Trends in Cognitive Sciences

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Opinion

# An Evolutionary Perspective on Why Food Overconsumption Impairs Cognition

Mark P. Mattson[1,2,*]

**Brain structures and neuronal networks that mediate spatial navigation, decision-making, sociality, and creativity evolved, in part, to enable success in food acquisition. Here, I discuss evidence suggesting that the reason that overconsumption of energy-rich foods negatively impacts cognition is that signaling pathways that evolved to respond adaptively to food scarcity are relatively disengaged in the setting of continuous food availability. Obesity impairs cognition and increases the risk for some psychiatric disorders and dementias. Moreover, maternal and paternal obesity predispose offspring to poor cognitive outcomes by epigenetic molecular mechanisms. Neural signaling pathways that evolved to bolster cognition in settings of food insecurity can be stimulated by intermittent fasting and exercise to support the cognitive health of current and future generations.**

## Highlights

Neuronal networks in brain regions critical for spatial navigation and decision-making evolved to enable success in competition for limited food availability in hazardous environments.

A major ecological factor that drove the evolution of cognition, namely food scarcity, has been largely eliminated from the day-to-day experiences of modern-day humans and domesticated animals.

Continuous availability and consumption of energy-rich food in relatively sedentary modern-day humans negatively impacts the lifetime cognitive trajectories of parents and their children.

Epigenetic molecular DNA and chromatin protein modifications are impacted by energy intake and can propagate to future generations.

The cellular and molecular mechanisms by which intermittent food deprivation enhances cognition and overfeeding impairs cognition are being elucidated.

A better understanding of the food-centric evolutionary foundations of human brain neuroplasticity is leading to the development of novel bioenergetic challenge-based patterns of eating and exercise aimed at improving cognitive health and resilience.

## Setting the Stage

Eating three energy-rich meals plus snacks every day with no physical exertion required is unusual when viewed in the light of evolution. Novel insights into mechanisms of human cognition emerge when information on how food scarcity drove brain evolution is considered in light of emerging data on how dietary energy intake impacts cognitive trajectories. These insights include: (i) an ecological factor that had a major role in the evolution of advanced cognitive capabilities (food scarcity) has been largely eliminated from day-to-day experiences of modern-day humans and domesticated animals; (ii) overindulgent sedentary lifestyles negatively impact cognition, and the underlying metabolic state and its associated poor cognitive outcomes can be transmitted epigenetically to offspring. The possibility that this state of excessive energy intake will continue has important implications for brain evolution and the cognitive trajectories of future generations; (iii) the cellular and molecular signaling pathways by which the challenge of intermittent food deprivation bolsters cognition have been elucidated in animal studies of intermittent food deprivation and exercise and/or running; and (iv) incorporation of feeding patterns that include **intermittent fasting** (IF; see Glossary) into the lifestyles of humans (and domesticated animals) can augment their cognitive capabilities and neuronal resilience.

## The Cognitive Repertoire as an Evolved Adaptation to Food Scarcity

Many animals in the wild and our human ancestors evolved in environments with sporadic food availability, such that they commonly experienced extended periods of many days or more without food. Accordingly, natural selection favored individuals capable of outperforming their competitors, cognitively and/or physically, when in a food-deprived state. The range of cognitive capabilities throughout the animal kingdom (spatial navigation, decision-making, sociality, and **creativity**) are largely concerned with food acquisition and reproduction. Success in food acquisition is tightly linked with reproductive success, a topic reviewed

[1]Department of Neuroscience, Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA
[2]Laboratory of Neurosciences, National Institute on Aging Intramural Research Program, Baltimore, MD 21224, USA

*Correspondence: mmattso2@jhmi.edu (M.P. Mattson).

elsewhere [1] and not considered further here. From a bioenergetic perspective, a major conserved adaptation to food scarcity was metabolic switching from utilization of liver-derived glucose to a **ketogenic state**, in which adipose cell-derived fatty acids and ketones are utilized by neurons and muscle cells as cellular fuels to sustain cognitive performance and physical endurance, respectively [2]. As discussed later in this article, such metabolic switching also stimulates neural signaling pathways that bolster cognition.

