting	Various types of fasting regimens followed for religious or spiritual discipline.	Ramadan Fasting: A fast from dawn to sunset practiced by Muslims during the sacred month. This is typically an 11-16 hour fast.	Faris et al. (2012) assessed proinflammatory cytokines in 50 subjects who practiced Ramadan fasting. These subjects fasted for 14-15 hours a day. [77]

Figure 1 Types of intermittent fasting regimens [14, 15].

4. Metabolic Reaction to Fasting

One of the more apparent benefits of dietary restriction is metabolic regulation through the reduction of metabolic markers associated with chronic diseases, such as insulin and glucose [18]. Typically, on dietary energy intake, blood sugar rises, and insulin is released to reduce blood glucose by pushing it into the cells. When high energy foods are consumed, more insulin is released to regulate the resulting elevated blood sugar. The chronic and excess glucose in the bloodstream becomes resistant to the effects of insulin, resulting in insulin overproduction [19]. Insulin can be reduced if there is an absence of glucose or food for some time. It can be achieved through fasting, and it is regularly practiced in clinical settings. For example, patients are required to fast for 8-12 h before drawing blood to achieve steady-state fasting levels for many metabolic substrates. Although the levels of glucose and insulin are lowered while fasting, the levels of ketone bodies (metabolic products produced during the breakdown of fatty acids) and adiponectin (involved in glucose regulation and fatty acid oxidation) are increased. Additionally, the levels of glucagon (converts stored glycogen into glucose) are increased and circulating leptin (inhibits hunger) levels are reduced [15].

4.1 Intermittent Fasting May Benefit the Brain by Regulating Metabolic Markers and Reducing Insulin and Increasing Insulin-Like Growth Factor (IGF)

Proper insulin metabolism is essential for brain health. Insulin and insulin-like growth factors (IGFs) regulate neuronal survival, energy metabolism, and plasticity, which are necessary for learning and memory [20]. However, peripheral hyperinsulinemia and insulin resistance syndrome result in the down-regulation of insulin transport to the brain [21]. With the lower levels of brain insulin, proper brain health is hard to be maintained, and cognition might be affected. This was evident in a study where rats were fed with high-fat and glucose diet, supplemented with a high-fructose corn syrup (to induce insulin resistance) and the rats showed impaired learning ability, reduced hippocampal dendritic spine density, and reduced long-term potentiation at Schaffer collateral—CA1 synapses [22]. Consistently, many studies have established an association between insulin resistance and neurodegenerative diseases. Mayo Clinic Alzheimer's disease (AD) Patient Registry reveals that 80% of AD patients have either type 2 diabetes or impaired fasting glucose levels [23-25]. Accordingly, when insulin was infused intravenously into healthy older adults and older adults with AD by the investigators, they found that a low dose of insulin facilitated memory in healthy older adults, though a subgroup of AD patients required higher doses [26].

The evidence for beneficial effects of intermittent fasting on metabolic regulation comes from both animal and clinical studies. For example, investigators found the mice that underwent alternate-day fasting (24 h of fasting) regimen for 20 weeks were similar in eating habits, and weight to ad libitum fed groups. They found that the limited daily feeding and the alternate-day fasting groups expressed similar levels of glucose and insulin, with both fasting groups being lower than the ad libitum fed group. However, levels of circulating IGF-1 were decreased in mice who were on the limited daily feeding diet but increased in mice on the alternate-day fasting diet [27]. According to past literature, increased IGF-1 signaling is associated with increased lifespan and neuroprotection [28, 29]. This is consistent with the finding of the significant increase in the

