A Brief Overview about Possible Correlation Between Intermittent Fasting and Cognitive Functions

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Abstract

Background: The importance of diet and the gut-brain axis for brain health and cognitive function is increasingly acknowledged. Dietary interventions are tested for their potential to prevent and/or treat brain disorders. Intermittent fasting (IF), the abstinence or strong limitation of calories for 12 to 48 h, alternated with periods of regular food intake, has shown promising results on neurobiological health in animal models. In this review article, we discuss the potential benefits of IF on cognitive function and the possible effects on the prevention and progress of brain-related disorders in animals and humans. We do so by summarizing the effects of IF which through metabolic, cellular, and circadian mechanisms lead to anatomical and functional changes in the brain. Clinical studies show benefits of IF for epilepsy, Alzheimer's disease, and multiple sclerosis on disease symptoms and progress. Findings from animal studies show mechanisms by which Parkinson's disease, ischemic stroke, autism spectrum disorder, and mood and anxiety disorders could benefit from IF. Future research should disentangle whether positive effects of IF hold true regardless of age or the presence of obesity. Moreover, variations in fasting patterns, total caloric intake, and intake of specific nutrients may be relevant components of IF success.

Keywords: Intermittent Fasting, Cognitive functions

Introduction

Dietary restriction (DR) is defined as a decrease in energy consumption without reducing nutritional value. This simple dietary intervention has been shown in a wide range of experimental animals to extend life span and decrease the incidence of several age related diseases **(1)**.

The definition of DR has been expanded from an alternative description of caloric restriction (CR) to also encompass a broader scope of interventions, including short- term starvation, periodic fasting, fasting-mimetic diets, and intermittent fasting (IF) **(1)**.CR has been demonstrated to mitigate the age‐associated decline of several pathophysiological parameters and to extend the maximum lifespan in various animal species **(2).**

There are some energy storage organs in the body, such as adipose tissue and the liver, that enable fasting **(1)**.It is defined as abstinence from or reduction of food, drink or both for a period typically lasting between 12 h and 3 weeks, in short‐ term, long‐ term or intermittent patterns **(3).**

Intermittent fasting:

Intermittent fasting (IF) is a term that covers types of diets which include cycles of fasting and non fasting**.** In fact, IF has been practiced by the Muslim population for over a thousand years in the month of Ramadan. This usually involves 12‑16 h of daily fasting by abstinence of both drink and food for one month **(4).**

The health benefits of IF have been extensively demonstrated in animal models **(5**). Furthermore, certain observational studies have been performed suggesting potential benefits of reduced cancer risk and metabolic disease associated with IF in humans **(6).**

General effects of Dietary restriction and Intermittent fasting:

Moderate DR or reduced calorie intake is known to reduce blood sugar, increase insulin sensitivity **(7),** alleviate aging, reduce age-related chronic diseases, and prolong life expectancy **(8).**

IF has been shown to increase lifespan, regulate energy metabolism, and reduce the risk of developing different age-related diseases. Notably, epidemiological studies have found that individuals with a reduced calorie intake have a reduced risk of AD **(9)**.

Human adult hippocampal neurogenesis (AHN), the postnatal process by which new neurons are generated from neural stem cells, has so far been shown to occur in a unique neurogenic niche within the dentate gyrus of the hippocampal formation throughout life **(10).**

Moreover, the rate of physical and mental performance increases during fasting due to improvement in metabolic processes (metabolic shift to ketone bodies) and neurotransmission through increased GABA and serotonin signaling. In previous animal experiments, DR increased the expression of neurotrophic factors and promoted neurogenesis in the mouse brain. Also many studies have been conducted into the beneficial effects of DR on the cardiovascular, immune, and endocrine systems **(11).**

DR and physical exercise have been proven as an effective measure to reduce the risk of cardiovascular disease in obese humans **(9)**. Additionally, long-term DR has been reported to reduce serum lipid concentrations and arterial blood pressure. Moreover, it has a neuroprotective effect as it can delay neuronal degeneration in AD. Initiation of DR early in the adulthood stage has been reported to be the only means of delaying the onset of the age associated diseases. Other studies reported that DR even initiated at late age or for a limited time can also have beneficial effects **(12)**.

