Available online on 15.03.2024 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

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Review Article

Exploring the Neuroprotective Effects of Intermittent Fasting: A Comprehensive Review on its Impact on Neurological Diseases

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Article Info:

Article History:

Received 12 Jan 2024
Reviewed 10 Feb 2024
Accepted 27 Feb 2024
Published 15 March 2024

Cite this article as:

Jeevitha M, Shanmuga Sundhram R, Sambath Kumar R, Exploring the Neuroprotective Effects of Intermittent Fasting: A Comprehensive Review on its Impact on Neurological Diseases, Journal of Drug Delivery and Therapeutics. 2024; 14(3):174-178

DOI: http://dx.doi.org/10.22270/jddt.v14i3.6486

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Abstract

Background: Intermittent fasting has various benefits for brain health, owing to the physiological alterations occurring in the human body during intervals of fasting. Fasting induces a metabolic condition that improves neuronal bioenergetics, plasticity, and resilience, potentially counteracting a variety of neurological disorders.

Objectives: In the current research, we reveal the impact of IF (Intermittent Fasting)on neurological diseases.

Methodology: A literature review was conducted to create recent studies on how IF impacts neurological illnesses, including neurodegenerative diseases and Central Nervous System (CNS) disorders.

Results: Fasting decreases the production of inflammatory mediators including homocysteine, IL6, and C-reactive protein which could reduce the creation of plaques that lead to atherosclerosis, which is the primary cause of stroke in individuals. IF and ketogenic diets involve significant mechanisms, including enhanced beta-hydroxybutyrate, that have been linked with improved seizure management in certain studies, as well as the induction of other systems that work together to sustain synaptic activity. IF may also improve health and QoL (Quality Of Life) for those who have relapsing-remitting Multiple Sclerosis. IF could prove to be a beneficial dietary treatment for the prevention and/or deceleration of dementia progression.

Conclusion: The creation of a self-empowering, affordable, and effective treatment alternative for a range of neurological issues in a time of rising medical costs and a rise in neurological diseases. In the future, if these studies are given priority, fasting regimens will be advised in addition to medication-based strategies, leading to the development of a single metabolic strategy that can alter the course and symptoms of the most prevalent and impairing neurological disorders that currently exist.

Keywords: Intermittent Fasting, Neurological disease, Brain health.

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1. INTRODUCTION:

1.1 Intermittent Fasting:

It is a technique for eating within a certain time range, not merely a diet. There are specific times when you can eat, and there are long periods of very little food consumption [1]. Some people follow a time-restricted diet, eating for eight hours each day and skipping meals for the remaining sixteen. Another well-known eating pattern is the 5:2 diet, which involves eating 5 days a week but eating little or nothing for two weeks at a time [2].

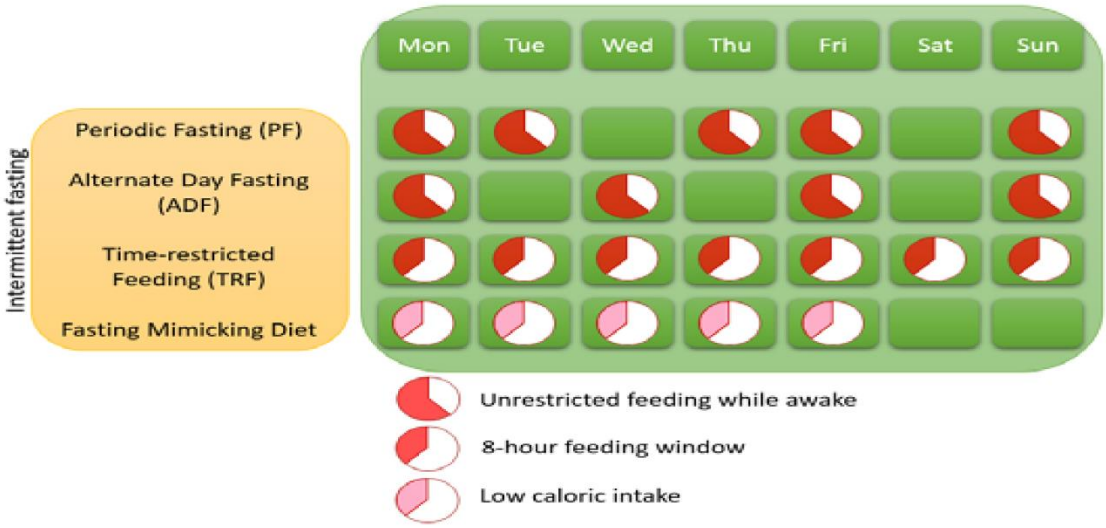
Because it offers so many benefits, IF is getting more popular. It's a revolutionary strategy for weight loss compared to the traditional protocols of regular exercise and/or dietary changes (20-40% yearly decrease in total) [3].

