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Intermittent fasting improves learning and memory functioning by enhancing neural plasticity mechanisms

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Essay

To fulfil the requirements for the Cognitive Neuroscience and Modeling track of the Research Master in Behavioral and Cognitive Neurosciences at the University of Groningen under the supervision of prof. dr. Anton Scheurink (Faculty of Science and Engineering, University of Groningen)

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Abstract

Intermittent fasting (IF) received growing popularity in recent years. Indeed, although the efficacy of IF on weight-loss compared to traditional caloric restriction (CR) diet is negligible, there is cumulating evidence that IF improves cardio-metabolic health, promotes longevity, and enhances learning and memory functioning. The key factor for the positive effects IF seems to be that after a certain amount of fasting, a metabolic switch occurs, which implies that the preferred fuel of the body and the brain shifts from glucose to fatty acids and ketone bodies. This metabolic switch induces various signalling pathways and cellular stress repair mechanisms, thereby facilitating synaptic plasticity processes occurring after the brain switched back to utilising glucose as its main fuel. Evidence from rodent studies supports the notion that hippocampal long-term potentiation (LTP), an important form of synaptic plasticity, is upregulated due to prolonged IF primarily in the fed state. Crucially, inhibition of N-methyl-D-aspartate (NMDA)-type glutamate receptors, alleviates the positive effects of IF on LTP and memory functioning. In conclusion, the available evidence indicates that IF induces cell repair mechanisms that promote enhanced synaptic plasticity, resulting in improved learning and memory functioning in the fed state. Nevertheless, further research is necessary to support these findings, as well as, due to the lack of randomized controlled trials on humans exploring this topic, it is unclear whether these results also translate to humans.
Keywords: intermittent fasting, health, learning, memory, synaptic plasticity

Introduction

People nowadays are more and more interested in optimizing their dietary habits to suit their needs and goals. The goal of most people who follow a specific diet is to maintain or lose weight, while others aim to improve their metabolic and mental health. In recent years, plenty of different regimes have surfaced and become progressively more common. Some diets restrict the amount of calories ingested, some restrict the intake of specific nutrients such as veganism, whereas other diets merely limit the time period of eating such as intermittent fasting (IF).

IF is a dietary restriction that involves alternating between periods of unrestricted eating and periods of fasting. People following this diet may restrict their caloric intake to a specific time window of the day, alternate days of fasting and eating, or fast one or two days a week. Thus, both the duration and timing of the fasting state may differ between selected regimes. Importantly, in the feasting state, one may consume anything without any caloric or nutritional restriction. Therefore, an increasing amount of people attempt to adhere to an IF regime in order to lose weight and/or to improve their metabolic and mental health.

Although there are potential disadvantages to an IF diet, recent evidence suggests that IF results in a number of different health benefits. Indeed, IF may be difficult to adhere to (Elortegui Pascual et al., 2023), and may result in feeling weak and fatigued (Harvie et al., 2011). On the other hand, IF has been shown to result in weight-loss (Coutinho et al., 2018), promote longevity in male mice (Mitchell et al., 2019), improve cardio-metabolic health and insulin sensitivity in pre-diabetic men (Sutton et al., 2018), and there is also evidence that IF improves cognitive performance, such as memory functioning, in people with mild cognitive impairment (MCI; Ooi et al., 2020), and in numerous rodent studies (Mattson et al., 2018).

IF affects numerous neurobiological processes that are known to be involved in learning and memory functioning (Gudden et al., 2021). The exact mechanisms by which IF improves learning and memory functioning are not clear. However, the metabolic changes related to IF seem to induce, for instance, cellular stress resistance processes that ultimately upregulate transcription factors important for synaptic plasticity (Mattson et al., 2018). In short, synaptic plasticity refers to the strength of structural and functional connections between neurons, and it is known to have a key role in proper learning and memory functioning (Goto, 2022).

In light of these considerations, the current essay aims to investigate the available evidence supporting and/or opposing the following hypothesis:

Main hypothesis

Intermittent fasting improves learning and memory functioning by enhancing neural plasticity mechanisms.

By examining the research and scientific literature, this essay will delve into the various aspects surrounding intermittent fasting and its impact on learning and memory functioning, with a particular focus on the role of synaptic plasticity.

What is intermittent fasting and why is it interesting?

To reiterate, IF is type of dietary restriction which involves periodical voluntary abstinence from caloric intake (Fanti et al., 2021). However, within the feeding window (also referred to as eating or feasting window) one may consume any type of nutrients without limit. The fasting periods may differ in duration (from twelve hours to two days) and timing between regimes (e.g. early or late eating window; Anton et al., 2018). Therefore, there are multiple terms used for the different regimes. Readers may refer to Box 1 for the definition of the terms used in this essay for the different regimes.

Box 1 – IF regimes

Time-restricted eating (TRE):
TRE refers to what most people think of when talking about an IF diet, that is, fasting for an extended period of time each day (ranging from 12-18 hours) with most people adopting an 8-12 hour eating window (Anton et al., 2018). To abbreviate, for example, fasting for 16 hours and eating within an 8 hour window is called a 16:8 TRE regime.
TRE in animals: Besides the usual protocol (i.e. limiting feeding to a specific time-window of the day), another way to achieve daily IF in animals is to feed them 60-70% of their usual daily food intake, a method often referred to as 30-40% CR (Mattson et al., 2018). In this case, the animals typically consume all the allocated food within two to four hours from feeding time (Acosta-Rodríguez et al., 2017; Mattson et al., 2018), putting themselves into a fasting state until the next feeding time.

Alternate-day fasting (ADF):
Another commonly used regime is ADF. In ADF, people fast every other day and eat unrestrictedly on non-fast days, also referred to as "feast" days (Anton et al., 2018).

5:2 diet:
The 5:2 diet, involves fasting for two days a week, while eating unrestrictedly on the rest of the days.

Modified fasting diets:
Modified fasting regimes include diets that follow either the ADF or 5:2 regime, but instead of cutting all caloric intake while fasting, people consume a reduced number of calories (25-55% of normal intake), and may consume less carbohydrates and protein, and more fat (Anton et al., 2018; Fanti et al., 2021).

As someone following this diet could continue eating their usual meals and could determine an eating window that matches well with their lifestyle, it was expected that it would be easier to adhere to an IF diet than a more traditional caloric restriction (CR) diet (Fanti et al., 2021). Contrary to this belief, although compliance rates vary greatly across studies (Elortegui Pascual et al., 2023; Fanti et al., 2021), most findings suggest that in general, it is similarly difficult to adhere to an IF regime as to a traditional CR regime. Indeed, a recent meta-analysis showed that the compliance rates between CR and IF protocols were comparable (~70%), both on the short and long-term (indicating interventions lasting less or more than 3 months), amongst most studies that applied both regimes (Elortegui Pascual et al., 2023). It is important to note however that, currently, there is a lack of long-term (> 2 years) studies investigating this subject. In general, compliance rates seem to decrease with longer interventions (Elortegui Pascual et al., 2023), and one study found that the decrease in compliance rates was more severe for IF than for CR within two years from the intervention (Pannen et al., 2021).

Similarly, the effectiveness of IF in weight-loss is not particularly convincing, although some regimes seem to be more effective than others. In their systematic review, Fanti and colleagues (2021) reported that studies investigating the effects of TRE and 5:2 diet have consistently found only small, 2-7% reduction in overall body weight. Modified ADF and ADF seem to be more effective for weight-loss than the other regimes, with some studies reporting up to 12% decrease in body mass (Coutinho et al., 2018; Elortegui Pascual et al., 2023; Fanti et al., 2021). Importantly, a recent meta-regression analysis did not show significant differences in weight loss between

different IF regimes and traditional CR regimes, indicating that these diets have similar benefits for reducing weight (Elortegui Pascual et al., 2023). However, interpretation of the current results is limited by the lack of long-term studies investigating the sustainability of weight maintenance. Moreover, most of the studies on humans merely used surveys, decreasing the validity and reproducibility of their findings. Thus, future longer-term, well-powered, randomized controlled trials (RCTs) are needed to determine the effectiveness and sustainability of IF for weight-loss in humans.