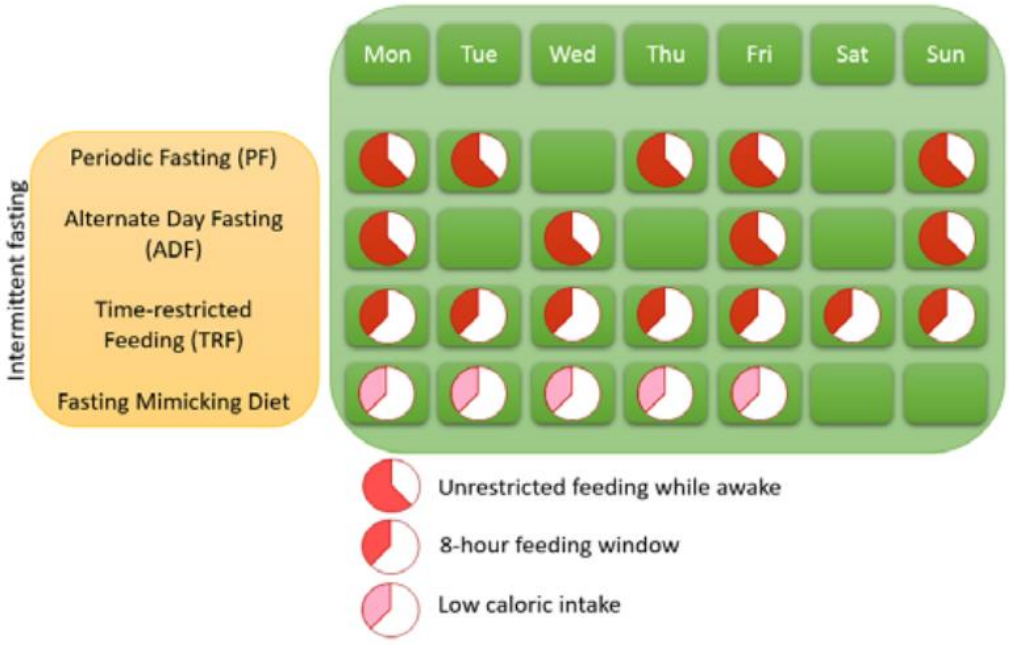

Figure 1. Different forms of intermittent fasting.

Intermittent fasting and oxidative stress:

Oxidative stress can promote the development of metabolic-related complications**.** It damages cellular structures together with under production or low bioavailability of antioxidants, which can exacerbate the development of obesity-related complications**.** While the mechanisms involved in the propagation of oxidative stress in obese states are complex, some principal processes include immune cell activation leading to downstream production of free radicals , synthesis of pro-inflammatory cytokines ,depletion of antioxidant sources , increased free fatty acid levels leading to endoplasmic reticulum stress , mitochondrial and peroxisomal oxidation **(13).**

IF has useful effects like weight loss and reduced oxidative stress which can be determined from the malondialdehyde (MDA) levels and tri acyl glycerol (TAG) in the blood**,** also amelioration of glucose regulation, increasing cellular stress resistance, and inflammation reduction**.** IF has a strong influence to ameliorate total circulating cholesterol, low-density lipoprotein-C, and triacylglycerol (TAG) **(**, increasing antioxidants, modifying behavioral patterns, and maintaining redox balance in certain tissues **(14).**

The body of a human being is able to deal with oxidative stress through enzymatic and non-enzymatic antioxidants, superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (Cat), which are the most abundant enzymes**.** The body is protected from superoxide by SOD which is the main antioxidant enzyme. Superoxide is catalyzed by SOD to become hydrogen peroxide, then by GPx and Cat to be converted into water which are able to lower oxidative stress. In the case of IF oxidative stress induces the antioxidant system to get rid of the free radicals, which repairs cell damage **(15).**

Effects of Intermittent fasting on metabolism:

Certain studies reported that fasting improves the metabolic state due to weight loss and a greater extent of fat burning**.** Flipping the metabolic switch entails that the body switches from its preference to extract energy through the process of glycogenolysis (breakdown of glycogen into glucose) to lipolysis (the utilization of stored fat in the form of lipids from adipose tissue). Subsequently, released lipids are metabolized to free fatty acids (FFAs) and are while first being transformed into the intermediate stage Acetyl CoA through the process of β-oxidation transformed to the ketones β-hydroxybutyrate (BHB) and acetoacetate (AcAc) **(1)**.