One form of dietary restriction called IF has been demonstrated to increase metabolism, decrease body fat and weight, and enhance brain function.[4] This study's objective is to assess the effect of IF on neurological conditions.

1.2 Different Variants of Intermittent Fasting:

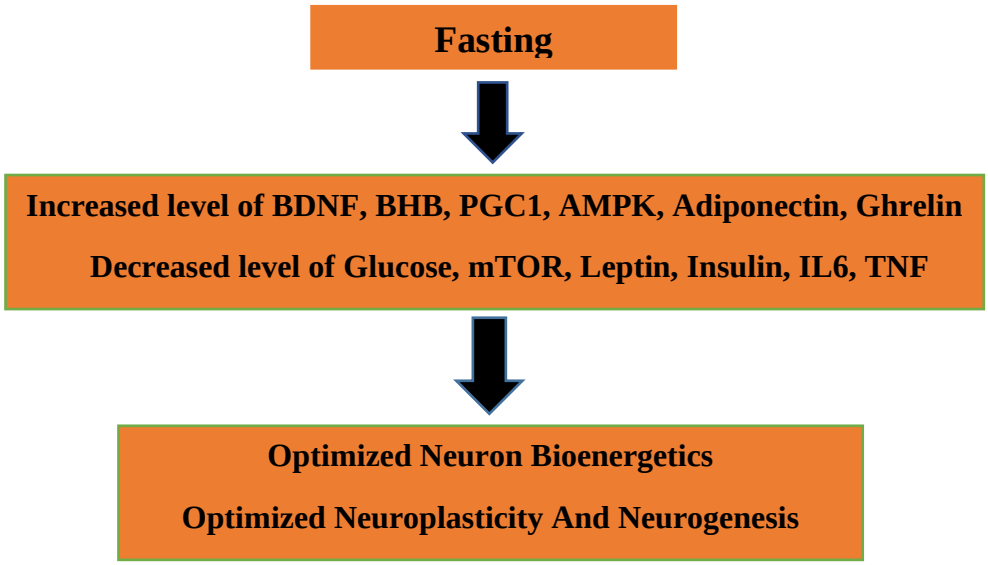
Three types of IF are there:

- **Alternate day fasting (ADF):** People who are all following alternate day fasting have to eat regularly one day and not eat at all the next day alternatively.
- **Periodic fasting (PF) or 5:2 Diet:** Periodic Fasting is followed by two days per week of severe food restriction or fasting, followed by five days of full eating.
- **Time-restricted eating (TRE):** A period of dietary habits that includes around eight hours per day—though research studies differ on this; eating windows that reach six to twelve hours per day are also regarded to be part of TRF [5].
- **Fasting Mimicking Diet (FMD):** The FMD requires following a low-carbohydrate diet, low-protein, and low-calorie for four to seven days.



1.3 Mechanism of Fasting:

Numerous transcriptional and metabolic processes are coordinated and disrupted during fasting, which may affect neurons. These changes result in a whole-body changed metabolic state that enhances neuron bioenergetics, stress responses, and plasticity all while maintaining or even improving cognitive performance [6].