survival of neurons in CA1 and CA3 regions of the hippocampus in alternate-day fasting mice upon administration of kainic acid [27]. Another study also found that mice that were kept on time-restricted feeding (16/8 method) for 18 weeks were protected against obesity, hyperinsulinemia, hepatic steatosis, and inflammation and had improved motor coordination [30]. In this study, both the control and time-restricted mice were fed a high-fat diet and had access to food ad libitum; however, the time-restricted mice had access for 8 hrs/day. Although both groups consumed the same amount of food, the time-restricted feeding mice maintained much lower body weight, unlike the former study, and had less body fat. It is noteworthy that, although an overall reduction in caloric intake was thought to be necessary for health benefits, both investigators [27, 30] demonstrated otherwise. Similarly, in a study conducted on mice deficient in brain-derived neurotrophic factor (BDNF), it was found that alternate-day fasting (24 h of fasting) for three months reversed their abnormal phenotypes. Alternate-day fasting lowered obesity and hyperphagia to similar levels of body weight and food intake of intermittent fasting wild type (WT) mice [31]. BDNF deficient intermittent fasting mice also exhibited a significant decrease in blood glucose levels under both fasting and feeding conditions compared with BDNF mice that were maintained on an ad libitum diet. Furthermore, BDNF deficient ad libitum fed mice showed remarkably higher serum insulin levels and insulin insensitivity. In contrast, BDNF deficient intermittent fasting mice showed significantly lower serum insulin levels and expressed insulin sensitivity similar to WT levels. Thus, this study suggests that intermittent fasting was able to reverse the associated abnormal phenotypes in an animal model that typically expresses characteristics of metabolic syndrome.

Clinical studies have also shown the benefits of intermittent fasting in metabolic regulation. In one study, the investigators used a short-term fasting intervention (28 h) in healthy subjects and found a decrease in both glucose and insulin levels [32]. Consistently, in another study conducted on obese subjects where 8-week alternate-day fasting (24 h of fasting) regimen was followed, participants had a reduction in glucose, insulin, leptin, and fat mass [33]. Though caloric restriction also lowers insulin levels, it was recently observed that intermittent fasting significantly reduced fasting insulin and insulin resistance compared to caloric restriction despite a comparable reduction in body weight. In this 12-month study, investigators used a modified alternate-day fasting regimen of 25% caloric energy needs on fast days and 125% caloric energy needs on feast days [34]. Despite a significant reduction in insulin resistance, the question of whether intermittent fasting can reverse metabolic syndrome or type 2 diabetes remained unanswered.

Nevertheless, in a recent clinical study, fasting was used as a therapy for a 69-year-old man diagnosed with type 2 diabetes for 35 years [35]. The patient had been on metformin for 35 years and insulin treatment for 11 years. In the four months of several fasting regimens along with a low carbohydrate diet, the patient was able to completely discontinue his insulin treatment, reduce glycated hemoglobin levels, and reduce weight and waist circumference. Similar results were achieved when investigators followed three patients with type 2 diabetes for 10, 20, and 25 years [36]. All three patients were able to discontinue insulin within a month following a fasting regimen and a low carbohydrate diet. These case studies show that intermittent fasting could work naturally for some subjects in reversing type 2 diabetes. More extensive clinical studies are warranted to examine the effects of intermittent fasting on type 2 diabetes and metabolic syndrome.

Hence, the studies discussed showed that intermittent fasting could positively benefit

metabolic regulators (Figure 2).

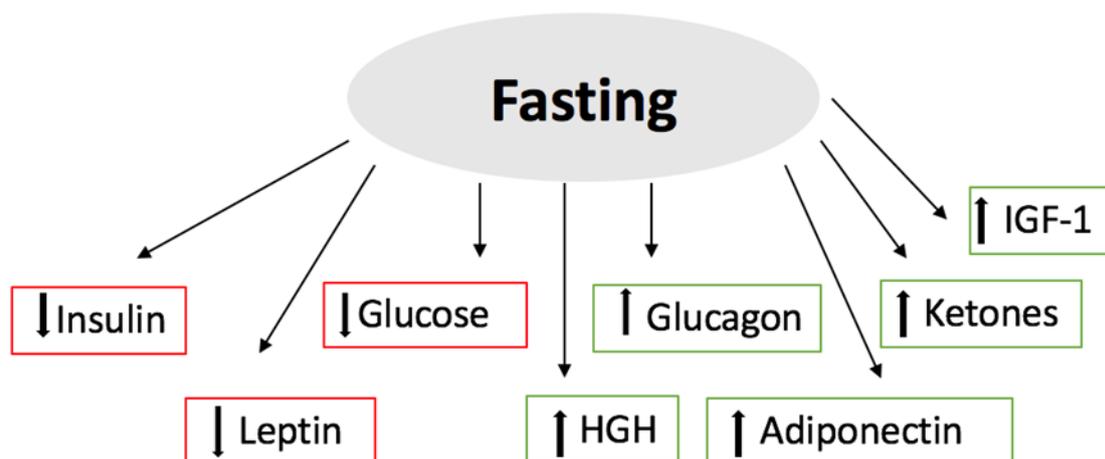


Figure 2 Effect of fasting on metabolic regulators [15, 37, 38].