During IF, glucose levels drop and through the process of lipolysis, fats (triacylglycerols and diacylglycerols) are metabolized to FFAs. These lipids are then transported to the liver where they through the process of β-oxidation and the intermediate stages acetyl CoA and hydroxy methyl glutaric COA (HMG-CoA) are transformed into the ketones: acetoacetate (AcAc) and β-hydroxybutyrate (BHB). BHB and AcAc are transported from the blood into the brain and then into neurons. In addition to ketones metabolized in the liver, astrocytes are also capable of ketogenesis, which may provide an important local source of BHB for neurons **(16).**

The reduction in availability of glucose and elevation of ketones lowers the AMP: ATP ratio in neurons, which activates the kinases AMPK and CaKMII and, in turn, through the activation of CREB and PGC1α stimulates autophagy **(16).**

In addition, lower levels of glucose during fasting decrease the activity of the mammalian target of rapamycin (mTOR)pathway, leading to autophagy. BHB can also upregulate the expression of brain-derived neurotrophic factor (BDNF) and may thereby promote mitochondrial biogenesis, synaptic plasticity, and cellular stress resistance. IF leads to lower levels of circulating insulin in the blood, which enhances neuroplasticity and protection against metabolic and oxidative stress through the insulin/IGF signaling pathway **(1)**.

What makes these ketones particularly interesting for cognition is that they become the preferred fuel for the brain during fasting periods. Namely, in addition to the role of ketones as an energy source, these also regulate transcription factors (for example, CREB or PGC1α) in neurons **(17)**.