There are numerous factors that might affect the effectiveness of an IF diet. For instance, daily timing of caloric intake may influence its degree of efficacy in weight loss and in preventing the development of metabolic disorders (Fanti et al., 2021). Indeed, eating patterns have significant effects on the circadian rhythm of several genes and proteins, which in turn affect metabolic processes (Manoogian & Panda, 2017). In line with this, rodent studies have established that consuming a high-fat diet results in significantly more weight gain in day-fed animals (inactive phase) than in night-fed animals (active phase), despite the equivalent levels of activity and caloric intake (e.g. Arble et al., 2009; Fanti et al., 2021). Moreover, in humans, shifting eating patterns due to night wok may result in obesity (Lowden et al., 2010). In addition, eating lunch early rather than late (i.e. before 15:00) has been shown to result in significantly more weight-loss when partaking in a weight-loss intervention program (Garaulet et al., 2013; Figure 1). As Garaulet and colleagues (2013) did not find significant differences in macronutrient composition, amount of calories ingested or in energy expenditure between late and early eaters, timing of caloric intake seems to be an important factor for weight-loss. This finding could be well explained by the notion that, for instance, insulin sensitivity and thermic effect of food are higher in the biological morning (Morris et al., 2015; Poggiogalle et al., 2018), resulting in more optimized food intake soon after waking hours (Cienfuegos et al., 2020; Poggiogalle et al., 2018). Furthermore, adverse eating patterns may lead to metabolic syndrome, also affecting weight maintenance (Mukherji et al., 2015). Thus, synchronizing feeding/fasting cycles with circadian rhythms may enhance metabolic regulation (Manoogian & Panda, 2017; Mattson et al., 2014), thereby promoting natural feeding patterns and preventing obesity, as it has been shown for instance by Arble and colleagues (2009). Similar benefits have been found in human studies of TRE with an early- or mid-day feeding window (Gabel et al., 2018; Jamshed et al., 2019). Although, some studies applying IF report significant weight-loss even with a late feeding window

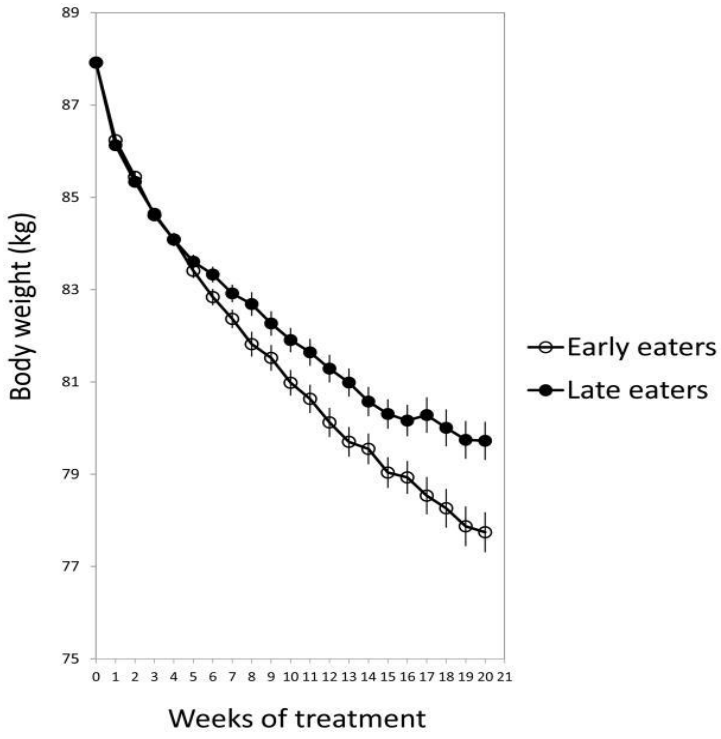

Figure 1. Change in body weight for late and early eaters throughout a twenty-week treatment. Repeated measures analysis of variance showed statistically significant difference in body weight between the two groups (p = .002), while controlling for the effect of sex, age and initial weight. Adapted from Garaulet et al., 2013.

(Cienfuegos et al., 2020). One potential issue from following a late TRE regime, is skipping breakfast in order to reduce the eating window (Fanti et al., 2021). Indeed, a large-scale cohort study in the United States found that skipping breakfast was associated with significantly higher risk for developing fatal cardiovascular diseases (Rong et al., 2019).

Another important factor to achieve weight-loss by IF may be the amount of nutrients ingested (Fanti et al., 2021). Indeed, in a recent clinical study, participants from all ages were randomly assigned to follow either a 16:8 TRE regime or to eat 3 structured meals throughout the day (Lowe et al., 2020). Lowe and colleagues (2020) found no significant between group differences in weight-loss and in estimated energy intake and expenditure, suggesting that, without additional interventions (e.g. increased activity), decreasing overall energy intake is necessary to achieve weight-loss with TRE. Importantly however, in Lowe and colleagues' study, they applied an eating window where the main meal was likely consumed after 15:00, which could have negatively affected the achievable weight-loss (Garaulet et al., 2013). Nevertheless, in line with the latter, most studies that showed significant weight-loss due to IF, found an (unintentional) overall decrease in caloric intake by 10-30% in both rodents and humans (Cienfuegos et al., 2020; Varady et al., 2021), despite compensatory increase in food intake on feast days or within the feeding window (e.g. Chausse et al., 2014; Cook et al., 2022; Varady et al., 2021). Indeed, although a common concern, current evidence suggest no over-compensatory eating due to IF (Cook et al., 2022; Harvey et al., 2018).

As it would not fit the scope of this essay, a few additional factors that may diversely influence the efficacy of an IF diet, such as diet composition (Varady et al., 2021), have not been discussed here.

There are also a number of potential disadvantageous, or even harmful (side-) effects of IF (Cook et al., 2022; Fanti et al., 2021). Some studies found that a few participants reported experiencing headaches and dizziness (Anton et al., 2019; Cienfuegos et al., 2020; Harvie et al., 2011; Hoddy et al., 2015), dry mouth (Cienfuegos et al., 2020), as well as feeling fatigued, weak and cold due to IF (Harvie et al., 2011; Hoddy et al., 2015). Moreover, there may be an increased risk for developing eating disorders, as adhering to IF has been associated with higher eating disorder symptomatology than the clinical norm in one survey study (Cuccolo et al., 2022). In contrast, another RCT, where obese participants followed a modified ADF regime for eight weeks, found an improvement in eating disorder symptomatology (Hoddy et al., 2015). Furthermore, it has been suggested that following a modified 5:2 diet may increase the risk for the occurrence of a hypoglycaemic episode in participants with Type 2 diabetes (Corley et al., 2018). Therefore, for people with Type 2 diabetes, it is only advised to follow an ADF or 5:2 regime if medical specialists closely monitor the process (Fanti et al., 2021).

However, despite its potential disadvantages, the general metabolic and health benefits of IF have been established in numerous animal models (Chaix et al., 2019; Mitchell et al., 2019), as well as in humans (Cienfuegos et al., 2020; Sutton et al., 2018; Varady et al., 2021). Indeed, it has been consistently shown that IF improves cardio-metabolic health markers (Sutton et al., 2018; Varady et al., 2021). For instance, it can significantly reduce insulin resistance and oxidative stress markers (Cienfuegos et al., 2020; Sutton et al., 2018; Figure 2A,B), pro-inflammatory markers (Patterson & Sears, 2017; Sutton et al., 2018), total cholesterol (Vasim et al., 2022) by decreasing LDL cholesterol (Vasim et al., 2022; Patterson

& Sears, 2017), and triglycerides (Patterson & Sears, 2017). Although, the evidence about the effects of IF on lipid profiles are more variable, with some studies showing no, or negative effects (Jamshed et al., 2019; Patterson & Sears, 2017; Sutton et al., 2018; Figure 2C,D). Moreover, there is increasing evidence that IF can reduce systolic (Conley et al., 2018; Sutton et al., 2018; Vasim et al., 2022; Figure 2E), and diastolic blood pressure (Sutton et al., 2018; Vasim et al., 2022; Figure 2F). Importantly, Sutton and colleagues (2018) showed that the health benefits after five weeks of IF in pre-diabetic males were evident even in the absence of weight loss. In animal models, IF improves longevity (Mattson et al., 2014; Mitchell et al., 2019), and induces cellular repair and maintenance mechanisms (Longo & Panda, 2016) that may contribute to the improved health markers. Finally, IF has been shown to improve cognitive functioning, such as learning and memory, in both animals (Mattson et al., 2018) and humans (Ooi et al., 2020). The effects of IF on learning and memory functioning is further discussed in the next chapter.

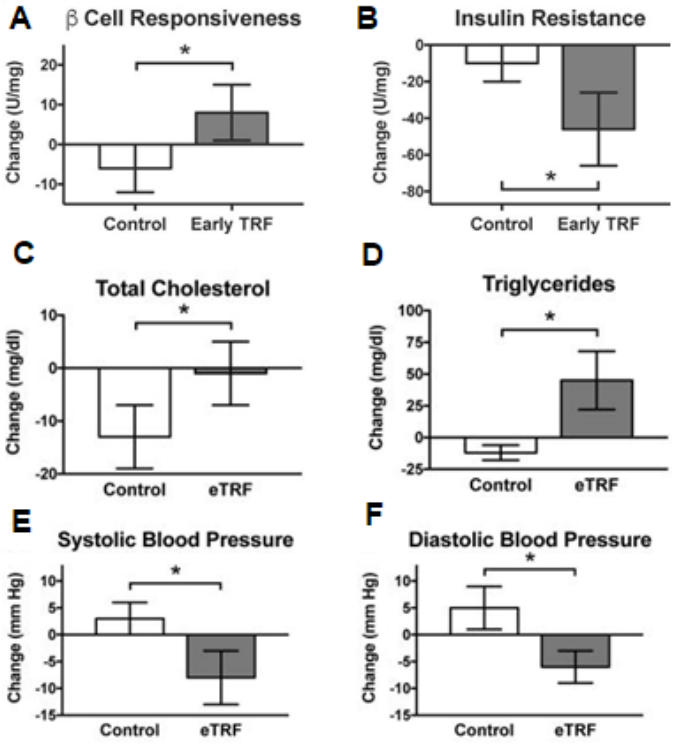

Figure 2. General health benefits and metabolic changes after IF. Early TRF improved (E) β cell responsivity and (F) insulin resistance. However, it increased morning values of (C) total cholesterol through increasing (D) triglycerides levels. Finally, early TRF drastically reduced (E) systolic and (F) diastolic blood pressure. Graphs represent paired data with $N = 8$ in each arm. Data are presented as least squares mean ± SEM. * $p \leq 0.05$. Modified and adapted from Sutton et al., 2018.