4.2 Intermittent Fasting May Benefit the Brain by Increasing Human Growth Hormone (HGH)

The role of short term or periodic fasting in increasing human growth hormone (HGH) is well established in the literature [37, 38]. The reciprocal association between HGH and insulin was initially established in 1963 [39]. HGH has also been implicated in brain health due to its neuroprotective and anti-aging effects [40, 41]. The regulation of metabolism by HGH involves complex mechanisms. It includes stimulation of lipolysis and increased fat utilization, stimulation of the IGF-I system, insulin resistance and hyperinsulinemia, and protein conservation [42]. Furthermore, HGH has also been implicated in retaining muscle mass [43]. Accordingly, in a review comparing intermittent fasting and caloric restriction, it was found that weight loss from caloric restriction typically results from a 75–80% decrease in fat mass and a 20–25% decrease in fat-free mass. In contrast, weight loss from intermittent fasting results from a 90% decrease in fat and 10% as fat-free mass, suggesting maintenance of lean mass [44]. The retention of lean mass could be due to the increase in HGH.

5. Fasting and Autophagy

All living cells have an essential process known as autophagy or “self-eating”. The autophagy–lysosomal system is a complex chain of events leading to the clearance of misfolded or damaged proteins and dysfunctional organelles. Autophagy also helps in membrane biogenesis and vesicular transport. It is a regulated process that degrades and recycles cellular components. This cellular reorganization is beneficial for general health. Autophagy was discovered when researchers noticed an increase in the number of lysosomes (part of the cell involved in waste removal) in rat liver cells upon glucagon infusion [45]. Glucagon is a hormone that is produced in the fasting state to maintain glucose levels in the bloodstream by converting stored glycogen to glucose [46].

Since the accumulation of abnormal proteins is exhibited by most neurodegenerative diseases, upregulation of autophagy can be beneficial in neurodegenerative diseases. Consequently, many

recent studies suggested that the upregulation of the autophagy-lysosome pathway could be beneficial to neuronal health, and the downregulation could result in neurodegeneration. Accordingly, two studies in 2006 [47, 48] showed that the transgenic mice lacking autophagy-related 5 or 7 (ATG5 or ATG7), genes essential for autophagy, exhibited neurodegeneration and behavioral deficits. These observations were made in the absence of other harmful substances, such as the accumulation of abnormal protein found in neurodegenerative diseases. Consequently, the investigators predicted that the role of autophagy would be critical in the presence of pathology associated with various neurodegenerative diseases. For instance, the autophagy-lysosomal pathway has been implicated in the generation and clearance of the AD-associated protein amyloid-beta [49, 50] and degradation of α -synuclein, a protein observed to be abnormal in Parkinson's disease (PD) [51]. Likewise, autophagy is defective in other neurodegenerative diseases, including Huntington's disease [52] and amyotrophic lateral sclerosis [53]. Furthermore, it has been proposed that it could be a possible therapeutic target for neurodegenerative diseases [54]. However, further studies are warranted to establish a time point of the disease when autophagy is induced and the point of intervention in the autophagy pathway, since autophagic upregulation could have deleterious effects at the wrong time point of disease or in excess. Consequently, autophagy is often called the "double-edged sword" in the literature. Therefore, modulation of autophagy is a potential therapeutic target for a variety of diseases, especially neurodegenerative diseases. Autophagy can be induced by fasting.

5.1 Intermittent Fasting Upregulates Autophagy

One of the cellular reactions to fasting is the initiation of the autophagy-lysosome system [55]. A nutritionally fasted state deactivates the signaling of mammalian target of rapamycin complex 1 (mTORC1) pathway, thereby initiating ketogenesis and autophagy [56, 57]. This process of autophagy is unique to persons who are fasting compared to those on caloric restriction, as an absence of nutrients is required for this cellular reorganization [58]. Though the idea of food restriction inducing autophagy in other organs and tissues is well established [59, 60], autophagy in the brain due to food restriction was unconventional. However, in 2010, researchers showed that short-term fasting produces upregulation of autophagy in cortical and Purkinje neurons [61]. Here, they used a transgenic mouse model that encoded a fusion between green fluorescence protein (GFP) and microtubule-associated protein light chain 3 (LC3). They observed a substantial increase in cortical and Purkinje neurons in these mice. This effect was observed within 24 h of fasting and increased at 48 h. Correspondingly, in another study using an AD mouse model, fasted (48 h) mice showed an increase in the number, size, and signal intensity of autophagosomes in neurons using time-lapse imaging. The autophagosome parameters were higher in the AD mice before fasting and increased rapidly during fasting compared to the control mice. However, the increased autophagy was insufficient to degrade the intracellular amyloid-beta that was increased by enhanced uptake from the extracellular space during fasting. Although the intracellular accumulation of endogenous amyloid-beta was increased by fasting, there was no significant decrease in the extracellular amyloid-beta accumulation [62]. Nonetheless, it is noteworthy to consider that the investigators injected a high amount/concentration of amyloid-beta to visualize the metabolism *in vivo*. Additionally, the AD mouse model used was 5xFAD. Typically, the level of expression of amyloid-beta in this model was much higher than in human AD patients. Therefore,