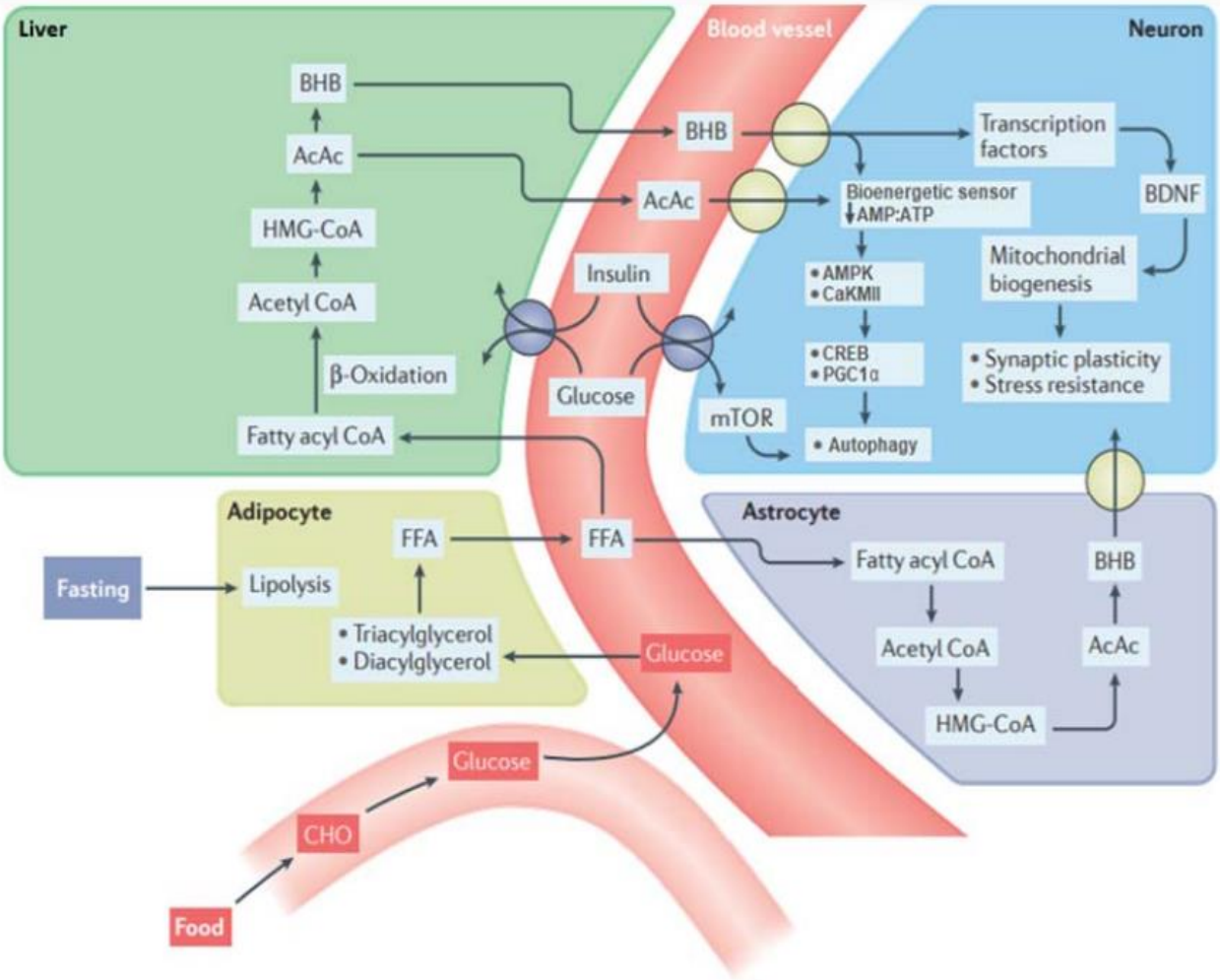

Figure 1. Biochemical pathways involved in the metabolic switch. During intermittent fasting, glucose levels drop and through the process of lipolysis, fats (triacylglycerols and diacylglycerols) are metabolized to free fatty acids (FFAs). These lipids are then transported to the liver where they through the process of β-oxidation and the intermediate stages acetyl CoA and HMG-CoA are transformed into the ketones: acetoacetate (AcAc) and β-hydroxybutyrate (BHB). BHB and AcAc are transported from the blood into the brain and then into neurons. In addition to ketones metabolized in the liver, astrocytes are also capable of ketogenesis, which may provide an important local source of BHB for neurons. The reduction in availability of glucose and elevation of ketones lowers the AMP: ATP ratio in neurons, which activates the kinases AMPK and CaKMII and, in turn, through the activation of CREB and PGC1α stimulates autophagy. In addition, lower levels of glucose during fasting decrease the activity of the mTOR pathway, leading to autophagy. BHB can also upregulate the expression of brain-derived neurotrophic factor (BDNF) and may thereby promote mitochondrial biogenesis, synaptic plasticity, and cellular stress resistance. IF leads to lower levels of circulating insulin in the blood, which enhances neuroplasticity and protection against metabolic and oxidative stress through the insulin/IGF signaling pathway. Retrieved from [18] with small modifications.

BHB and AcAc are transported from the liver to the brain where they are metabolized back to acetyl CoA and HMG-CoA, which results in the upregulation of brain-derived neurotrophic factors (BDNF) **(1)**.The upregulation of BDNF is associated with the promotion of mitochondrial biogenesis, synaptic plasticity and cellular stress resistance in animal models **(1)**.

Enhanced BDNF levels during IF are also found in humans **(18)** and it is hypothesized that enhanced circulating BDNF also leads to an increase in BDNF in the brain **(1)**.

In animal models, the lowered levels of glucose during IF also leads to a reduction in the ATP:AMP ratio in neurons, which after some hours of fasting activates the AMPK and CaKMII kinases **(19)**. Activation of their downstream transcription factors (CREB and PGC1α) enables these kinases to inhibit anabolic processes, thus inhibiting cell growth and protein biosynthesis **(19)**. This, in turn, triggers repair by stimulating autophagy, a process where neurons remove dysfunctional or damaged components **(19)**.

Neurons are able to regulate the synthesis of proteins in response to fluctuations in the availability of nutrition, namely through the mTOR pathway. In a non-fasting state, activation of the mTOR pathway leads to protein and lipid synthesis. In contrast, activity of the mTOR pathway decreases during fasting periods and this leads to global inhibition of protein synthesis and the recycling of dysfunctional proteins by autophagy. Autophagy is also responsible for the body's ability to cope with oxidative stress which deteriorates by age and during the progress of neurodegenerative diseases. Inhibition of the mTOR pathway leads to an improvement in antioxidant defenses , DNA repair, and stimulation of BDNF **(20)**.