- "TNF (Tumor necrosis factor)
- mTOR (mammalian target of rapamycin),
- PGC1_ (Peroxisome proliferator-activated receptor coactivator 1),
- IL6 (Interleukin 6),
- BDNF (Brain-derived neurotrophic factor),
- BHB (Beta-hydroxybutyrate),
- AMPK (AMP-activated protein kinase)",

2. METHODOLOGY:

A literature review was conducted to create recent studies on how IF impacts neurological illnesses, including disorders of the CNS and neurodegenerative illnesses like PD ("Parkinson's Disease") and AD ("Alzheimer's Disease")

3. BENEFITS OF IF ON BRAIN FUNCTION:

Protein sparing, reduced inflammation, autophagy, and increased BDNF production all help to strengthen our brain. On the one hand, they protect brain tissue by lowering inflammation and removing waste from the brain. However, maintaining appropriate brain function by assisting in cell repair, promoting the creation of new brain cells, and stimulating the connections that allow internal brain communication. This process is helped, in particular, by BDNF, and mutations in this protein have been linked to age-related brain deterioration, including dementia

3.1 INTERMITTENT FASTING ON STROKE:

A stroke is an unexpected neurological deficit that results from a disruption in blood flow that affects the retina, brain, or spinal cord [7]. Neuronal network remodelling, neuronal death, neuroinflammation, and altered neuronal function are the outcomes of ischemic strokes, which account for most strokes worldwide. There isn't much human research on how fasting impacts ischemic stroke patients. But fasting decreases levels of pro-inflammatory factors, including homocysteine, IL6, and C-reactive protein[8], which may limit the development of "atherosclerotic plaques", a prominent cause of stroke in humans.

3.2 INTERMITTENT FASTING ON DEMENTIA:

Dementia is a chronic neuropsychiatric disorder defined by memory impairment and cognitive impairment, which eventually lead to disability or constraints in daily activities [9]. There are two types of dementia: AD and vascular dementia [10]. Alzheimer's is defined by visuospatial abilities and memory loss, which leads to overall cognitive decline [11]. Dementia is distinguished by vascular alterations, and its onset is defined as a less progressive progression than AD, which means a step-by-step cognitive loss [12]. Alzheimer's disease is irreversible, whereas vascular dementia is reversible.

Intermittent fasting controls inflammatory pathways, supports hippocampus neuronal function, including memory [13], and lowers neuronal cell death by altering autophagic circulation[14]. Cerebrovascular dysfunction is a common characteristic in dementia patients[15]. It damages the blood-brain barrier, induces neuroinflammation and oxidative stress in the brain, and accelerates the production of amyloid plaque by upregulating tau protein phosphorylation, beta-secretase, and the enzyme that cleaves amyloid precursor proteins. [16].

A new study discovered that vascular stiffness might increase amyloid beta buildup and exacerbate cognitive impairment [17]. Calorie restriction was demonstrated to minimize the risk of atherosclerosis while also reducing blood pressure and cholesterol levels in the blood vessels [18]. According to recent research, IF decreases the risk of CVD and enhances endothelial dysfunction [19]. Intermittent fasting has been demonstrated to enhance endothelium relaxation and help reduce high blood pressure [20]. Several studies have indicated that intermittent fasting dramatically lowers blood pressure while increasing vascular function [21]. Intermittent fasting improves insulin sensitivity in neurons while also correcting glucose metabolic abnormalities [22]. Dementia affects neurogenesis, causing cognitive deterioration [23]. Neurogenesis in the subventricular zone [24] and the dentate gyrus is inhibited by increased APP accumulation in AD. By producing new neurons in response to oxidative stress, intermittent fasting promotes hippocampus neurogenesis and reduces brain damage.[25,26]. Previous research has demonstrated that cognitive impairment can be improved by prolonged intermittent fasting.[27] Additional studies found that intermittent fasting reduces oxidative stress-induced hippocampus neuronal damage, which in turn reduces memory loss.[28] Therefore, A useful dietary intervention for delaying the onset of dementia or reducing its progression may be IF.

3.3 INTERMITTENT FASTING ON EPILEPSY:

Neuron hyperexcitability, resulting in a persistent tendency to trigger seizures, is the defining characteristic of epilepsy. Since Hippocrates' day, fasting has been used to cure epilepsy effectively. Epilepsy was thought to be an illness caused by 'consuming food too much' till the nineteenth century. Marie and Guelpa, both French physicians, published the 1st scientific study on the benefits of fasting in epilepsy in the early twentieth century [29]. Since epileptic patients could not sustain simple fasting for an extended length of duration, Dr. Wilder of the Mayo Clinic recommended in 1921 that a high-fat diet with resulting ketonemia could prevent seizures, and he termed this high-fat diet the KD ("Ketogenic Diet"). He evaluated three patients with refractory epilepsy, and KD greatly reduced their seizures. [30]