the authors suggested that autophagy induced by fasting could reduce amyloid-beta in humans. However, another research team also found that alternate-day fasting (24 h of fasting) for 14 months in the triple-transgenic mouse model of AD (3xTgAD) mice did not reduce amyloid-beta but showed positive cognitive effects [63]. Therefore, one assumption of these results would be that fasting-induced autophagy could aid in the earlier phases of amyloidosis in a preventive manner. However, it may not be effective in conditions of established pathology with high levels of amyloid. Another consideration would be that intermittent fasting has no effect on amyloid-beta but may show positive effects through other neuroprotective mechanisms.

In a more recent study, utilizing the MCAO/R rats, which is a rat model of focal cerebral ischemia, the investigators found that two weeks of alternate-day fasting (24 h of fasting) activated neuronal autophagy and diminished the MCAO/R-induced accumulation of autophagosomes. Furthermore, this short-term intermittent fasting attenuated MCAO/R-induced autophagic flux. Autophagic flux is a balanced cycle of the generation and degradation of autophagosomes. Additionally, investigators also found that intermittent fasting attenuated neuronal death, apoptosis, infarct volume, brain edema, and behavioral deficits induced by MCAO/R [64]. The investigators also found that alternate-day fasting (24 h of fasting) in mice for six weeks restored autophagic flux in the pancreatic islets with diet-induced obesity [65], and it required intact lysosomal function. In another study utilizing Charcot–Marie–Tooth disease (CMT1A) mouse model, a progressive demyelinating disorder of the peripheral nervous system, five months of alternate-day fasting (24 h of fasting) was observed to increase the expression of autophagy-associated proteins. CMT1A exhibited an imbalance in the peripheral myelin protein 22 (PMP22). By following an intermittent fasting diet, the expression of PMP22 protein aggregates reduced by 50% compared to their ad libitum counterparts. These findings indicated that autophagy was increased in the nerves of intermittent fasting neuropathic mice, and the regimen stimulated the autophagy-lysosomal pathway in peripheral nerves [66].

These studies, in conjunction, suggested that intermittent fasting could induce autophagy. Furthermore, intermittent fasting regimens induce neuronal autophagy. In some animal models of diseases, intermittent fasting-induced autophagy was observed to have benefits of reversal of pathology. This finding could be of clinical relevance as autophagy has implications in many neurodegenerative diseases. Notably, intermittent fasting also stimulates growth hormone (as previously discussed). In other words, simultaneous signals to clean up and to grow and reproduce could have possible age-reversing effects. However, there is limited data, and more studies are warranted to study the effect of fasting-induced autophagy, specifically on neuroprotection and neurodegeneration.

6. Fasting and Neuroinflammation

Neuroinflammation is defined as the inflammatory response that occurs in the brain or spinal cord in response to injury, infection, or environmental cues, which is a part of the immune system's defense against foreign substances. It increases the activation of glial cells and the secretion of pro-inflammatory cytokines, chemokines, reactive oxygen species, and secondary messengers. The studies suggest that neuroinflammation plays a significant role in neurodegeneration and associated diseases [67, 68], such as AD [69, 70]. For example, overactive microglia were observed to induce amyloid-beta synthesis by activation of astrocytes in AD [71].

Inflammation and microglial activation are also common aspects of other neurodegenerative diseases, including PD, Huntington's disease, multiple sclerosis, and amyotrophic lateral sclerosis [72].