Effects of Intermittent fasting on cognition:

DR has antioxidant and anti-inflammatory properties. IF in animal models is a DR regimen in which food is allowed but only every other day. It can prevent neuro inflammation and oxidative stress **(9)**.Thus, it is important to change the current feeding habits and to find a new easy applicable strategy to prevent these health hazards. For example, mice on a high fat diet display increased anxiety-like behavior and impaired learning **(21)**.

IF is a new DR method that is proven to boost body metabolism, decrease body fat, and body weight, as well as cognitive impairment. Across-sectional study of 428 children concluded that poor diet quality is associated with worse cognition**.** Whilst on the other end of the ageing spectrum, good nutritional status may delay functional decline in the elderly **(22).**

Effect of Intermittent fasting on mood and anxiety:

Mood-and anxiety disorders comprise a group of disorders that share a key feature of a general distorted emotional state, leading to feelings of sadness or anxiety, which clinically manifests in ensuing behavioral, emotional, cognitive, and physiologic responses. It was found that the effects of IF on mood- and anxiety disorders together as there is high co-morbidity between these disorders **(23)**.

BDNF levels, that are associated with both chronic stress and chronic depression, were increased by a 9 h fast in a recent mice study also inducing antidepressant effects **(24)**.

These effects of fasting were reversed by a 5-hydroxy trptamine(5-HT2a) receptor agonist, showing a link between fasting and this mood-related neurotransmitter system. In healthy humans, 6 months of IF improved mood as measured with the Hospital Anxiety and Depression Scale and World Health Organization Wellbeing Index **(25)**.

Three months fasting in combination with CR in aged men reduced emotional reactivity symptoms such as tension and anger on the Profile of Mood States questionnaire, but not depression symptoms **(26).**

Intermittent fasting and neurodegenerative disorders:

Previous experiments demonstrated that IF could have a protective role in many neurodegenerative disorders, including Parkinson's disease (PD) in both rodents and humans **(9)**.

Neurogenesis is the formation of new neurons in the brain. Normally, the hippocampus is the main site for neurogenesis under the effect of several neurotrophic factors. The most prevalent neurotrophic factor is BDNF, which is considered to play an integral role in stimulating the growth of new brain cells and the performance of existing neurons; BDNF is best described as the brain's growth hormone. Several factors affect the expression of BDNF, such as exercise, sleep, aging, and dietary habits **(27)**.

The process of neurogenesis is controlled by a variety of factors, such as neurotrophic factors, blood glucose level, insulin, lipid profile, corticosterone level, and oxidative stress **(27)**

BDNF and neurotrophin 3 (NT3) are members of the neurotrophin family that play important roles in the functioning of the central nervous system, such as synaptic plasticity and the maturation, growth, and maintenance of neurons, which have a great effect on cognitive function and emotion **(28)**.

IF has been proposed to be neuroprotective against acute brain injuries, such as stroke, and neurodegenerative diseases. In addition, IF enhances hippocampal neurogenesis and LTP at hippocampal synapses. Neural progenitor cell production is up regulated with antidepressant treatment and conversely, Hippocampal neurogenesis is reduced in depressed patients **(29)**.

Similarly, animal models of depression result in reduced hippocampal neurogenesis and antidepressants serve to increase cell proliferation and neurogenesis **(30)**.