The latest research examined the impact of a 2-month modified Time Restricted Feeding regimen in 6 epileptic children who had an unsatisfactory response to a ketogenic diet and discovered that four of the 6 children showed small enhancements in seizure control [31]. These findings are not expected given that fasting and ketogenic diets share several processes, such as increasing BHB, which was connected to better seizure control in certain studies, and generating other mechanisms that together maintain synaptic activity. However, there could be major variations in the anti-seizure systems underlying ketogenic diets and fasting, even though some children who fasted showed a small improvement in seizure control over those who followed a ketogenic diet.[32,33]

3.4 INTERMITTENT FASTING ON MS (MULTIPLE SCLEROSIS):

It is a chronic autoimmune illness of the CNS that causes cell loss, gliosis, demyelination, and inflammation[34]. Dietary things that promote regulatory rather than inflammatory immune cell differentiation and cytokine production may minimize new inflammatory lesion development and clinical relapses in MS by activating pathways comparable to standard disease-modifying drugs. IF resulted in increased gut bacteria variation, elevation of the Prevotellaceae, Bacteroidaceae, and Lactobacillaceae families, and altered antioxidative microbial metabolic pathways. IF changed T cells in the gut, dropping IL-17-producing T cells and raising regulatory T cells [35]. In the present research including 17 patients with relapsing-remitting multiple sclerosis, it was shown that alterations in the gut flora brought about by a modified fasting regimen were identical to those seen in rodent EAE models. FMD may improve relapsing-remitting MS patients' clinical and quality-of-life results.[36] This systematic review comprised five research, four of which were randomized controlled trials and one was a pilot study. Each of the studies was rated as good quality. These study findings recommend that fasting regimens might be a helpful dietary strategy for controlling symptoms and enhancing QoL in persons with MS. To summarize, intermittent fasting may be a useful dietary strategy for MS.

3.5 INTERMITTENT FASTING ON NEURODEVELOPMENTAL DISORDERS:

ASD is a neurodevelopmental disease expressed by anxiety, repetitive habits, and difficulty with language and social interaction. In addition, gastrointestinal problems are frequently comorbid symptoms in children with ASD. Alterations in the gut microbiome during the early stages of development are hypothesized to be connected with a greater chance of developing ASD and its phenotype [37]. As a result, IF and other dietary interventions may be effective in altering ASD-like behavior. Dietary treatments such as IF might influence ASD-like behavior. IF may also affect ASD-like behavior by altering the gut flora, perhaps raising BDNF and levels of ketone, or raising mTOR pathway activity [38]. For instance, in an animal ASD model, amino acid dietary treatments lowered mTOR activity. Further studies in clinical trials are needed to determine whether IF has a favorable effect on ASD symptomatology [39,40].

3.6 INTERMITTENT FASTING ON PD :

A neurodegenerative disorder influencing mostly dopaminergic neurons within substantia nigra of the brain, which are responsible for making dopamine. Dopamine normally helps and coordinates the millions of nerve and muscle cells involved in movement by interacting with other neurotransmitters. This balance is upset in the absence of sufficient dopamine, leading to PD symptoms such as tremors (trembling of the legs, arms, hands, and jaw), rigidity (limb stiffness), slowness of movement, and impaired balance and coordination. Supplements and dietary approaches have occasionally been investigated as potential therapeutic options to alter disease development and severity in associated neurodegenerative illnesses. One such strategy is Intermittent fasting.

An animal model of PD may be created by introducing mitochondrial poisons that build up in dopaminergic neurons.

In this model, the degeneration of nigrostriatal neurons results in behaviours similar to those of Parkinson's disease. By using this method, animals with neurotoxic-induced PD on a fast-mimicking diet were able to maintain more of their motor skills and lost fewer dopaminergic neurons in the "Substantia Nigra". More specifically, the Fast Mimicking Diet changed the gut microbiota's physiology, which in turn corrected the balance of microglia and astrocytes in the Substantia Nigra—which are considered to be in charge of the inflammatory reactions associated with PD —through metabolite signalling.[41] After receiving a neurotoxic injection to mimic PD, monkeys on a time-restricted feeding schedule showed higher levels of BDNF, which lessened motor impairments and reduced dopamine depletion.[42] There are currently no human clinical trials that started early in the course of the illness and continued long enough to find evidence of the disease-modifying effects of IF.