Neuroinflammation is considered a target for the treatment of neurodegenerative diseases by many researchers. With numerous failed attempts to treat AD with anti-amyloid beta strategies, many scientists in the field are increasingly interested in the role of neuroinflammation. Several studies indicated a dose-related negative correlation between the use of long-term nonsteroidal anti-inflammatory drugs (NSAIDs) during midlife and the probability of developing AD later [73-75]. However, a subsequent meta-analysis in 2015 analyzed seven studies that tested the efficacy of NSAIDs in the treatment of AD and concluded that they did not have any beneficial effect on cognition or overall AD severity [76]. These results suggested that NSAIDs or other anti-inflammatory agents might be useful for the prevention of AD or in its earlier stages, but may not be helpful for the treatment of advanced pathology. In accordance, neuroinflammation might be preceding or inducing amyloid-beta pathology, and subsequent neurodegeneration and the suppressed inflammation due to NSAIDs may no longer signal for the cascade of neurodegenerative pathology. By comprehensively linking neurodegeneration and neuroinflammation, it is suggested that the reduction of neuroinflammation, such as by fasting, could aid in preventing neurodegeneration.

6.1 Intermittent Fasting Reduces Neuroinflammation

Fasting reduces inflammation in the brain as well as in the periphery [77, 78]. For example, when researchers investigated the effects of Ramadan fasting in healthy subjects (14–15 h of fasting/day), it was found that inflammatory markers were reduced. The researchers observed significantly reduced levels of leukocytes and circulating pro-inflammatory cytokines (interleukin-1 β (IL-1 β), interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α)) in subjects' serum samples during the Ramadan fasting period compared to before and after fasting [77]. Similarly, another study used a modified alternate-day fasting regimen (less than 20% caloric needs on fasting days) intervention for eight weeks in overweight asthma patients [79] and found an improvement in bronchial responsiveness and reduction in several inflammatory markers suggesting that intermittent fasting can reduce systemic inflammation. Additionally, glucocorticoids, known for its anti-inflammatory effects, are elevated during fasting [80]. Evidence for reduced inflammation in the brain following a fasting regimen are observed in animal studies.

In a study, the researchers investigated the effects of intermittent fasting on stroke and examined the pro-inflammatory cytokines such as TNF- α , IL-1 β , and IL-6 implicated in ischemic brain injury. They found that the levels of TNF- α and IL-6 were significantly lower in the cortex and striatum of mice who were maintained on an alternate-day fasting (24 h of fasting) regimen for three months compared to those on the ad libitum diet. In response to ischemic stroke, the levels of both TNF- α and IL-6 significantly increased in both the ipsilateral and contralateral cortex and striatum. However, intermittent fasting suppressed the ischemia-induced increase in TNF- α and IL-6 levels. This dietary intervention was the most effective in young mice and least in old mice [81]. Consistently, another study utilized a rat model of sepsis by injecting lipopolysaccharide (LPS), and found that levels of multiple markers of neuroinflammation induced by LPS were reduced in rats maintained on the alternate-day fasting regimen for 30 days compared to those on the control

diet. The levels of the inflammatory markers such as iNOS and pro-inflammatory cytokines such as TNF- α , IL-1 β , IL-6, IL-1 α , RANTES (regulated upon activation, normal T cell expressed and secreted), and the LPS receptor TLR4 reduced in the hippocampus [82]. Similarly, a study investigated the benefits of alternate-day fasting in vascular dementia by utilizing a rat model of chronic cerebral hypoperfusion [83], which had bilateral common carotid artery occlusion (2-vessel occlusion (2VO)). They found an elevation of inflammatory proteins, including toll-like receptor 4 (TLR4), TNF- α , IL-1 β , and IL-6, in the hippocampi of 2VO-ad libitum rats compared with their controls. There was a significant increase in the numbers of ionized calcium-binding adaptor molecule 1 (Iba1)-positive microglia in both the CA1 and dentate gyrus regions of 2VO-ad libitum rats compared with the control group. However, 2VO rats that underwent intermittent fasting pre-treatment showed lower 2VO surgery-induced neuroinflammation with lowered inflammatory proteins and fewer Iba-1-positive microglia in the CA1 and dentate gyrus regions than the 2VO-ad libitum rats. Furthermore, intermittent fasting also alleviated oxidative stress markers in the hippocampi of 2VO intermittent fasting rats compared to the 2VO-ad libitum rats. Thus, evidence from these studies suggested that an intermittent fasting regimen could reduce neuroinflammation and oxidative stress in the hippocampus of rodent models.