Alzheimer's Disease

The underlying mechanism that causes Alzheimer's disease (AD) is unknown. It is known, however, that AD is pathologically characterized by beta-amyloid (Aβ) plaques and neurofibrillary tangles, leading to neuronal death, which is clinically characterized by a decay in cognitive abilities. Several studies using animal models have indicated that IF could reduce the accumulation of Aβ plaques and slow down cognitive decline Since the exact mechanism of AD is not yet fully understood, the mechanisms by which IF can have effects on AD is also only open for speculation. It is argued that IF can decrease and/or prevent AD-related neuropathology and cognitive decline by upregulating neuronal stress-resistance pathways and suppress inflammatory processes through decreased activity of the mTOR pathway. on prevention of age-related neurological disorders and cognitive decline). In the brain, there is a reduction in glucose metabolism rates with age, which can be present long before the onset of AD and is associated with Aβ plaque density. Ketones may present an alternative energy source in a hypometabolic state. In patients suffering from AD or mild cognitive impairment, injected BHB (a ketone) after approximately 12 to 16 h of fasting has led to improved cognitive functioning, assessed in various neuropsychological tests administered 90 min after injection. In terms of IF, a 14-h TRF diet for 30 consecutive days has shown to reduce amyloid precursor protein (APP), the precursor of Aβ, in the blood of fourteen healthy subjects. Ooi and colleagues found that a 3-year PF diet enhanced cognitive functioning in older adults with mild cognitive impairment compared to age-matched adults who irregularly practice PF and age-matched adults who do not practice PF. **(31).**

Parkinson's Disease

Parkinson's disease (PD) is characterized by the presence of α-synuclein-containing Lewy bodies and the loss of dopaminergic neurons in the substantia nigra (SN), which is clinically manifested by motor control problems (i.e., rigidity, bradykinesia, and tremor) and cognitive deficiencies. An animal model of PD, in which the degeneration of nigrostriatal neurons causes PD-like behavior, can be induced by the administration of mitochondrial toxins that accumulate in dopaminergic neurons. Using this model, neurotoxic-induced PD mice on a FMD showed greater retention of motor skills and less dopaminergic neuronal loss in the SN. Specifically, a FMD reshaped the composition of the gut microbiota which through the signaling effects of metabolites restored the balance of astrocytes and microglia in the SN which are believed to be responsible for the inflammatory reactions in PD. BDNF, important for the survival of dopaminergic neurons was enhanced in mice practicing a FMD and was therefore speculated to have a role in the FMD-mediated neuroprotection. Higher levels of BDNF were also found in macaque monkeys on a TRF regimen who were neurotoxically injected to mimic PD, which led to reduced motor deficiencies and attenuated dopamine depletion. In humans, no clinical trials are yet initiated early in the disease process and continued long enough (1 year or longer) to detect a disease-modifying effect of IF. **(32)**

Multiple Sclerosis

Multiple sclerosis (MS) is an autoimmune disorder in which abnormal T-cell mediated inflammatory response of the body causes demyelination and axonal damage, leading to neuronal death. Clinically, patients with MS show deficits in complex attention, efficiency of information processing, executive functioning, processing speed, and long-term memory. MS is more common in Western countries with nutrition being a potential contributing factor, which led researchers to examine the role between IF and MS. Three cycles of a FMD completely reversed disease progression in MS-induced mice. A possible mechanism of IF on MS disability might be modulation of the gut microbiota, as 4 weeks of ADF activated microbial metabolic pathways and increased gut microbiota richness in a MS animal model. This, in turn, led to lowered levels of T-lymphocytes, which are believed to be causative of MS pathogenesis. Interestingly, transplantation of gut microbiota of MS-mice on an IF diet reduced MS pathogenesis for MS-mice without an IF diet. In humans, a 7-day cycle of FMD led to lowered self-reports of MS disability in 60 MS patients. **(33)**

3.2. IF and Acute Central Nervous System Injury

Ischaemic Stroke

Ischaemic stroke is characterized by a blockage of blood flow to a part of the brain leading to neuronal death and loss of (cognitive) functionality. In animal models of focal ischemic stroke, rodents on a 3-month ADF diet prior to cerebral vessel occlusion exhibited reduced cortical neuronal loss and reduced cognitive decline in comparison with animals fed ad libitum. Same results were obtained for the recovery of spatial memory deficits in rats maintained on a 3-month TRF diet before cerebral vessel occlusion compared with rats fed ad libitum. During an ischemic attack, quick reperfusion of blood flow is associated with better clinical outcomes, but reperfusion is contradictorily associated with exacerbation of tissue injury. Reactive oxygen species (ROS), a type of free radicals, have a critical role in initiating cell death and therefore enlarge tissue injury. Enhanced levels of ketones during a fast are thought to mediate the excitoprotective effects of IF by decreasing the levels of ROS. Injected ketones after cerebral vessel occlusion in rats were found to decrease levels of ROS, which led to enhanced stress resistance as well as suppression of neuroinflammation, which are both positive for cell survival. Interestingly, fasting initiated just after injury and maintained for 24 h reduced neuronal loss in rats which could be clinically relevant for humans but up to this date has not yet been tested in clinical or randomized controlled trials. However, the Ulsan University Hospital of South Korea is currently examining the efficacy of TRF in a RCT by randomly assigning ischemic stroke patients to a 6-months TRF group or a control group. In an observational study, Bener and colleagues reviewed the number of ischemic stroke hospitalizations for Muslims while fasting during the Ramadan (which is a type of TRF) and compared this incidence to non-fasting months. However, they found no differences in the number of hospitalizations for stroke between Ramadan and non-fasting months. **(16).**

