

The Effects of Intermittent Fasting on Neuroplasticity and Brain Health

Genesis Vanesa Flores

Department of Kinesiology, University of Waterloo

KIN 470: Determinants of Brain Health & Mental Well-being

Dr. Robert Hick

December 14, 2021

The Effects of Intermittent Fasting on Neuroplasticity and Brain Health

From 1990 to 2016, the rate of death and disability-adjusted life-years (the sum of life lost in years with the years living with disability) from neurological diseases has increased (Feigin et al., 2019). With the increase in research, it has been proven that certain lifestyle factors, like diet/caloric restriction, can help prevent neurological diseases and promote brain health (Gudden et al., 2021). Intermittent fasting (IF) has increased in popularity within research to observe the effects timing and the frequency of meals have on cognition (Patterson & Sears, 2017). There are many different types of IF regimes, but the most popular ones are alternate day fasting (ADF), time-restricted fasting (TRF), and modified fasting (5:2 split, MF) (Anton et al., 2018). ADF refers to a 24-hr fast where an individual consumes food every other day (Patterson & Sears, 2017). TRF entails a time window in which an individual is not allowed to eat, this could be from 12-16-hours a day (eating only 6-8 hours of the day) (Patterson & Sears, 2017). Lastly, MF is characterized as being able to eat ad-libitum (AL) for five days of the week, and for two days, consuming 20-25% of caloric intake (Patterson & Sears, 2017). Overall, IF is maintained when an individual does not consume any food for a 12–48-hour period (Anton et al., 2018).

A key physiological element that occurs in IF is called the metabolic switch (Mattson et al., 2018). This refers to the metabolic transition of using glucose to utilizing ketone bodies (BHB and AcAc) as the primary source of fuel for the brain (Mattson et al., 2018). Ketone bodies are created during the fasting state through a process called lipolysis from adipocytes. Ketone bodies can freely enter the blood-brain barrier to generate ATP (Mattson et al., 2018).

A detailed review study by Mattson et al. (2018), discussed the three postulated signalling pathways that IF affects the brain. The three pathways triggered by the metabolic switch are Neurotrophic-factor-dependent and activity-dependent signalling pathway, and the AMPK driven

autophagy pathway (Mattson et al., 2018). The Neurotrophic-factor-dependent and activity-dependent signalling pathway express transcription factors like cAMP response element-binding (CREB) protein, NF- κ B, NRF2 and MEF2. These induce gene expression of BDNF, PGC1 α and SIRT3 (Mattson et al., 2018). The expression of these genes has been suggested to promote neuroplasticity and increase resistance to stress (Mattson et al., 2018). Furthermore, the AMPK-driven autophagy pathway occurs due to the decrease in the AMP to ATP ratio (Mattson et al., 2018). This attenuates the mTOR pathway and facilitates the autophagy process that engulfs damaged proteins and organelles (Mattson et al., 2018). According to Mattson et al. (2018), these signalling pathways have shown to enhance neuronal stress resistance, increase neuroplasticity, and ameliorate the recovery from brain injuries and resistance to neurodegeneration.

Most studies in the literature observe the hippocampal structure and brain-derived neurotrophic factor (BDNF) levels. The hippocampus is an important structure embedded deep in the temporal lobe (Anand & Dhikav, 2012). This structure is responsible for short-term memory, memory consolidation, learning and spatial navigation (Anand & Dhikav, 2012). Additionally, BDNF is located throughout the nervous system (Bathina & Das, 2015). This protein is responsible for supporting the survival of existing and new neurons (Bathina & Das, 2015). BDNF can influence neuronal proliferation and differentiation, regulate synaptic plasticity by promoting long-term potentiation thereby enhancing learning (Li et al., 2020).

Phases of IF have been reported to have health benefits like increasing insulin sensitivity, reducing abdominal fat, resting heart rate and blood pressure (Anton et al., 2018). Research primarily done on animals has shown promising effects on cognitive functions whereas human studies are limited (Gudden et al., 2021). In this literature review, three animal studies and two human studies will be examined to determine the effects IF has on neuroplasticity and brain health.

The first study examined was done by Lee et al. (2002). Colleagues looked at the effect of ADF on BDNF and hippocampal neurogenesis in 8-week-old mice. To test this, they obtained wild-type (WT) and BDNF knock-out (KO) mice that were divided into two diet groups: ad-libitum feeding (AL) and ADF groups. The mice remained in their allocated diets for three months (Lee et al., 2002). They study found the ADF-WT mice had a significant increase in the survival and synthesis of hippocampal cells. However, the AL-BDNF-KO mice resulted in a reduction in neurogenesis that was related to significant atrophy in the hippocampal dentate gyrus. These findings suggest that BDNF is crucial for regulating hippocampal neurogenesis in mice and that ADF promotes survival of the neuronal cell and amplifies neurogenesis through upregulation of BDNF (Lee et al., 2002). Thus, the findings insinuate that it may be possible to enhance brain function and resistance to brain injuries and pathologies in humans through ADF (Lee et al., 2002).