Abbreviations: eTRF = early time restricted feeding, SEM = standard error of the mean.

Effects of intermittent fasting on cognitive functioning: with a focus on learning and memory

Evidence for the effects of IF on cognitive functioning, and especially, learning and memory will be summarized in the following sub-chapters. Studies investigating the effects of Ramadan fasting, where followers abstain from eating and drinking anything from sunrise to sunset for 28 days (Currenti et al., 2021b), were not included in this essay. Ramadan fasting may disrupt circadian rhythms, thereby affecting sleep quality, and ultimately influencing cognitive outcomes (Currenti et al., 2021b). Although findings about the effect of Ramadan fasting on sleep quality are variable (Currenti et al., 2021b), nevertheless, Ramadan fasting is not comparable with regular TRE due to its extreme regime and specific duration.

Evidence from studies involving humans

Although not many studies investigated the effects of IF on cognitive functioning, and specifically on learning and memory in humans, most of those that are available, point to a positive effect (Ooi et al., 2020; Seidler & Barrow, 2022). For example, in a longitudinal cohort study, Ooi and colleagues (2020) recruited Malaysian elderly people with MCI, who were or were not practicing IF. Subjects underwent baseline measurements of cognitive performance, which was then repeated after 36 months. At 36 months, Ooi and colleagues found that subjects practicing IF showed better working memory and general cognitive functioning than subjects not practicing IF. Moreover, 87.5% of subjects practicing IF reverted to successful or normal aging category from MCI, in contrast to the 33.3% of subjects not practicing IF (Ooi et al., 2020). However, Ooi and colleagues did not control for the effect of any other variables that may influence changes in cognitive functioning (e.g. smoking status), in addition, it may well be that people practicing IF live a healthier lifestyle in general. Similarly, a large-scale Italian cohort study showed that people who had an eating window of more than ten hours (TRE) were less likely to have cognitive impairment than people with unrestricted eating windows, while controlling for several potential confounding variables such as age, smoking status and physical activity level (Currenti et al., 2021a). However, Currenti and colleagues (2021a) used the Short Portable Mental Status Questionnaire (Pfeiffer, 1975), which includes merely ten questions to assess general cognitive functioning, and does not measure learning or memory functioning.

There is a lack of long-term (>6 months) RCTs investigating the effects of IF on memory, or cognitive functioning in general. The available RCT studies showed variable results. For instance, Teong and colleagues (2021) randomly assigned overweight and obese women to a 4:3 IF or CR (both involving 30% caloric restriction) for eight weeks. After eight weeks, both groups showed significant improvement in the Digit Symbol Substitution Test (Teong et al., 2021), which is a measure of general cognitive functioning (Jaeger, 2018). Moreover, in another study, obese people aged 35-75 were randomly assigned to CR or modified 5:2 diet with 600 kcal-containing food packs on fast days and 12 hour eating-window for four weeks (Kim et al., 2020). At the end of the intervention, the two groups showed

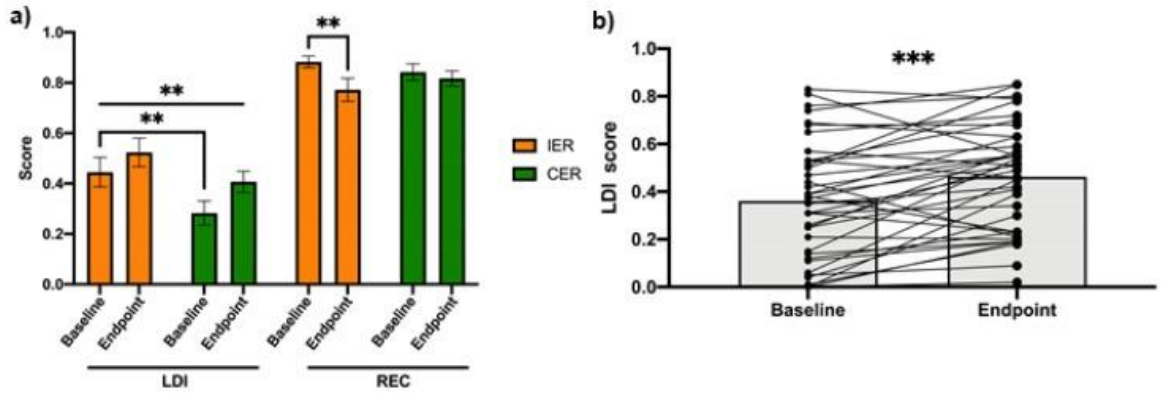

Figure 3. Effects of IF and CR on cognitive performance. (a) Both groups improved their LDI score, which measures pattern separation, but the IER group showed generally higher LDI scores than the CER group. Moreover, the IER group showed a significant reduction in recognition memory after the intervention. (b) When the groups were treated as a single cohort, there was a significant increase in LDI score. ** $p < 0.01$, *** $p < 0.001$. Adapted from Kim et al., 2020.

Abbreviations: IER = intermittent energy restriction, CER = continuous energy restriction, LDI = lure discrimination index, REC = recognition memory, IF = intermittent fasting, CR = caloric restriction.

improvements in pattern separation, with the modified IF group showing generally higher performance than the CR group (Kim et al., 2020; Figure 3). However, the modified IF group displayed significant decline in recognition memory (Kim et al., 2020; Figure 3). Furthermore, another finding showed that 4 weeks of 5:2 dieting followed by 22 weeks of 6:1 dieting did not affect general cognitive proficiency index as measured by a multi-domain screening test in a population of patients with metabolic disorder symptoms (Bartholomew et al., 2021). Importantly however, confounding variables that may have influenced the cognitive measures were not considered in any of the above mentioned studies.

Overall, due to the scarce availability of (long-term) studies that investigated the effects of IF on learning and memory functioning, and due to the variable IF regimes and methods used to measure cognitive functioning, it is difficult to draw conclusions about whether IF improves learning and memory functioning in humans. Moreover, all RCTs included participants of all (adult) age groups (Bartholomew et al., 2021; Kim et al., 2020; Teong et al., 2021), thus, it is plausible that the positive effects of IF on cognitive functioning is not displayed in young adults due to a ceiling effect in their cognitive test scores (Gudden et al., 2021).

Evidence from studies involving animals

Contrary to human studies, evidence from animal research clearly point to the beneficial effects of IF on learning and memory functioning (Chu et al., 2022; Mattson et al., 2018). IF is particularly effective in delaying age-associated cognitive decline (Chu et al., 2022; Mattson et al., 2018). For example, Fontán-Lozano and colleagues (2007) assigned 8-week old male mice to either ADF or *ad libitum* (AL) feeding for six to eight months. At the end of the intervention, ADF mice learned associations faster in a conditional learning paradigm and showed superior object recognition memory compared to AL fed mice (Fontán-Lozano et al., 2007). Moreover, even a late-onset, short-term ADF intervention was effective in improving spatial learning and memory functioning in old-aged, male rats (Singh et al., 2012). Specifically, 21-months-old, AL fed rats were switched to an ADF regime for three months, which resulted in better training and test performance in the Morris water maze (MWM) task compared to rats that were maintained on the AL diet for the duration of the intervention (Singh et al., 2012; Figure 4). Similarly, placing eight-months-old male rats on TRF with ketogenic or macronutrient matched control diet for 13 months, resulted in better spatial memory performance in the bi-conditional association test at old age than AL feeding with regular chow diet (Hernandez et al., 2022). In more detail, TRF was induced by ~15% daily CR, wherein rats consumed the provided food within three hours from feeding (Hernandez et al., 2022). Hernandez and colleagues (2022) also compared their results to previous data of young rats completing the same paradigm, and found that old rats receiving TRF since adulthood showed significantly better spatial memory functioning than AL fed rats regardless of age or dietary macronutrient composition, whereas old AL fed rats performed significantly worse than their younger counterparts. In addition, IF also seems to be effective in alleviating diet-induced memory deficits in rodents (Hazzaa et al., 2021). For instance, Hazzaa and colleagues (2021) showed that, even short-term, four or twelve weeks of ADF could alleviate high-fat diet induced spatial memory impairments in the Y-maze in adult male rats. Although, the twelve-

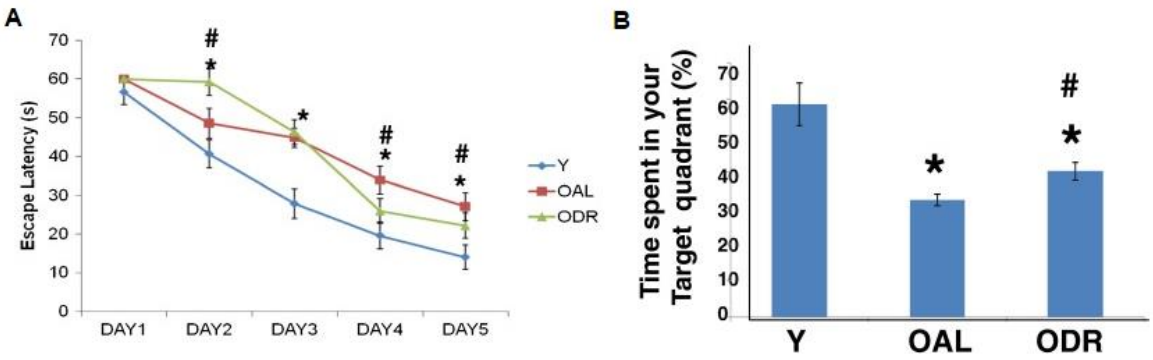

Figure 4. Spatial learning and memory performance of old and young AL-fed and IF rats in the Morris water maze. OAL rats showed (A) significantly longer latencies to find the platform during training, and (B) spent significantly less time in the target quadrant during test than ODR or young rats. ODR rats showed (A) significantly longer latencies to find the platform during training, and (B) spent significantly less time in the target quadrant than young rats. Values are mean ± SEM of five experiments ($N = 20$). * $p < 0.05$ young vs old AL and DR rats, # $p < 0.05$ old AL vs old DR rats, Bonferroni's test after one-way ANOVA. Modified and adapted from Singh et al., 2012.