3.7 INTERMITTENT FASTING ON NEUROPSYCHIATRIC DISORDER:

A common characteristic of mood and anxiety disorders is a generalized distorted emotional state that results in feelings of sadness or concern. Clinically, these illnesses manifest as the following behavioural, emotional, cognitive, and physiological symptoms.[43] A new study on mice found that a nine-hour fast raised BDNF levels, which are linked to chronic stress and depression, as well as having antidepressant benefits.[44,45] Six months of IF increased mood in healthy persons as determined by the WHO ("World Health Organization") Well-Being Index and the Hospital Anxiety along with Depression Scale. [46]. In older males, three months of fasting combined with calorie restriction reduced emotional reactivity symptoms on the Mood States questionnaire Profile, such as tension and rage, but not depressive symptoms [47]. In 34 healthy adults, Moro et al. observed that TRF lowers the inflammatory markers IL-1b, TNFα, and Il-6, which are associated with behavior resembling anxiety and sadness [48]. Ramadan IF was shown by Farooq et al. to lessen manic and depressive signs in 62 people with bipolar affective disorder [49]. Still, certain analyses have indicated that individuals with bipolar illness may experience a relapse during Ramadan (IF) or an escalation of their symptoms of schizophrenia.

CONCLUSION:

In an era of rising medical expenses and a rising incidence of neurological illness, the development of a cost-free, self-empowering, and efficient treatment alternative for a range of neurological illnesses In the future, if these studies are given priority, fasting regimens will be advised in addition to medication-based strategies, leading to the development of a single metabolic strategy that can alter the course and symptoms of the most prevalent and impairing neurological disorders that currently exist.

Conflict of Interest: None

Funding Statement: Funding for this review was not received.

REFERENCES:

1. Gandhi S., Abramov A.Y. Mechanism of Oxidative Stress in Neurodegeneration. *Oxidative 1ed. Cell. Longev.* 2012;2012:428010. https://doi.org/10.1155/2012/428010.
2. Nematy M., Alinezhad-Namaghi M., Rashed M.M., Mozhdehifard M., Sajjadi S.S., Akhlaghi S., Sabery M., Mohajeri S.A., Shalaey N., Moohebati M., et al. Effects of Ramadan fasting on cardiovascular risk factors: A prospective observational study. *Nutr. J.* 2012;11:69. https://doi.org/10.1186/1475-2891-11-69.
3. Reddy P.H., Beal M.F. Amyloid beta, mitochondrial dysfunction, and synaptic damage: Implications for cognitive decline in aging and Alzheimer's disease. *Trends Mol. Med.* 2008;14:45–53. https://doi.org/10.1016/j.molmed.2007.12.002.
4. Reddy P.H. Amyloid beta, mitochondrial structural and functional dynamics in Alzheimer's disease. *Exp. Neurol.* 2009;218:286–292. https://doi.org10.1016/j.expneurol.2009.03.042.
5. Mattson, M.P.; Allison, D.B.; Fontana, L.; Harvie, M.; Longo, V.D.; Malaisse, W.J.; Mosley, M.; Notterpek, L.; Ravussin, E.; Scheer, F.A.J.L.; et al. Meal frequency and timing in health and disease. *Proc.Natl.Acad.Sci.USA* 2014,111,16647-16653 https://doi.org/10.1073/pnas.1413965111
6. Mattson, M.P.; Moehl, K.; Ghena, N.; Schmaedick, M.; Cheng, A. Intermittent Metabolic Switching, Neuroplasticity and Brain Health. Nat. Rev. Neurosci. 2018, 19, 63–80. https://doi.org/10.1038/nrn.2017.156
7. Sacco, R.L.; Kasner, S.E.; Broderick, J.P.; Caplan, L.R.; Connors, J.J.; Culebras, A.; Elkind, M.S.V.; George, M.G.;Hamdan, A.D.; Higashida, R.T.; et al. An Updated Definition of Stroke for the 21st Century. Stroke 2013, 44,2064–2089. https://doi.org/10.1161/STR.0b013e318296aeca.
8. Aksungar, F.B.; Topkaya, A.E.; Akyildiz, M. Interleukin-6, C-Reactive Protein and Biochemical Parameters during Prolonged Intermittent Fasting. Ann. Nutr. Metab. 2007, 51, 88–95. https://doi.org/10.1159/000100954.
9. Livingston G, Sommerlad A, Orgeta V, Costafreda SG, Huntley J, Ames D, et al. Dementia prevention, intervention, and care. *Lancet.* 2017;390:2673–2734 https://doi.org/10.1016/S0140-6736(17)31363-6.
10. Masters CL, Bateman R, Blennow K, Rowe CC, Sperling RA, Cummings JL. Alzheimer's disease. *Nat Rev Dis Primers.* 2015;1:15056. https://doi.org/10.1038/nrdp.2015.56.
11. Cummings JL. Alzheimer's disease. *N Engl J Med.* 2004;351:56–67 https://doi.org/10.1056/NEJMra040223.
12. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR, Jr, Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement.* 2011;7:263–269. https://doi.org/10.1016/j.jalz.2011.03.005.
13. Longo VD, Mattson MP. Fasting: molecular mechanisms and clinical applications. Cell Metab 2014;19:181-192. https://doi.org/10.1016/j.cmet.2013.12.008
14. Jeong JH, Yu KS, Bak DH, Lee JH, Lee NS, Jeong YG, et al. Intermittent fasting is neuroprotective in focal cerebral ischemia by minimizing autophagic flux disturbance and inhibiting apoptosis. Exp Ther Med 2016;12:3021-3028. https://doi.org/10.3892/etm.2016.3852
15. Reactivity in Alzheimer's disease and vascular dementia assessed by arterial spinlabeling magnetic resonance imaging. Curr Neurovasc Res 2013;10:49-53. https://doi.org/10.2174/156720213804806016
16. Iadecola C. The pathobiology of vascular dementia. Neuron 2013;80:844-866. https://doi.org/10.1016/j.neuron.2013.10.008
17. Hughes TM, Wagenknecht LE, Craft S, Mintz A, Heiss G, Palta P, et al. Arterial stiffness and dementia pathology: Atherosclerosis Risk in Communities (ARIC)-PET Study. Neurology 2018;90:e1248-e1256. https://doi.org/10.1212/WNL.0000000000005259
18. Fontana L, Meyer TE, Klein S, Holloszy JO. Long-term calorie restriction is highly effective in reducing the risk for atherosclerosis in humans. Proc Natl Acad Sci U S A 2004;101:6659-6663. https://doi.org/10.1073/pnas.0308291101
19. Headland ML, Clifton PM, Keogh JB. Effect of intermittent energy restriction on flow mediated dilatation, a measure of endothelial function: a short report. Int J Environ Res Public Health 2018;15:E1166. https://doi.org/10.3390/ijerph15061166
20. Erdem Y, Özkan G, Ulusoy Ş, Arıcı M, Derici Ü, Şengül Ş, et al. The effect of intermittent fasting on blood pressure variability in patients with newly diagnosed hypertension or prehypertension. J

Am Soc Hypertens 2018;12:42-49. https://doi.org/10.1016/j.jash.2017.11.008

21. Partial energy restriction on postprandial metabolism among overweight/obese participants. Br J Nutr 2016;115:951-959. https://doi.org/10.1017/S0007114515005346

22. Anson RM, Guo Z, de Cabo R, Iyun T, Rios M, Hagepanos A, et al. Intermittent fasting dissociates beneficial effects of dietary restriction on glucose metabolism and neuronal resistance to injury from calorie intake. Proc Natl Acad Sci U S A 2003;100:6216-6220. https://doi.org/10.1073/pnas.1035720100

23. Thompson PM, Hayashi KM, Dutton RA, Chiang MC, Leow AD, Sowell ER, et al. Tracking Alzheimer's disease. Ann N Y Acad Sci 2007;1097:183-214. https://doi.org/10.1196/annals.1379.017

24. Wolf SA, Kronenberg G, Lehmann K, Blankenship A, Overall R, Staufenbiel M, et al. Cognitive and physical activity differently modulate disease progression in the amyloid precursor protein (APP)-23 model of Alzheimer's disease. Biol Psychiatry 2006;60:1314-1323. https://doi.org/10.1016/j.biopsych.2006.04.004