In a study done by Vasconcelos et al. (2014), looked at how lipopolysaccharide-induced neuroinflammation is affected by IF on rat models. Lipopolysaccharide (LPS) is a bacterial ligand that binds to the toll-like receptor 4 (TLR4) expressed on microglia and astrocytes (Vasconcelos et al., 2014). When the ligand binds to TLR4, it initiates the immune response to infections (Vasconcelos et al., 2014). In this study, 12-week-old male rats were assigned to an ADF regime for 30 days and then were randomly assigned to receive LPS or saline injection. They had four groups: AL diet with saline injection (control), AL diet with LPS injection (LPS), IF with saline injection (IF), and IF with LPS injection (IF+LPS). Half of the rats were selected to perform behavioural tests, and the other half were euthanized after the last LPS injection to examine the hippocampal structural changes (Vasconcelos et al., 2014). The behavioural tests administered were to examine their spatial learning, long-term memory, motor performance, and spontaneous locomotor activity (Vasconcelos et al., 2014). The changes in the hippocampal structure they were

interested in examining were pro-inflammatory cytokines and BDNF levels since LPS can increase the expression of pro-inflammatory cytokines (like IL-1 α , IL-1 β and TNF- α) and inhibit BDNF production (Vasconcelos et al., 2014). Moreover, the study found that when performing the behavioural tests, the LPS group showed worse spatial learning and long-term memory versus both IF groups (IF+LPS and IF) ($P < 0.05$). This suggests that IF had a protective mechanism against learning impairments and improved long-term memory consolidation in rats with LPS. Now, when looking at the protein levels of pro-inflammatory cytokines and BDNF, they found that IF sustained BDNF levels and decreased activation of pro-inflammatory cytokines in LPS-induced conditions (Vasconcelos et al., 2014). Additionally, the presence of LPS receptor TLR4 found in both IF groups decreased in comparison to the LPS group (Vasconcelos et al., 2014). This further illustrates the inhibitory effects IF has on LPS-induced neuroinflammation and prevention of BDNF level depletion in the hippocampus (Vasconcelos et al., 2014). Therefore, in this animal model study, they propose that IF has a neuroprotective effect against LPS-induced inflammation by which it can decrease inflammation and preserve cognitive function (Vasconcelos et al., 2014).

In the third animal study by Baik et al. (2019), they examined the effects IF has on hippocampal neurogenesis. Most importantly, the study was interested in finding which mechanism of IF induced neurogenesis by focusing on the Notch 1 signalling pathway and proteins associated with neurogenesis (BDNF and CREB). They obtained 3-month-old male mice that were randomly assigned to 4 diet groups for 3 months: AL feeding (control), 12-hour, 16-hour, and 24-hour fast (ADF) (Baik et al., 2019). The mice were euthanized to examine the expressed hippocampal proteins and markers for the Notch signalling and BDNF/CREB (Baik et al., 2019). When analyzing the results, researchers found that IF (12-hour, 16-hour, and 24-hour groups) when compared to the AL diet group, had an increase in the activation of the Notch 1 signalling

and BDNF/CREB pathway. For the Notch 1 signalling pathway, this was seen in the increased expression of transcription factor HES5 that induces the upregulation of Nestin (a marker for neural stem cell) which facilitates neurogenesis (Baik et al., 2019). Additionally, for the BDNF/CREB pathway, there was an elevation of BDNF and CREB which promotes neuronal formation (Baik et al., 2019). Also, in the IF groups, an increase in hippocampal PSD95 expression was examined (Baik et al., 2019). This is a major scaffolding protein found in the excitatory postsynaptic density of neurons that regulates synaptic strength (Baik et al., 2019). Most importantly, when comparing the effects of IF diets (12-hour, 16-hour, and 24-hour) to the control group, they found that the 16-hour diet group had statistically significant results for enhancing the Notch signalling and BDNF/CREB pathways ($P < 0.05$) (Baik et al., 2019). Thus, this study found that IF enhances the Notch and BDNF/CREB pathway and that the 16-hour fast was the most advantageous at promoting the beneficial effects of neuroplasticity (Baik et al., 2019).

The direct effects of IF and the prevention of neurological diseases in humans have not been previously researched as it requires longitudinal studies that participants partake in IF regimes (Gudden et al., 2021; Mattson et al., 2018). In a review article done by Gudden et al. (2021), they found that although limited, positive findings have been associated with different types of IF regimes that decrease seizure frequency, increase cognition improvement in Alzheimer's disease (AD) patients, decrease the risk of strokes, increase self-reported motor movement in MS patients, and benefits for mood and anxiety disorder. However, more controlled longitudinal clinical trials are needed to confirm that these effects are coming from IF itself (Gudden et al., 2021).

In a meta-analysis by Benau et al. (2014), they collected studies done on the healthy adult population (18–28-year-olds). The results from the studies analyzed were very inconsistent and negative or did not affect cognitive function when in an IF diet (Benau et al., 2014). Thus, when

observing the effects of IF on a healthy individual, there is still a lot of variability in the literature, and the direct effects cannot be confidently determined (Benau et al., 2014).