Abbreviations: ANOVA = analysis of variance, Y = young, OAL = old ad libitum, ODR = old dietary restriction, IF = intermittent fasting, SEM = standard error of the mean.

week intervention resulted in superior performance on some aspects of the test, compared to the four-week intervention (Hazzaa et al., 2021), suggesting that the benefits are greater the longer the intervention.

Interestingly, some evidence suggests that the benefit of IF is more pronounced for long-term than for short-term memory. For instance, in a recent study, eight-week-old female mice were randomly assigned to ADF, 10% CR or AL feeding for three months (Dias et al., 2021). After the intervention, the mice were tested in the MWM one day and ten days after training (Dias et al., 2021). Results showed no differences in spatial memory retention between the groups after 24 hours, however, after ten days, mice in the ADF group performed significantly better than the other groups in one quadrant of the test (Dias et al., 2021). However, as it is unknown whether 10% CR resulted in a self-induced fasting state (Dias et al., 2021), it is difficult to draw conclusions about potential differences in efficacy between CR and IF diet. Furthermore, Li and colleagues (2013) showed that, eleven months of ADF resulted in better spatial memory functioning in the Barnes maze twelve, but not five, days after training than AL feeding (Figure 5A). However, mice on the ADF diet performed better than their AL counterparts in a context-cued, but not in a tone-cued, fear conditioning test 24 hours after training (Li et al., 2013; Figure 5B), suggesting that IF may variably enhance memory functioning on the short- and on the long-term depending on the memory test.

In animals, IF has been repeatedly shown to alleviate learning and memory deficits induced by various neuropathological conditions (Chu et al., 2022; Mattson et al., 2018). Indeed, ADF in rats has been shown to be efficient in alleviating learning and memory impairments caused by, for instance, lipopolysaccharide-induced sepsis (Vasconcelos et al., 2014), or chronic cerebral hypo-perfusion induced vascular dementia (Hu et al., 2019). Moreover, ADF (for various durations) was an efficient treatment for learning and memory deficits in numerous different mice models of Alzheimer's disease (AD; Halagappa et al., 2007; Liu et al., 2019; Zhang et al., 2017).

In conclusion, the benefits of IF in improving learning and memory in rodents are evident. However, it is important to note that, most of the studies discussed here used the same few behavioural tasks to test (mainly spatial) memory functioning in the rodents. Thus, although useful for comparing the findings, it is plausible that IF has differential effects depending on the type of memory tested (e.g. social memory). As it would have not fit the scope, a comparison of the effects of IF on memory functioning in different types of tasks was not included in this essay.

Overall, the benefits of IF on learning and memory functioning seems to be more robust in rodents than in humans. However, an important distinction between rodent and human studies is that, rodents living in laboratory cages with AL feeding do not face the same environmental challenges as rodents living in the wild. Therefore, the robust improvements found in laboratory rodents' cognitive functioning may better translate to humans living sedentary, overindulging lifestyles, than humans who voluntarily limit their food intake, and engage in physically and intellectually challenging activities (Mattson, 2015).

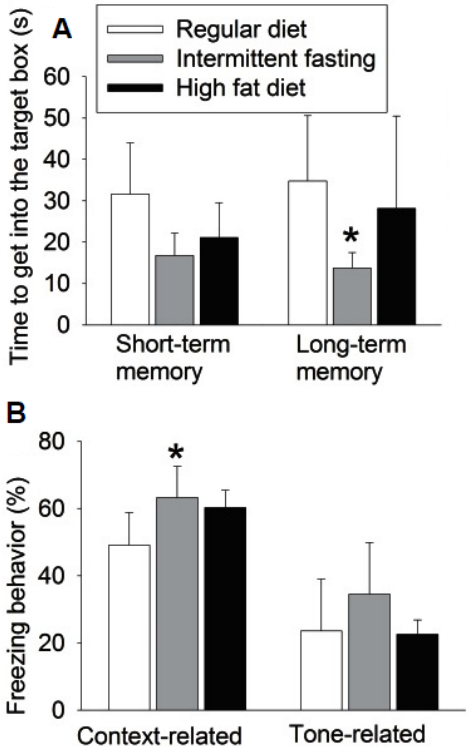

Figure 5. Effects of various feeding protocols on learning and memory. (A) Time to get into the target box in the Barnes maze test five (short-term memory) and twelve (long-term memory) days after training. (B) Percentage of freezing behaviour in the fear conditioning test 24 hours after training. Results are means ± SEM (N =15 – 35). * $p < 0.05$ compared with mice on regular chow *ad libitum*. Modified and adapted from Li et al., 2013.

Abbreviations: SEM = standard error of the mean.

Neurobiological mechanisms of learning and memory

Learning and memory refer to the capacity of living organisms to register and store their experiences, and utilize this information to modify their responses and adapt to their surroundings (Dunning & During, 2003). In recent years, significant research efforts have been dedicated to elucidating the molecular mechanisms that underlie learning and memory. Now it is clear that memory formation and storage requires synaptic plasticity, which refers to the strengthening or weakening of synapses in neural assembles representing the learnt information (Goto, 2022). Moreover, research has identified several molecular signalling pathways necessary for synaptic plasticity (Asok et al., 2019).

The hippocampus is one of the most important brain regions for learning and memory in both humans and rodents (Dunning & During, 2003; Goto, 2022). Moreover, a fundamental type of synaptic plasticity that occurs in the hippocampus is long-term potentiation (LTP; Asok et al., 2019; Goto, 2022). LTP refers to the long-lasting, activity-dependent increase in synaptic transmission efficacy (Lüscher & Malenka, 2012). N-methyl-D-aspartate (NMDA)-type glutamate receptor-dependent LTPs in the hippocampal C1 region has been widely studied

(Goto, 2022). During LTP, activation of NMDA receptors leads to an influx of calcium ions (Ca^{2+}) into the postsynaptic cleft (Goto, 2022). This influx of Ca^{2+} activates calcium/calmodulin-dependent kinase II (CaMKII), which phosphorylates various proteins, such as α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA)-type glutamate receptors (Goto, 2022; Lüscher & Malenka, 2012). Phosphorylation of AMPA receptor subunits increases their conductance, as well as, the increased activity of CaMKII facilitates the insertion of AMPA receptors, thereby strengthening the synapses (Goto, 2022; Lüscher & Malenka, 2012).

Furthermore, the learning-induced influx of Ca^{2+} promotes protein synthesis, and thereby, postsynaptic structural modifications and increased sensitivity to neurotransmitters, which results in long-term stabilization of synaptic transmission (Goto, 2022). Indeed, elevation of Ca^{2+} in the hippocampus activates CaM-dependent stimulation of adenylyl cyclase, which promotes cyclic adenosine monophosphate (cAMP) production (Xia & Storm, 2012). cAMP is a second messenger that activates protein kinase A (PKA), which promotes the phosphorylation of transcription factors such as cAMP element binding protein (CREB; Kreutzmann et al., 2015; Xia & Storm, 2012). The activation of CREB promotes gene-expression for proteins important for synaptic plasticity, and thereby, for memory formation (Kreutzmann et al., 2015; Xia & Storm, 2012).

In addition, brain-derived neurotrophic factor (BDNF) is a protein that plays a critical role in neuronal growth, survival, and synaptic plasticity, all of which are essential for learning and memory processes (Bathina & Das, 2015). BDNF binds to its receptor, tyrosine kinase B, which activates intracellular signalling pathways that contribute to the upregulation of synaptic plasticity by facilitating the growth and strengthening of synapses (Bathina & Das, 2015).

Metabolic and neurobiological aspects of intermittent fasting

Nowadays, acquiring food to refill energy stores is not a challenge for humans anymore, at least not in developed countries, where food is available 24/7. However, historically, animals in the wild (including humans) regularly had to face challenges due to a limited availability of food resources (Mattson, 2015; Mattson et al., 2018). Therefore, animals who could overcome these challenges by outsmarting their prey or by cooperating with others, were more likely to survive in the occasion of food scarcity (Mattson, 2015). Thus, evolution favoured individuals whose central nervous system (CNS) was resilient to such challenges due to a boost in motivation, and in cognitive, sensory, and motor function under fasting conditions (Mattson, 2015).

Under physiological conditions, the primary source of energy for most tissues in the body is glucose (Mattson et al., 2018). However, under fasting conditions or due to extended exercising, the body shifts from utilizing glucose as a main energy source, to utilizing fatty acids and ketone bodies, referred to as the *metabolic switch* (Mattson et al., 2018; Randle et al., 1963). Already in the 1960s, a theory of energy metabolism during feeding and fasting conditions has been proposed: the “glucose-fatty acid cycle”, wherein glucose and fatty acids compete for oxidation (Randle et al., 1963; Stockman et al., 2018). Today, it is also often referred to as the *fed-fast cycle* (Stockman et al., 2018; Vasim et al., 2022). This metabolic flexibility allows individuals to maintain high-levels of performance, even during extended periods of food scarcity (Anton et al., 2018).