7. Fasting and Other Benefits

7.1 Intermittent Fasting Increases BDNF Levels in the Brain

Brain-derived neurotrophic factor (BDNF), a member of the nerve growth factor family, is commonly identified as a protein necessary for the support and survival of neurons in the hippocampus [84]. BDNF in the brain has been implicated in memory and learning, and its deficit has been reported in neurodegenerative diseases, including AD [85].

Intermittent fasting has been associated with increased levels of BDNF in several studies. In an earlier mentioned study, investigators showed that systemic inflammation occurring in intermittent fasting prevented the reduction of BDNF levels in the hippocampus of rats [82]. More evidence on the beneficial effects of intermittent fasting on the brain BDNF comes from another study that utilized mice deficient in BDNF. It was found that mice that had been maintained on alternate-day fasting for three months exhibited a two- to three-fold increase in BDNF levels in each brain region of wild type (WT) mice compared to their ad libitum fed groups. Similarly, BDNF levels were also increased by two- to three-fold in each brain region of BDNF deficient mice that had been maintained on alternate-day fasting regimen compared with ad libitum fed group [31]. This result is consistent with the findings of another study on BDNF knockout mice. The investigators found that alternate-day fasting for three months enhanced neurogenesis in the dentate gyrus of both WT and BDNF knockout mice compared to the ad libitum fed groups and these newly generated neurons contained BDNF [86]. These studies suggested that neurogenesis observed in rodents following an intermittent fasting regimen could be due to increased BDNF levels and its subsequent actions on mature neurons. Additionally, the increased parasympathetic activity and reduced heart rate seen with intermittent fasting could be due to increased action of BDNF on the brainstem [87]. Collectively, these reports showed that intermittent fasting could increase BDNF levels in the brain and, subsequently, enhance protection against neurodegenerative diseases.

7.2 Intermittent Fasting Improves Memory Task Performance

A number of the previously discussed studies also included a behavioral component, demonstrating the positive influence of fasting on cognitive performance. A study that utilized 3xTg-AD mice found that caloric restriction or intermittent fasting diet for 14 months significantly increased activity levels in the open field. They also found them to be beneficial in the Morris water maze (MWM) test. Although old 3xTg-AD mice exhibited impaired memory retention compared to non-transgenic control mice, caloric restriction, and intermittent fasting diet ameliorated this age-related memory deficit in the MWM task [63]. Similarly, another study, which utilized an alternate-day fasting regimen for three months, also found intermittent fasting regimen's effect on MWM performance to be beneficial as a late intervention utilizing older rats (24-month-old). The older intermittent fasting rats performed poorly compared to the younger rats. However, intermittent fasting spared age-related spatial memory issues in the MWM [88]. Physical fitness was also improved in older intermittent fasting rats compared to the ad libitum rats in the rotarod task. The benefits of intermittent fasting on the rotarod task was discovered by other investigators as well [66, 89]. Another study investigating long-term (6–8 months) effects of intermittent fasting performed a series of behavioral tests on the mice, including rotarod, operant conditioning, eyeblink classical conditioning, and object recognition memory. Consistent with the results from other studies, alternate-day fasting mice outperformed their ad libitum counterparts in the rotarod task. In both operant and eyeblink conditioning paradigms, ad libitum and intermittent fasting mice learned the task in seven to eight sessions. However, intermittent fasting mice were faster, with significant differences observed in the second to fourth sessions. In the object recognition memory task, only intermittent fasting mice exhibited intact short-term (1 h) and long-term (24 h) memory. In contrast, when a 15-minute training protocol was performed, no differences were observed between the two groups [90]. Collectively, these studies suggested that intermittent fasting could benefit general activity levels, motor skills, and memory in rodents.

8. Limitations, Clinical Implications, and Future Studies

Though evidence for different health benefits was discussed in this review, the effects of intermittent fasting still need further research. A number of questions need to be answered, e.g., does intermittent fasting has primary benefits in reducing inflammation, upregulating autophagy, or balancing BDNF levels, and other related effects? Or a state of fasting (e.g., reduced insulin levels) activates different mechanisms? Given the variety of intermittent fasting regimens, which works best in humans with the least adverse outcomes? Could intermittent fasting be harmful in particular diseases or certain stages? The molecular mechanisms of fasting and its beneficial interactions need further understanding to identify possible novel targets for the prevention and treatment of disease.