Epilepsy

Epilepsy is a neurological disorder characterized by recurrent bursts of abnormal excessive neuronal activity, named seizures, in which motor control and often consciousness is lost. There is accumulating evidence that metabolic and biochemical effects of IF, including reduced blood glucose levels, inhibition of mTOR signaling, decreased inflammatory markers, increased AMPK signaling, and increased autophagy, leading to antiseizure and antiepileptogenic effects in animal models. In an animal model of epilepsy, rats maintained on ADF for several months exhibited less neuronal hippocampal damage and showed improved performance on a spatial water maze after being induced with a seizure compared to seizure-induced rats fed ad libitum Similar results have been found for 7–10 weeks and 6 months of ADF in epilepsy-induced rats In children with epilepsy not responding to antiepileptic treatment, a PF regimen for two months improved seizure control in four out six children. **(16).**

Effect of Intermittent fasting on microbiota-gut-brain axis and its relationship on brain health:

An interesting mechanism mediating the effect of IF on brain health and cognition is the microbiota-gut-brain axis (MGBA). The human gastrointestinal tract is colonized by trillions of microorganisms or gut microbiota, collectively termed the gut microbiome. A higher diversity (richness) of microbiota is associated with healthier metabolic markers such as increased insulin sensitivity **(34)**.

The composition of the gut microbiota is particularly interesting for cognition and brain-related disorders because there is increasing evidence that the composition of the gut microbiota directly influences the brain through neural, endocrine, and immune pathways, collectively called the microbiota-gut-brain axis. The MGBA has several modes of action through which the gut microbiota can affect the brain. First, the microbiota modulates the interaction between the enteric nervous system and the central nervous system through the vagus nerve . Second, the gut microbiota produces microbial (neuro) metabolites, signaling molecules which exert their effect by functioning as substrates for metabolic reactions **(16).** Third, the gut microbiota also has an indirect effect on the brain and behavior through the effects on immune system activation **(35)**.

The diversity in gut microbiota composition depends on several factors, of which diet is a major one as well as dietary timing. The abundance of±15% of microbiota dynamically oscillates in activity and relative abundance throughout the day in response to circadian and hormonal fluctuations and moments of dietary intake **(36)**.

Microbiota play a role in processes like the digestion of food components, host metabolism, and the maturation and function of the immune system, all of which show some degree of circadian control. It is hypothesized that dynamically oscillating microbiota respond to and accommodate diurnal fluctuations in the environment such as feeding timing **(36)**. A western diet, eating close to or during the rest period, dampens microbiota oscillations, leading to a less diverse gut microbiota **(36)**.

Interestingly, thyroid releasing factor (TRF) is able to restore these cyclic fluctuations and thereby contribute to a richer diversity of the gut microbiota, even when nutritional intake is unaltered **(37)**. The gut microbiota may, through their role in metabolism, circadian rhythms, and immune functioning, mediate the effects of IF on brain health and cognition. Several animal studies have indeed found that IF changes the composition of the gut microbiota **(38)**.In the study of Liuand colleagues, IF enriched the gut microbiome composition and altered microbial metabolites which led to improved cognitive functioning, for example in spatial memory tasks **(38)**.Antibiotics treatment, detrimental for the gut microbiota, suppressed this improvement **(38)**.

Conflicts of Interest: The authors declare no conflict of interest.

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