The fed-fast cycle

The fed-fast cycle has four stages (Stockman et al., 2018; Vasim et al., 2022). The metabolic aspects associated with each stage will be discussed in the following sub-chapters.

Fed state

After eating, glucose is utilized for energy via glycolysis, a metabolic process that happens in the cytosol, wherein glucose is broken down by enzymatic processes to produce energy (i.e. adenosine triphosphate, ATP; Chaudhry & Varacallo, 2022). Morover, insulin secretion is increased, stimulating the liver to induce glycogenesis, which refers to the process of storing excess glucose in the form of glycogen (the primary carbohydrate) in the liver and muscle tissue (Anton et al., 2018; Mattson et al., 2018; Vasim et al., 2022). The liver can store up to 700-900 calories worth of glycogen (Mattson et al., 2018). When liver glycogen stores are fully replenished, excess calories are stored as triglycerides in adipocytes (Stockman et al., 2018; Vasim et al., 2022). Finally, during the fed state, lipolysis, which is the metabolic process by which triglycerides are broken down into free fatty acids and glycerol (Edwards & Mohiuddin, 2022), is inhibited (Stockman et al., 2018; Vasim et al., 2022). The fed state lasts approximately up to 3 hours in the absence of energy expenditure (Stockman et al., 2018).

Post-absorptive or early-fasting stage

The fed state is followed by the post-absorptive or early-fasting stage (Stockman et al., 2018; Vasim et al., 2022). As circulating glucose levels are decreasing, insulin production is reduced, and the pancreas starts secreting glucagon, a hormone that prevents an excessive drop in blood sugar levels by inducing glycogenolysis (Stockman et al., 2018). Glycogenolysis refers to the metabolic process whereby stored glycogen is broken down into glucose for energy utilization (Paredes-Flores & Mohiuddin, 2022). The metabolic switch happens towards the end of this stage, when liver glycogen stores are depleted, which occurs approximately 10-18 hours after cessation of caloric intake, depending on the amount of energy expenditure of the individual during this early-fasting stage (Mattson et al., 2018; Stockman et al., 2018; Vasim et al., 2022). Thus, when liver glycogen stores are depleted, and as the body starts seeking after other sources of energy, lipolysis is initiated (Stockman et al., 2018).

Fasting stage

During this stage, the body's metabolism switches from utilizing glucose through the process glycogenolysis, to utilizing fatty acids and fatty acid-derived ketone bodies through the process of lipolysis, as the main, preferred source of energy (Anton et al., 2018; Mattson et al., 2018; Stockman et al., 2018; Vasim et al., 2022). Indeed, there is growing evidence suggesting that ketones are the preferred energy source for the body, but especially for the brain, during periods of fasting and extensive exercising (Anton et al., 2018; Puchalska & Crawford, 2017). Free fatty acids metabolised in adipocytes enter the bloodstream, and are converted to ketone bodies mainly by hepatocytes in the liver (Mattson et al., 2018; Vasim et al., 2022), but also by astrocytes in the brain (Anton et al., 2018). Specifically, free fatty acids undergo β-oxidation, resulting in the production of the ketones β-hydroxybutyrate (BHB) and acetoacetate (AcAc; Anton et al., 2018). Ketones are transported into metabolically active cells, such as neurons and muscle cells, wherein ketones are utilized to generate ATP (Anton et al., 2018). This process not only allows for the sustained function of neurons, but it also preserves muscle cells while fasting and during extended periods of exercise (Anton et al., 2018). The fasting stage may last up to 48 hours from cessation of caloric intake (Stockman et al., 2018).

Box 2 – Circulating glucose and ketone levels in humans and rodents during IF

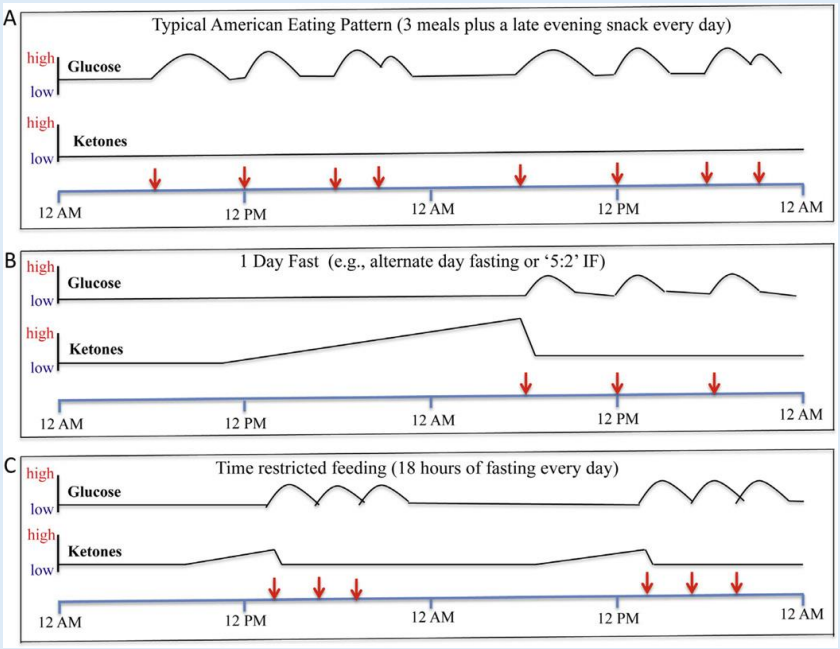

Figure 6. Illustration of the effect of three different eating patterns on circulating glucose and ketone levels in humans over a 48-hour period based on multiple findings. (A) Usual eating pattern in developed countries, characterized by three larger meals coupled with snacking. While glucose levels rise and then slowly return to baseline following each meal, ketone levels remain low throughout. (B) Fast day followed by a feast day with usual eating patterns. During the fast day, glucose levels remain at baseline, while ketone levels rise steadily. Following the first meal, blood ketone concentrations quickly drop and glucose levels rise. (C) Typical TRF protocol, characterized by a 6-hour eating window and 18 hours of fasting. After approximately 8-10 hours into the fast, ketone levels start to slowly rise, while glucose levels remain low until the next meal. Red arrows indicate time of food intake. Figure retrieved from Mattson et al., 2017.

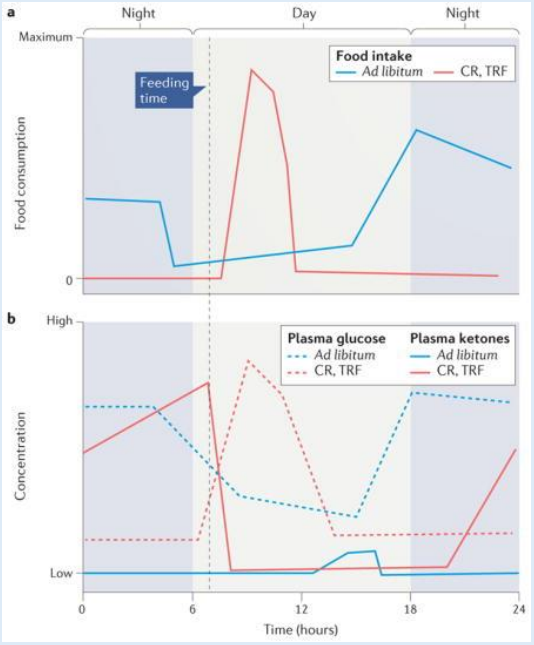

Figure 7. Data of (a) food intake, and (b) plasma glucose (dashed lines) and ketone levels (solid lines) during fed and fast states (in a 24-hour period) in rodents kept on 30-40% CR (TRF) or AL feeding, combined from multiple studies. In line with what was earlier mentioned, rodents kept on CR diet consume their daily allotment within 4 hours (Acosta-Rodríguez et al., 2017), resulting in 20 hours of self-induced fasting (a). While in AL fed rodents ketone levels only minimally rise by the end of the day (subjective night), in calorie restricted animal plasma ketone concentrations start rising approximately 10 hours after cessation of food intake, and continue to rise steadily until the next feeding time. On the other hand, glucose levels remain low throughout the fast. Figure retrieved from Mattson et al., 2018.

Long-term fasting or starvation state

This is the last stage of the fed-fast cycle, which is usually not reached when following an IF regime (Stockman et al., 2018). The long-term fasting stage is characterized by further drop in insulin levels, increase in ketone bodies, and reduced break-down of amino acids from muscle cells, which serves to preserve muscle (Stockman et al., 2018). However, as fat stores are depleted, the body needs to seek out other sources of energy, and in the lack of other resources, cells in the body start to break down amino-acids (Anton et al., 2018; Fryburg et al., 1990; Stockman et al., 2018). Long-term starvation is associated with a plethora of adverse side effects, for example, nausea and vomiting, extensive loss of muscle tissue, thiamine deficiency, and death (Anton et al., 2018).

Effects of intermittent fasting on neurobiological processes

In response to the metabolic switch, several signalling pathways are induced in the brain (Brocchi et al., 2022; Mattson et al., 2018; Stockman et al., 2018). In the following, the most relevant IF-induced changes in neurobiological processes and pathways for the proposed hypothesis will be discussed, as an all-encompassing review would have not fit the scope of this essay.