25. Wang Z, Andrade N, Torp M, Wattananit S, Arvidsson A, Kokaia Z, et al. Meteorin is a chemokinetic factor in neuroblast migration and promotes stroke-induced striatal neurogenesis. J Cereb Blood Flow Metab 2012;32:387-398. https://doi.org/10.1038/jcbfm.2011.156

26. Garza JC, Guo M, Zhang W, Lu XY. Leptin increases adult hippocampal neurogenesis in vivo and in vitro. J Biol Chem 2008;283:18238-18247. https://doi.org/10.1074/jbc.M800053200

27. Hu Y, Yang Y, Zhang M, Deng M, Zhang JJ. Intermittent fasting pretreatment prevents cognitive impairment in a rat model of chronic cerebral hypoperfusion. J Nutr 2017;147:1437-1445. https://doi.org/10.3945/jn.116.245613

28. Hu Y, Zhang M, Chen Y, Yang Y, Zhang JJ. Postoperative intermittent fasting prevents hippocampal oxidative stress and memory deficits in a rat model of chronic cerebral hypoperfusion. Eur J Nutr 2019;58:423-432.https://doi.org/10.1007/s00394-018-1606-4

29. Guelpa G., Marie A. La lutte contre l'épilepsie par la désintoxication et par la rééducation alimentaire. *Rev. Ther. Medico-Chirurgicale.* 1911;78:8–13 https://doi.org/10.1016/j.yebeh.2019.03.018

30. Wilder R.M. High fat diets in epilepsy. *Mayo Clin. Bull.* 1921;2:308.

31. Hartman, A.L.; Rubenstein, J.E.; Kosso_, E.H. Intermittent Fasting: A'New' Historical Strategy for Controlling Seizures? Epilepsy Res. 2013, 104, 275–279. https://doi.org/10.1016/j.eplepsyres.2012.10.011

32. Huttenlocher, P.R. Ketonemia and Seizures: Metabolic and Anticonvulsant Effects of Two Ketogenic Diets in Childhood Epilepsy. Pediatr. Res. 1976, 10, 536–540. https://doi.org/10.1203/00006450-197605000-00006

33. Van Delft, R.; Lambrechts, D.; Verschuure, P.; Hulsman, J.; Majoie, M. Blood Beta-Hydroxybutyrate Correlates Better with Seizure Reduction Due to Ketogenic Diet than Do Ketones in the Urine. Seizure 2010, 19, 36–39. https://doi.org/10.1016/j.seizure.2009.10.009

34. Noyes K, Weinstock-Guttman B. Impact of diagnosis and early treatment on the course of multiple sclerosis. Am J Manag Care. 2013 Nov;19(17 Suppl):s321-31.

35. Cignarella, F.; Cantoni, C.; Ghezzi, L.; Salter, A.; Dorsett, Y.; Chen, L.; Phillips, D.;Weinstock, G.M.; Fontana, L.;Cross, A.H.; et al. Intermittent Fasting Confers Protection in CNS Autoimmunity by Altering the Gut Microbiota. Cell Metab. 2018, 27, 1222–1235. https://doi.org/10.1016/j.cmet.2018.05.006

36. Choi, I.Y.; Piccio, L.; Childress, P.; Bollman, B.; Ghosh, A.; Brandhorst, S.; Suarez, J.; Michalsen, A.; Cross, A.H.;Morgan, T.E.; et al. Diet Mimicking Fasting Promotes Regeneration and Reduces Autoimmunity and Multiple Sclerosis Symptoms. Cell Rep. 2016, 15, 2136–2146. https://doi.org/10.1016/j.celrep.2016.05.009.

37. Butler M.G., Dazouki M.J., Zhou X.P., Talebizadeh Z., Brown M., Takahashi T.N., Miles J.H., Wang C.H., Stratton R., Pilarski R., et al. Subset of individuals with autism spectrum disorders and extreme macrocephaly associated with germline PTEN tumour suppressor gene mutations. *J. Med. Genet.* 2005;42:318–321. https://doi.org/10.1136/jmg.2004.024646.