In conclusion, the effect of IF on neuroplasticity and brain health is still in its infancy. From the first study reviewed by Lee et al. (2002), they concluded that the caloric restriction from ADF up-regulates BDNF expression and thereby, enhances neurogenesis in rodents. This suggests that IF may be possible at enhancing brain function and resistance to brain insults and diseases in humans (Lee et al., 2002). In the second study by Vasconcelos et al. (2014), they found that IF can suppress inflammation and sustain BDNF levels in the hippocampus during LPS-induced neuroinflammation. They suggested that IF should be tested on humans suffering from or at risk for developing a neurological condition involving inflammations (like AD, traumatic brain injuries, or ischemic strokes) (Vasconcelos et al., 2014). Moreover, the study by Baik et al. (2019) also suggested that IF increased neuroplasticity, however, specified a 16-hour fast regime that statistically increased hippocampal neurogenesis. The review article done by Gudden et al. (2021) suggested that IF was neuroprotective for neurological disorders. Lastly, the systematic review by Benau et al. (2014) denoted IF effects on healthy adults do not lead to any beneficial outcome. Notably, more research should be done to determine if IF has a causational effect on neuroplasticity and brain health. The studies done on animal models' advice for their findings to be applied to human studies to indicate whether these effects are observed during clinical trials. Also, more longitudinal studies should be done to observe the long-term effects IF has on preventing neurological disorders and the effects for the healthy population (if any). As of now, there are randomized clinical trials of IF on the participant with or at risk of neurological disorders being done so it would be fascinating to see what the results are (Mattson et al., 2018).

References

- Anand, K. S., & Dhikav, V. (2012). Hippocampus in health and disease: An overview. *Annals of Indian Academy of Neurology*, 15(4), 239– 246. <https://doi.org/10.4103/0972-2327.104323>
- Anton, S. D., Moehl, K., Donahoo, W. T., Marosi, K., Lee, S. A., Mainous III, A. G., ... Mattson, M. P. (2018). Flipping the Metabolic Switch: Understanding and Applying the Health Benefits of Fasting. *Obesity*, 26(2), 254–268. <https://doi.org/10.1002/oby.22065>
- Baik, S. H., Rajeev, V., Fann, D. Y. W., Jo, D. G., & Arumugam, T. V. (2020). Intermittent fasting increases adult hippocampal neurogenesis. *Brain and Behavior*, 10(1), 1–6. <https://doi.org/10.1002/brb3.1444>
- Bathina, S., & Das, U. N. (2015). Brain-derived neurotrophic factor and its clinical implications. *Archives of medical science : AMS*, 11(6), 1164–1178. <https://doi.org/10.5114/aoms.2015.56342>
- Benau, E. M., Orloff, N. C., Janke, E. A., Serpell, L., & Timko, C. A. (2014). A systematic review of the effects of experimental fasting on cognition. *Appetite*, 77, 52–61. <https://doi.org/10.1016/j.appet.2014.02.014>
- Feigin, V. L., Nichols, E., Alam, T., Bannick, M. S., Beghi, E., Blake, N., ... Vos, T. (2019). Global, regional, and national burden of neurological disorders, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet Neurology*, 18(5), 459–480. [https://doi.org/10.1016/S1474-4422\(18\)30499-X](https://doi.org/10.1016/S1474-4422(18)30499-X)
- Gudden, J., Arias Vasquez, A., & Bloemendaal, M. (2021). The effects of intermittent fasting on brain and cognitive function. *Nutrients*, 13(9), 1–25. <https://doi.org/10.3390/nu13093166>

- Lee, J., Duan, W., & Mattson, M. P. (2002). Evidence that brain-derived neurotrophic factor is required for basal neurogenesis and mediates, in part, the enhancement of neurogenesis by dietary restriction in the hippocampus of adult mice. *Journal of Neurochemistry*, 82(6), 1367–1375. <https://doi.org/10.1046/j.1471-4159.2002.01085.x>
- Li, W., Wu, M., Zhang, Y., Wei, X., Zang, J., Liu, Y., ... Wei, W. (2020). Intermittent fasting promotes adult hippocampal neuronal differentiation by activating GSK-3 β in 3xTg-AD mice. *Journal of Neurochemistry*, 155(6), 697–713. <https://doi.org/10.1111/jnc.15105>
- Mattson, M. P., Moehl, K., Ghena, N., Schmaedick, M., & Cheng, A. (2018). Intermittent metabolic switching, neuroplasticity and brain health. *Nature Reviews Neuroscience*, 19(2), 81–94. <https://doi.org/10.1038/nrn.2017.156>
- Patterson, R. E., & Sears, D. D. (2017). Metabolic Effects of Intermittent Fasting. *Annual Review of Nutrition*, 37, 371–393. <https://doi.org/https://doi.org/10.1146/annurev-nutr-071816-064634>
- Vasconcelos, A. R., Yshii, L. M., Viel, T. A., Buck, H. S., Mattson, M. P., Scavone, C., & Kawamoto, E. M. (2014). Intermittent fasting attenuates lipopolysaccharide- induced neuroinflammation and memory impairment. *Journal of Neuroinflammation*, 11(85), 1–14. <https://doi.org/doi:10.1186/1742-2094-11-85>