In general, the neurobiological pathways that are activated in response to the metabolic switch seem to improve cellular stress resistance, and upregulate pathways important to maintain optimal cell function, and thereby improve cellular and functional plasticity that occur after switching back to glucose as the main energy source (Anton et al., 2018; Brocchi et al., 2022; Gudden et al., 2021; Mattson et al., 2018; Stockman et al., 2018). Indeed, BHB is a specific inhibitor of class I histone deacetylases, thereby potentially promoting cellular resistance to oxidative stress (Shimazu et al., 2013; Stockman et al., 2018). For instance, Shimazu and colleagues (2013) showed that administration of BHB, 24-hour fasting and 40% CR all increased BHB and global histone acetylation in the fasted state. Importantly, inhibition of class I histone deacetylases by BHB administration increased histone acetylation at forkhead box O3 (FOXO3A) and Metallothionein 2 (MT2) promoters, genes that encode for their associated oxidative stress resistance factors (Shimazu et al., 2013). Furthermore, fasting-induced decrease in glucose levels reduces ATP:AMP ratio, eventually activating AMP-activated protein (AMPK) and CaMKII kinases and, downstream from them, the transcription factors CREB and peroxisome proliferator-activated receptor-gamma coactivator 1 (PGC1; Gudden et al., 2021). As a result, besides other processes, autophagy is induced, which is a cell repair mechanism whereby damaged cellular components are recycled (Gudden et al., 2021; Mattson et al., 2018). Autophagy is thought to be induced by (an AMPK mediated) suppression of mammalian target of rapamycin (mTOR) in the fasting state (Mattson et al., 2018), leading to an overall inhibition of protein synthesis and to the activation of cellular repair mechanisms (Alirezaei et al., 2010; Gudden et al., 2021; Mattson et al., 2018). In contrast, during the fed state, mTOR is active and promotes active protein synthesis (Gudden et al., 2021). In addition, BHB has been shown to be protective against neuro-inflammation through several different pathways (Brocchi et al., 2022; Stockman et al., 2018).

Moreover, there is robust evidence indicating that BDNF expression is upregulated due to IF and increased levels of ketones (Brocchi et al., 2022; Gudden et al., 2021; Mattson et al., 2018), which also promotes mitochondrial biogenesis (Gudden et al., 2021; Marosi & Mattson, 2014), cellular stress resistance (Brocchi et al., 2022; Marosi & Mattson, 2014) and synaptic

plasticity (Gudden et al., 2021; Mattson et al., 2018). Indeed, BHB treatment induced BDNF expression in mouse cerebral cortical neurons in vitro, potentially through the upregulation of nuclear factor B (Marosi et al., 2016). Moreover, 40% CR for three months resulted in increased BHB levels during the fasting state, and increased expression of BDNF levels compared to AL feeding in both lean and obese mice (Stranahan et al., 2009). In addition, the increased levels of BDNF significantly correlated with an increased dendritic spine density in hippocampal dentate granule neurons found in the CR group (Stranahan et al., 2009). Supporting evidence for the increased levels of BDNF expression due to IF has been shown in several rodent studies (Mattson et al., 2018; Zhang et al., 2022), and even in humans adhering to an early TRF regime (Jamshed et al., 2019).

The role of synaptic plasticity in intermittent fasting-induced changes in learning and memory functioning

Currently, there are only a few studies available that investigated the effects of IF on synaptic plasticity processes, and even fewer that simultaneously measured learning and memory functioning. In the following paragraphs, the available evidence will be summarized, while findings discussed in the previous chapters will be considered for the interpretation of the results. Finally, the following paragraphs will reveal whether the currently available evidence overall supports or opposes the proposed hypothesis that, IF improves learning and memory functioning via enhancing neural plasticity mechanisms.

Current findings suggest that IF promotes synaptic plasticity processes (Dasgupta et al., 2018; Talani et al., 2016), and upregulates proteins and transcription factors important for synaptic plasticity (Dasgupta et al., 2018; Talani et al., 2016). For instance, Dasgupta and colleagues (2018) investigated the effects of IF on metaplastic processes in vitro. Specifically, adult mice were randomly allocated to AL feeding, daily fasting for 12 hours (12:12 TRE) or 16 hours (16:8 TRE), or ADF for six months (Dasgupta et al., 2018). At the end of the intervention, hippocampal slices were collected and early- or late-LTP was evoked using either a weak or a strong stimulation protocol, respectively, and synaptic capture (an associative property of synaptic plasticity) was evoked by a weak, followed by a strong stimulation (Dasgupta et al., 2018). Findings of this study indicated no effect of any of the IF regimes on the magnitude of early- or late-LTP, but showed prolonged synaptic capture in ADF and 16:8 TRE mice compared to AL fed mice (Dasgupta et al., 2018). Synaptic capture refers to the notion that synapses involved in short-lived enhancements of synaptic transmission during a learning event can achieve persistent modulation of synaptic transmission by associatively interacting with a stronger learning event within a specific timeframe (Shivarama Shetty & Sajikumar, 2017). Moreover, genes promoting synaptic plasticity, such as BDNF, were elevated in all IF groups compared to AL fed mice (Dasgupta et al., 2018). However, it is unclear when were the brains obtained for tissue collection (Dasgupta et al., 2018), thus, it is not possible to draw conclusions about whether the found effects are general to IF, or specific to one of the stages of the fed-fast cycle. Furthermore, Fontán-Lozano and colleagues (2007) investigated the effects of six to eight months of ADF on synaptic plasticity processes in mature mice in vivo. Electrophysiological recordings were performed on fed days, and the results showed that the LTP magnitude evoked by a weak stimulus was significantly enhanced in ADF than in AL fed mice (Fontán-Lozano et al., 2007; Figure 8A,B). In addition, in another experiment, mice were injected with an NMDA receptor antagonist, and this intervention alleviated the positive effects of ADF on the magnitude of LTP, indicating that NMDA receptor function is essential to achieve improved synaptic plasticity processes by IF (Fontán-Lozano et al., 2007; Figure 8C,D).

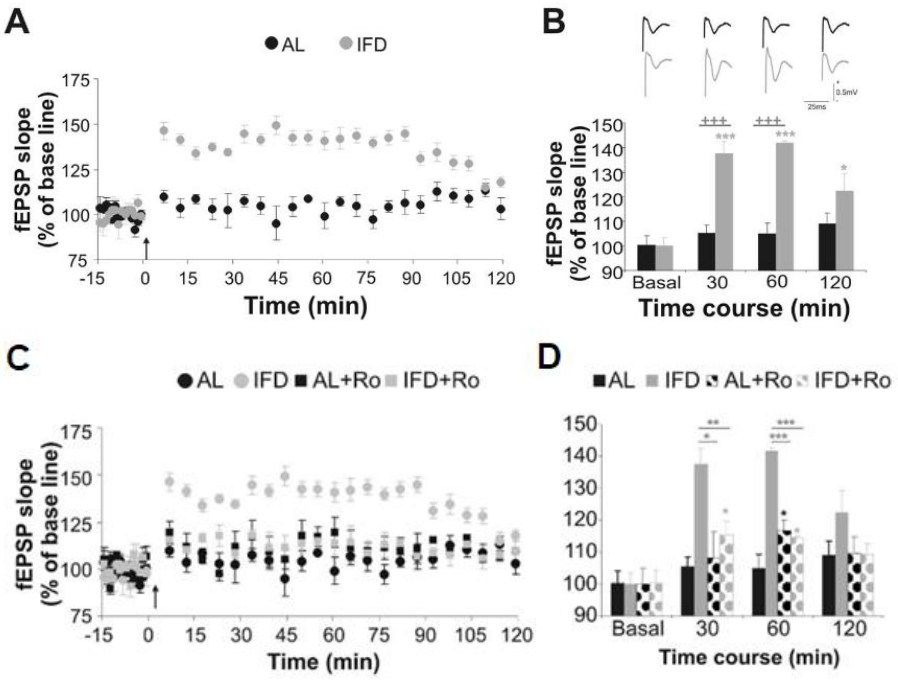

Figure 8. ADF enhances hippocampal LTP, and administering Ro, an NMDA receptor antagonist, alleviates the positive effects of ADF on LTP magnitude. (A) A single HFS train (arrow) evoked LTP that lasted for up to two hours in IFD mice, but not in AL mice. (B) Summary of the changes in fEPSP slope (mean ± SEM) at different times after a single HFS train. Representative fEPSP recordings obtained simultaneously from AL and IFD mice are also presented. (C) Ro administration reversed the positive effect of IF on LTP magnitude, but did not affect the same synapse in AL mice. (D) Summary of percentage change in fEPSP slope (mean ± SEM) at different times after a single HFS train in AL and IFD mice, with or without Ro. Each group had $N = 6$ animals. $^{+}$Difference between AL and IFD mice in the same session; *Statistical significance of the each session with respect to baseline recording in the same group. * $p < 0.05$; ** $p < 0.01$; $^{+++}$/*** $p < 0.001$. Modified and adapted from Fontán-Lozano et al., 2007.

Abbreviation: AL = ad libitum, ADF = alternate day feeding, IFD = intermittent fasting diet, LTP = long-term potentiation, NMDA = N-methyl-D-aspartate, Ro = Ro25-6981, HFS = high frequency stimulation, fEPSP = field excitatory postsynaptic potentials, SEM = standard error of the mean.