38. Han J.C., Thurm A., Golden Williams C., Joseph L.A., Zein W.M., Brooks B.P., Butman J.A., Brady S.M., Fuhr S.R., Hicks M.D., et al. Association of brain-derived neurotrophic factor (BDNF) haploinsufficiency with lower adaptive behaviour and reduced cognitive functioning in WAGR/11p13 deletion syndrome. *Cortex.* 2013:49;2700-2710. https://doi.org/10.1016/j.cortex.2013.02.009.

39. Huber K.M., Klann E., Costa-Mattioli M., Zukin R.S. Dysregulation of mammalian target of rapamycin signaling in mouse models of autism. *J. Neurosci.* 2015;35:13836. https://doi.org/10.1523/JNEUROSCI.2656-15.2015.

40. Wu J., de Theije C.G.M., da Silva S.L., Abbring S., van der Horst H., Broersen L.M., Willemsen L., Kas M., Garssen J., Kraneveld A.D. Dietary interventions that reduce mTOR activity rescue autistic-like behavioral deficits in mice. *Brain. Behav. Immun.* 2017;59:273–287. https://doi.org/10.1016/j.bbi.2016.09.016.

41. Zhou Z.L., Jia X.B., Sun M.F., Zhu Y.L., Qiao C.M., Zhang B.P., Zhao L.P., Yang Q., Cui C., Chen X., et al. Neuroprotection of Fasting Mimicking Diet on MPTP-Induced Parkinson's Disease Mice via Gut Microbiota and Metabolites. *Neurotherapeutics.* 2019;16:741–760. https://doi.org/10.1007/s13311-019-00719-2.

42. Maswood N., Young J., Tilmont E., Zhang Z., Gash D.M., Gerhardt G.A., Grondin R., Roth G.S., Mattison J., Lane M.A., et al. Caloric restriction increases neurotrophic factor levels and attenuates neurochemical and behavioral deficits in a primate model of Parkinson's disease. *Proc. Natl. Acad. Sci. USA.* 2004;101:18171–18176. https://doi.org/10.1073/pnas.0405831102.

43. Videbeck S.L. *Psychiatric-Mental Health Nursing.* Lippincott Williams & Wilkins; Philadelphia, PA, USA: 2010.

44. Taliaz D., Loya A., Gersner R., Haramati S., Chen A., Zangen A. Resilience to chronic stress is mediated by hippocampal brain-derived neurotrophic factor. *J. Neurosci.* 2011;31:4475–4483. https://doi.org/10.1523/JNEUROSCI.5725-10.2011.

45. Bus B.A.A., Molendijk M.L., Tendolkar I., Penninx B.W.J.H., Prickaerts J., Elzinga B.M., Voshaar R.C.O. Chronic depression is associated with a pronounced decrease in serum brain-derived neurotrophic factor over time. *Mol. Psychiatry.* 2015;20:602–608. https://doi.org/10.1038/mp.2014.83.

46. Kessler C.S., Stange R., Schlenkermann M., Jeitler M., Michalsen A., Selle A., Raucci F., Steckhan N. A nonrandomized controlled clinical pilot trial on 8 wk of intermittent fasting (24 h/wk) *Nutrition.* 2018;46:143–152.e2. https://doi.org/10.1016/j.nut.2017.08.004

47. Hussin N.M., Shahar S., Teng N.I.M.F., Ngah W.Z.W., Das S.K. Efficacy of Fasting and Calorie Restriction (FCR) on mood and depression among ageing men. *J. Nutr. Health Aging.* 2013;17:674–680. https://doi.org/10.1007/s12603-013-0344-9.

48. Moro T., Tinsley G., Bianco A., Marcolin G., Pacelli Q.F., Battaglia G., Palma A., Gentil P., Neri M., Paoli A. Effects of eight weeks of time-restricted feeding (16/8) on basal metabolism, maximal strength, body composition, inflammation, and cardiovascular risk factors in resistance-trained males. *J. Transl. Med.* 2016;14:290. https://doi.org/10.1186/s12967-016-1044-0.

49. Farooq S., Nazar Z., Akhter J., Irafn M., Subhan F., Ahmed Z., Khatak I.H., Naeem F. Effect of fasting during Ramadan on serum lithium level and mental state in bipolar affective disorder. *Int.Clin.Psychopharmacol.* 2010;25:323–327. https://doi.org/10.1097/YIC.0b013e32833d18b2.