A critical concern of the current applications of intermittent fasting on brain health is the lack of optimized guidelines, especially for associated food choices, exercise, and duration of fasting. The recommendation of intermittent fasting without consideration of other factors, such as the types of foods to consume, could have the unintended consequence of enhancing unhealthy food choices. For example, when following a 16/8 pattern but consuming highly processed and sugary (inflammatory) foods, liver glycogen will be depleted in a longer time. Therefore, the time to

achieve benefits of fasting may be increased in comparison to alternate-day fasting and/or a time-restricted feeding pattern with a focus on the quality of foods consumed. For beneficial effects, intermittent fasting might be best if combined with healthier food choices (e.g., less inflammatory foods). This idea is consistent with the previously discussed study that employed a fasting therapy combined with a low-carbohydrate diet for their diabetic patients [35]. The sustainment of benefits after ceasing an intermittent fasting regimen is also unknown, which is an essential consideration in facilitating long-term compliance with the regimen. Ultimately a combination of beneficial lifestyle factors could yield the most considerable benefits [91, 92].

The long-term effects of intermittent fasting on humans have also not been assessed. Although fasting was studied in rodents and significant benefits were observed, long-term trials in humans are required. The studies discussed in this review raise some interesting questions about intermittent fasting and its therapeutic potential. The clinical trials have already yielded positive effects of fasting on cancer (chemotherapy protection), diabetes, and rheumatoid arthritis. However, more studies are required, particularly on brain diseases. It is also essential to understand the difference in effects of fasting with those of other lifestyle factors such as exercise, in addition to the manner in which these interact with each other. Exercise has similar beneficial effects as intermittent fasting [93], such as reduced neuroinflammation and improvement in mood and cognitive function in both healthy rodents and diseased models [94-96]. Therefore, future studies should utilize an exercise group, a fasting group, and a combination of both groups, which could aid in our understanding of which intervention is the most beneficial across several measures, as well as to determine the effects of combining fasting and exercise. The combination could have stressful and detrimental effects on the body.

Furthermore, studies should also investigate the differences between the ketogenic diet and intermittent fasting. The shift to ketogenesis that occurs during intermittent fasting has implications on neuroprotection, as ketone bodies are neuroprotective in rodent models of neurodegenerative diseases [97], and ketogenic diets have been suggested in treatment for patients with epilepsy [98] and neurodegenerative diseases [99]. Similar to intermittent fasting, ketone bodies are also produced in a ketogenic diet. Ketone bodies are produced from the stored fat in intermittent fasting; however, in the ketogenic diet, they are produced from the consumption of high fats and low carbohydrates. Additionally, it should be further investigated whether intermittent fasting of Western diet foods can yield long-term positive effects.

Most studies on intermittent fasting use an approach of alternate-day fasting. Different intermittent fasting regimens should be further investigated to understand their outcomes. For example, the intermittent fasting regimen, which is the most beneficial with the least consequences, should be identified. Moreover, the consequences of different intermittent fasting regimens on different individuals (based on age, sex, disease states, etc.) should be assessed. Furthermore, studies should consider investigating the effects of intermittent fasting on quality of life, mood, and behavioral changes. Additionally, the amount of time the benefits are sustained following an intermittent fasting regimen should be examined. These studies should assess cognitive function, brain imaging, neural network activity, and biochemical analyses of cerebrospinal fluid in human subjects before, during, and after the period of intermittent fasting. The studies should utilize patients with various neurological disorders and healthy controls to assess the effects of these interventions in the diseased state.

9. Conclusions

This review provides evidence for possible benefits of intermittent fasting, such as reduced insulin, increased IGF, improved metabolic regulation, increased autophagy, reduced neuroinflammation, increased levels of BDNF, and improved behavior. The key point is the effect of modifiable lifestyle factors in healthy aging. Many other lifestyle factors, such as diet, exercise, cognition, and social enrichment, have also been implicated in longevity, healthy brain aging, and prevention/treatment of neurodegenerative diseases [5, 95, 96, 100]. Since pharmacological interventions alone are ineffective in combating age-related diseases, scientists have advocated the incorporation of a combination of these modifiable lifestyle factors, which could aid in healthy aging and thus decrease the risk of neurodegenerative diseases. Although whether intermittent fasting could be considered a modifiable lifestyle factor to protect the aging brain is still questionable.

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Author Contributions

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Competing Interests

The author has declared that no competing interests exist.

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