Moreover, in a large-scale study, several mouse lines were kept on AL feeding or ADF for varying durations, and the animals were tested in a number of behavioural tests at different time-points (Liu et al., 2019). First, the authors tested mice that either had a knock-in or a knock-out of the gene encoding for the mitochondrial protein deacetylase sirtuin 3 (SIRT3), which is involved in the reduction of oxidative stress (Liu et al., 2019). Results showed that four months of ADF did not significantly change LTPs evoked in hippocampal slices by a single stimulation (Figure 9A,B), however, it is unclear whether the tissues were obtained before or after feeding time (Liu et al., 2019). Importantly, the magnitude of LTP was significantly decreased in IF mice lacking SIRT3, indicating an important role of SIRT3 in adapting to IF (Liu et al., 2019; Figure 9A,B). Findings showed that SIRT3 expression is higher in IF mice compared to AL fed mice in the fasted state, the longer the intervention has been running (Liu et al., 2019; Figure 9C). Indeed, IF seems to have an adaptation period, which was indicated by that an acute food deprivation episode of one day in AL fed mice significantly increased their anxiolytic behaviour in the fasted state, whereas mice maintained on ADF for one month showed no increase in anxiolytic behaviour in the fast state compared to the non-fasted state (Liu et al., 2019; Figure 9D). Furthermore, the study also tested the effects of 5:2 IF diet on LTP in a mouse model of AD and in wild-type (WT) mice. They showed that, LTP

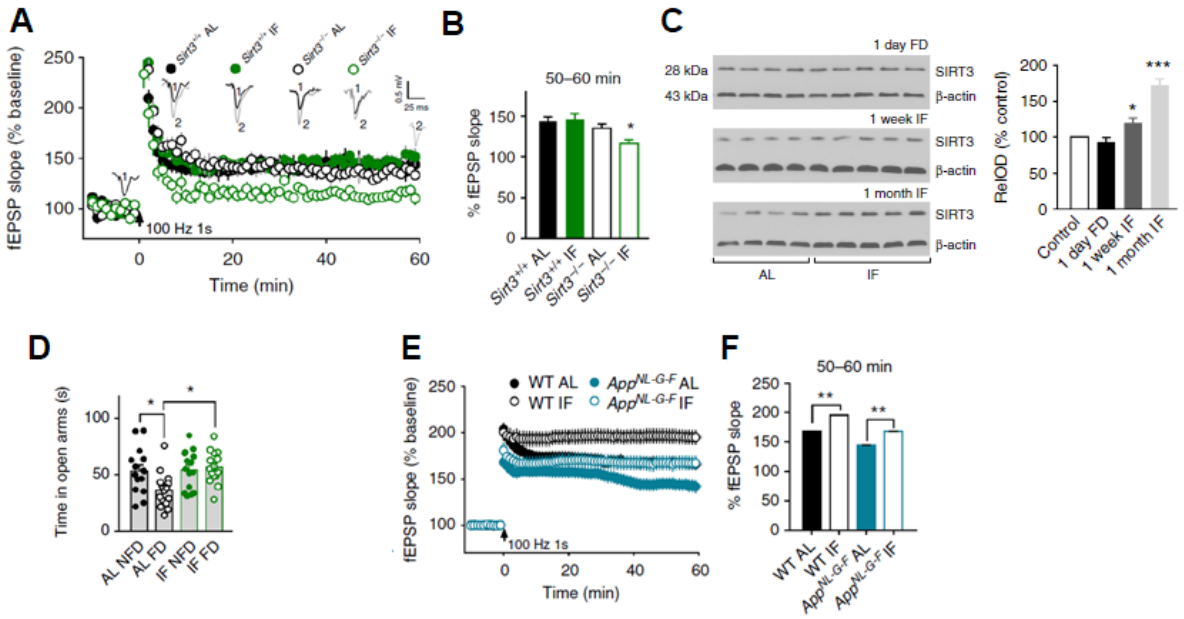

Figure 9. Effects of IF on LTP magnitude, SIRT3 expression and anxiolytic behaviour. (A) LTP evoked by a single HFS train (arrow) was not affected by diet-type, but was significantly lower in SIRT3$^{-/-}$ IF mice. (B) Summary of the changes in fEPSP slope (mean ± SEM) at the end of the recording period (i.e. 50-60 min) after a single HFS train. (C) Immunoblots show relative levels of SIRT3 protein in hippocampus of mice that were food deprived for one day or maintained on ADF for 1 week or 1 month. (D) Mice were tested in the elevated plus maze either after a 24 h period of FD or NFD. (E) LTP evoked by a single HFS train (arrow) in WT mice and in a mouse model of AD. (F) Summary of the changes in fEPSP slope (mean ± SEM) at the end of the recording period (i.e. 50-60 min) after a single HFS train. All error bars represent SEM. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. Modified and adapted from Liu et al., 2019.

Abbreviation: AL = ad libitum, AD = Alzheimer's disease, ADF = alternate day feeding, IF = intermittent fasting, FD = food deprivation, NFD = no food deprivation, LTP = long-term potentiation, HFS = high-frequency stimulation, fEPSP = field excitatory postsynaptic potentials, SEM = standard error of the mean, SIRT3 = sirtuin 3, WT = wild-type.

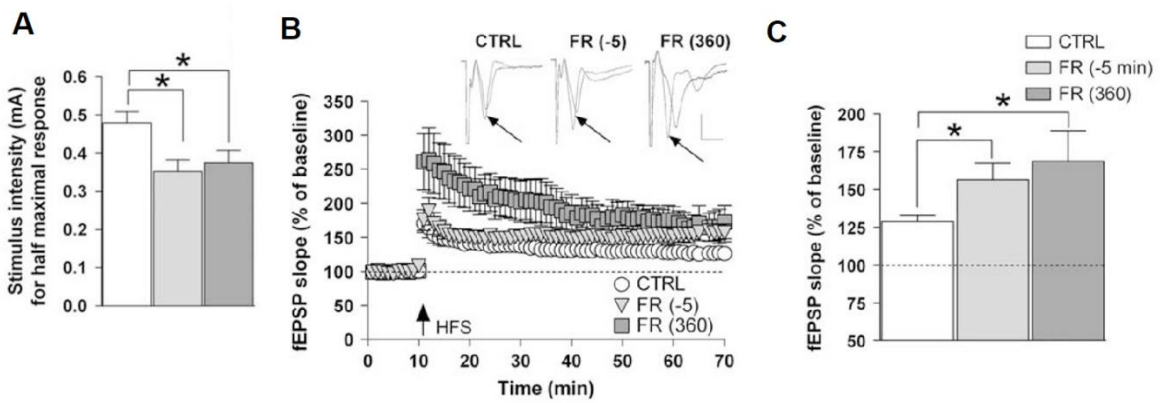

Figure 10. Effects of IF on neural excitability and LTP magnitude 5 minutes before or 6 hours after feeding time. (A) Bar graph representing the current intensity required to produce the half-maximal response. (B) LTP evoked by a single HFS train (arrow), and above are the representative traces of fEPSPs before and one hour after stimulation (black arrow). (C) Summary of the changes in fEPSP slope (mean ± SEM) at the end of the recording period (i.e. 60-70 min). * < 0.05 vs CTRL. Modified and adapted from Talani et al., 2016.

Abbreviations: CTRL = control, FR = food restriction, IF = intermittent fasting, LTP = long-term potentiation, HFS = high-frequency stimulation, fEPSP = field excitatory postsynaptic potentials, SEM = standard error of the mean.

magnitude was significantly improved after nine months of 5:2 diet compared to AL feeding in WT mice, whereas LTP was significantly reduced in AD compared to WT mice fed AL, but maintaining the AD mice on the 5:2 diet for nine months significantly ameliorated the negative effects of AD on LTP (Liu et al., 2019; Figure 9E,F). Although findings regarding the effects of IF on LTP magnitude were inconsistent within this study, given that WT mice showed improvement, the results suggest that LTP can be induced by IF and SIRT3 availability may be necessary to adapt to IF.