## Lessons from Rodents, Corvids, and Non-Human Primates

Accurate navigation in complex environments is fundamental for success in food acquisition. The neuronal networks and cellular and molecular mechanisms that control spatial navigation and decision-making in rodents are being elucidated [3]. This research has established a fundamental role for the hippocampus and its functional connections with the entorhinal cortex, **prefrontal cortex** (PFC), cingulate cortex, and associated cerebral cortical networks involved in processing and responding to neural representations of objects and sounds in the environment. Evidence that individual neurons encode the current position and orientation of the animal, as well as 'imagined' future navigation paths, emerged from electrophysiological recordings and brain-imaging studies of rodents navigating through space [4,5] or in virtual reality scenarios [6–8]. This research established that neurons in the hippocampus called '**place cells**' encode the current location of an animal within an environment, neurons called '**grid cells**' in the entorhinal cortex have hexagonally arranged firing fields, and other neurons encode head orientation [9]. Similar to findings from electrophysiological recordings in rodents, fMRI analyses of humans navigating in virtual environments revealed grid-like signals in the entorhinal cortex during imagined navigation, with activity patterns exhibiting sixfold rotational symmetry similar to rodents [10]. In a recent study, food-deprived rats were trained to run laps on a linear track to acquire a food reward while activity of scores of neurons in the CA1 region of the hippocampus were recorded [11]. The study focused on 'hippocampal replays', which are episodes of sequential activity in place cells during sharp-wave ripple oscillations. The data revealed both forward and reverse replays of food locations. Interestingly, reverse replays increased with increasing food rewards, whereas forward replays were unchanged [12]. Therefore, in the natural environment, reverse replays might be expected to have a key role in food patch-leaving decisions.

Studies of food-caching behaviors in **corvids** have revealed a remarkable breadth of cognitive abilities that include remembering the past, planning for the future, and interpreting the behaviors of others. Corvids and parrots have forebrain neuron counts greater than those of primates with larger brains, which may contribute to the advanced **intelligence** of the birds [13,14]. As with primates, corvids have a prominent hippocampal formation that has key roles in the generation of 'cognitive maps' and episodic memory, and interconnected brain structures involved in executive functions (goal-oriented planning, strategizing, and self-monitoring) and decision-making. Moreover, corvids exhibit 'theory of mind', in that they understand that other individuals have mental states and intents similar to their own [15]. Studies of scrub jays demonstrated that they routinely use **mental time travel**, problem solving, and social cognition to acquire, hide, and recover foods (caching behavior) [16]. These birds remember what happened when and where based on a single past experience so that they can discriminate between many similar previous episodes. Thus, they can learn the 'shelf life' of foods and eat the more perishable foods first.

There is also evidence that expansion of the PFC during the evolution of non-human primates enabled the critical decision-making required for success in foraging in arboreal canopies [17]. Food sources are usually distributed in patches, which forces the animal to decide between

## Glossary

**Brain-derived neurotrophic factor (BDNF):** a protein that is produced by neurons in response to bioenergetic challenges that has key roles in synaptic plasticity and learning and memory.
**Corvid:** a species of bird in the crow family.
**Creativity:** the ability to mentally manipulate information in ways that generate new ideas that can then be implemented to produce novel objects or plans of action.
**Epigenetic modifications:** molecular modifications of DNA, histones, and other chromatin-associated proteins that can result in changes in gene expression; examples include methylation, acetylation, and ubiquitination.
**Grid cells:** neurons in the entorhinal cortex with firing fields that form a regularly spaced hexagonal or triangular grid pattern.
**Intelligence:** the ability to acquire or infer, and retain information, and then apply it towards adaptive behaviors within an environment or occupation.
**Intermittent fasting (IF):** a feeding pattern that includes periods of time of sufficient length to deplete liver glycogen stores and elevate blood ketone levels.
**Ketogenic state:** a metabolic state that occurs during extended food deprivation or fasting in which liver glycogen stores have been depleted, and fatty acids mobilized from adipose cells are used to produce cetate); the ketones are used by neurons to sustain their bioenergetic demands.
**Mental time travel:** the ability to recount one's past and plan for the future.
**Neurogenesis:** the process by which new neurons are generated from self-renewing stem cells.
**Place cells:** neurons in the hippocampus that fire selectively when an animal is at one or only a few locations in its environment; place cells are prominent in the hippocampus.
**Prefrontal cortex:** the most anterior region of the frontal cortex, which has a major role in decision-making; it uses information about the current behavioral context to rapidly generate goals based on the current biological needs.