Finally, in another study rats were fed AL or within a 2-hour window every day for three weeks (TRE group), and then LTP and BDNF levels were measured in hippocampal slices of brains obtained five minutes before or six hours after feeding time (Talani et al., 2016). Results showed that significantly lower stimulations were sufficient to evoke higher field excitatory postsynaptic potentials (fEPSPs) in slices obtained from TRE rats sacrificed before or after feeding time than in slices obtained from AL fed rats (Talani et al., 2016; Figure 10A). Moreover, a single high frequency stimulation was applied to evoke LTP (Talani et al., 2016). Talani and colleagues (2016) found that, by the end of the recording period (i.e. 50-60 min after stimulation), the magnitude of LTP was significantly higher in the TRE group than in the control group, regardless of when the tissue was collected (Talani et al., 2016; Figure 10C). However, at the beginning of the recording period, it seems that the magnitude of the evoked LTP was only higher in the TRE group than in the AL fed group if the slices were obtained after feeding time, whereas LTP evoked in slices obtained from the TRE group before feeding time slowly increased by the end of the recording period (Talani et al., 2016; Figure 10B). Furthermore, BDNF levels were elevated in the hippocampus of TRE rats compared to AL fed rats, regardless of the timing of tissue collection (Talani et al., 2016). These findings suggest that IF enhances synaptic plasticity and the excitatory potential of hippocampal neurons, regardless of whether one is in the post-absorption or fasting stage, with a potentially increased benefit in the post-absorption stage. The latter

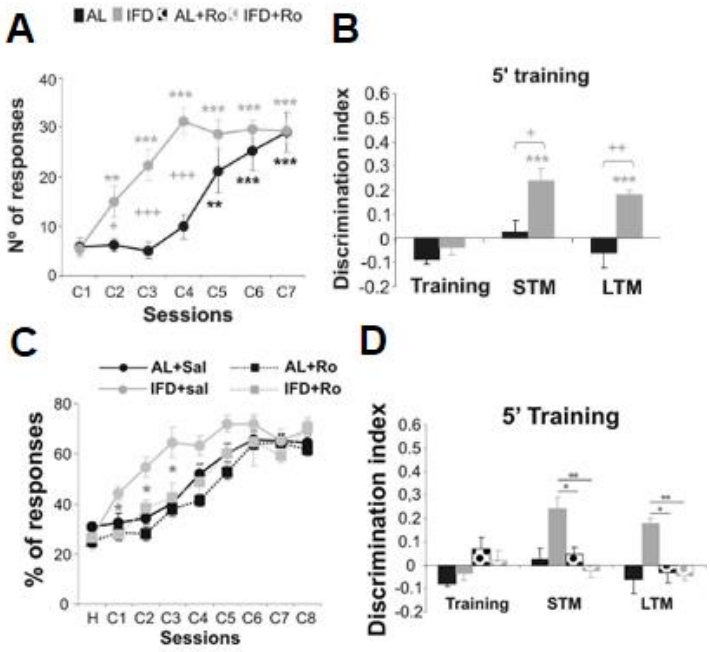

Figure 11. IF improves learning and memory functioning, and administration of Ro (NMDA receptor antagonist) ameliorates these positive effects. (A) Frequency of conditioning responses per session following training in an operant conditioning paradigm. (B) Performance in the object recognition memory paradigm with 5-minutes training sessions (N = 8 in both groups) during training, STM, and LTM sessions (1 and 24 h after training, respectively). Moreover, pre-training administration of Ro prevents the enhancement of (C) trace eye-blink classical conditioning and (D) object recognition memory induced by IF. $^{+/}$* $p < 0.05$; $^{++/}$** $p < 0.01$; $^{+++/}$*** $p < 0.001$. Error bars represent SEM. Modified and adapted from Fontán-Lozano et al., 2007.

Abbreviations: AL = ad libitum, ADF = alternate day feeding, IFD = intermittent fasting diet, LTP = long-term potentiation, NMDA = N-methyl-D-aspartate, Ro = Ro25-6981, Sal = saline, STM = short-term memory, LTM = long-term memory, SEM = standard error of the mean.

would be in line with the notion that synaptic plasticity mechanisms are enhanced primarily in the fed state, due to upregulated cellular stress resistance mechanisms that occur in the fasting state (Mattson et al., 2018).

In summary, the latter findings indicate that IF enhances synaptic plasticity processes, which is observable primarily in the fed state, and is potentially mediated by increased cellular stress resistance mechanisms that occur in the fasted state. However, only some of these studies investigated the association between changes in synaptic plasticity processes and memory functioning (Fontán-Lozano et al., 2007; Liu et al., 2019; Talani et al., 2016), which will be discussed in the following paragraphs.

Rodents kept on IF for various durations showed improved learning and memory functioning (Fontán-Lozano et al., 2007; Liu et al., 2019; Talani et al., 2016). For instance, Talani and colleagues (2016) showed that three weeks of 22:2 TRE compared to AL feeding significantly improved rats' performance in the Barnes maze twelve, but not five, days after training, indicating that the intervention had a stronger effect on long- than on short-term memory functioning, which is in line with previous findings (Dias et al., 2021). Furthermore, as earlier mentioned, Fontán-Lozano and colleagues (2007) found that ADF mice demonstrated accelerated learning in a conditional learning paradigm (Figure 11A) and exhibited better object recognition memory when compared to mice fed AL (Figure 11B). Finally, in the large-scale study by Liu and colleagues (2019), SIRT3$^{+/+}$, WT, and AD rats showed significantly better memory retention in a water maze test when maintained on an IF diet compared to AL feeding (Figure 12).

These results indicate that maintaining an IF diet increases memory functioning and the magnitude of LTP in rodents. However, so far, it is unclear whether there is a causal relationship between the effects of IF on synaptic plasticity processes and memory functioning.

Crucially, the downregulation of molecular pathways known to be involved in synaptic plasticity processes resulted in significant changes in LTP, learning and memory functioning in rodents (Fontán-Lozano et al., 2007). Indeed, besides alleviating the positive effects of IF on the magnitude of LTP (Figure 8C,D), inhibition of NMDA receptors also ameliorated the improvements in conditional learning (Figure 11C) and object recognition memory in ADF mice (Figure 11D), supporting the notion that NMDA receptor functioning is necessary for increasing synaptic plasticity processes, and thereby also for memory functioning (Fontán-Lozano et al., 2007; Goto, 2022). In addition, knock-out of signalling pathways important for

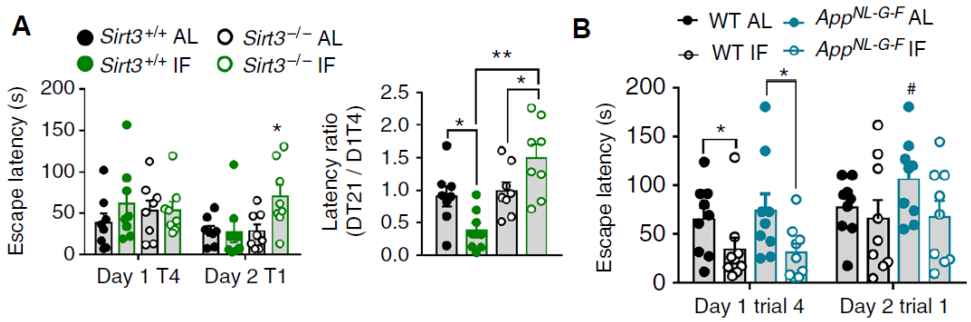

Figure 12. Performance in the MWM in different strains of animals with AL feeding or IF. (A) Escape latencies on testing day 1 trial 4, and testing day 2 trial 1 (left), and latency ratios (right) in SIRT3$^{+/+}$ and SIRT3$^{-/-}$ animals. (B) Escape latencies on testing day 1 trial 4, and testing day 2 trial 1 in a mouse model of AD and WT mice. All error bars represent SEM. $^{\#}p < 0.05$, App^{NL-G-F} AL compared to the other three groups. * $p < 0.05$; ** $p < 0.01$. Modified and adapted from Liu et al., 2019.

Abbreviation: AL = ad libitum, AD = Alzheimer's disease, IF = intermittent fasting, MWM = Morris water maze, SEM = standard error of the mean, SIRT3 = sirtuin 3, WT = wild-type.

oxidative stress reduction, resulted in similar effects (Liu et al., 2019). Specifically, in SIRT3$^{-/-}$ mice, besides the decreased magnitude in LTP, ADF also resulted in worse performance in the water maze test than AL feeding (Figure 12A), indicating that SIRT3 is necessary to achieve increased LTP, and improved learning and memory functioning during IF (Liu et al., 2019). Importantly, in all the above mentioned studies, learning and memory functioning was tested in the fed state.

Overall, the minimal evidence available on the topic suggest that, IF in rodents enhances synaptic plasticity (which is especially evident in the fed state), and thereby learning and memory functioning is also enhanced in these animals. Potentially, cellular repair mechanisms upregulated in the fasting state result in increased synaptic plasticity and better communication between neurons in the fed state, which in turn improves learning and memory functioning, especially in the fed state. However, due to the lack of evidence on the topic, further research is necessary to support these findings.

Conclusion

In conclusion, the available evidence suggest that adhering to IF improves learning and memory functioning (at least in part) by enhancing synaptic plasticity in the hippocampus. In the fasting state, the abundance of glucose decreases and circulating fatty acid and ketone levels increase, thus the brain switches from utilising glucose to utilising fatty acids and ketones as its main fuel. The metabolic switch induces signalling pathways that stimulate proteins important for enhancing cellular stress resistance mechanisms (e.g. SIRT3). These processes are known to facilitate synaptic plasticity. There is supporting evidence from rodent studies that IF promotes oxidative stress resistance pathways in the fasting state, and improves synaptic plasticity and memory functioning in the fed state. Importantly, pharmacological blockade of NMDA receptors alleviated the positive effects of IF on synaptic plasticity, and thereby, on learning and memory functioning. It is plausible that to achieve the proposed benefits of IF, one has to consider a number of factors that may influence the efficacy of this diet, such as the timing of the eating-window. Indeed, synchronising eating patterns to align with circadian oscillations of metabolic signalling pathways may be important to achieve the benefits. In addition, the duration of the intervention may be important, with longer interventions potentially inducing stronger benefits. Moreover, it is unclear whether these findings also translate to humans. IF seems to improve cognitive functioning in the elderly and in people with cognitive deficit, but results are variable for young, healthy individuals. Overall, although the available evidence indicates that IF improves learning and memory functioning (at least in part) by enhancing synaptic plasticity, further research is needed to support these findings.

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