staying in a patch in which food is depleted and leaving that patch to search for a different food-rich patch. It has been reported that travel time between patches informs leaving decisions by changing the threshold and/or the rate at which the decision variable grows [18]. In this study, activity of neurons in the anterior cingulate cortex was recorded while the monkeys experienced diminishing amounts of a juice reward and were faced with the decision of 'leaving the patch' to obtain a larger juice reward after a time delay. Neurons responded every time the monkeys made a choice and the firing frequency increased with time in the current patch. The monkeys abandoned the patch when a threshold level of neuronal activity was reached, and the threshold was associated with a particular travel time. How information encoded in cingulate cortex is integrated with neuronal networks in the visual cortex, PFC, hippocampus, and motor cortex to regulate foraging decisions remains to be determined. However, such findings in non-human primates support the notion that the increase in overall brain size and expansion of the prefrontal, visual, and parietal cortices during primate evolution was driven, in part, by food scarcity [17].

**Self-domestication:** an evolutionary process that selects for individuals that cooperate with others to enhance group cohesiveness and the allocation of food and other vital resources.

**Social intelligence:** the awareness and active interpretation of the ongoing and likely future behaviors of oneself and others.

### Food-Centric Origins of Human Creativity, Language, and Culture

Here, I encapsulate evidence supporting the notion that advanced cognitive capabilities of the human brain (tool manufacture, **creativity**, **social intelligence**, and language) originally evolved, at least in part, as adaptations that enabled successful food acquisition. As reviewed by Chang *et al.*, major expansion of the human brain coincided with new behaviors that enabled acquisition of higher calorie diets (e.g., meat and cooking). I quote: 'These observations suggest the possibility that social information and information about primary motivators like food are translated into a common framework or currency that drives both learning and decision making.' [19]. However, cooperation in food acquisition and sharing the evolution of sociality and large group living are associated with several other factors that may have contributed to the evolution of large brains with advanced cognitive repertoires. For example, cooperation among individuals in large groups reduces the risk of predation [20]. For readers interested in the importance of social pressures for the evolution of large brain size, several excellent review articles are available [19,21].

Findings from the field of anthropology establish that most, if not all, of the early tools used by our human ancestors were created for purposes of food acquisition and processing. These include not only flaked stones, spears, and bows and arrows, but also fire, the wheel, and animal and plant domestication [22,23]. Advances in the design and production of tools for hunting and foraging and food preparation set the stage for the agricultural revolution, a remarkable period of cultural evolution that facilitated the diversification of human ingenuity and the emergence of philosophy, science, and advanced technologies. Brain regions involved in tool making expanded prominently during human evolution, including visual association cortices, PFC, posterior parietal cortex, and insular cortex. These brain regions also have critical roles in communication and complex social interactions. Indeed, it is believed that tool making was a precursor to the development of language and cooperation in food acquisition and distribution in large societies [24,25]. Even human artistic expression has roots in mental representations of food-centric objects and events, as demonstrated by the earliest known cave drawings that depict scenes with game animals or domesticated food animals. Therefore, it appears that the neuronal network-based mechanisms of human creativity that evolved, in part, to cope with food scarcity were sufficient to enable creative cognition in realms unrelated to food acquisition and processing.

In summary, there is ample evidence that the need to acquire food had a major role in the evolution of the cognitive repertoire of many species, including the superior creativity and

decision-making capabilities of humans. A question that arises from the evolutionary perspective is whether the food-replete environments of modern-day humans and domesticated animals affect their cognitive capabilities and transgenerational trajectories of brain evolution in their descendants.

## Use it or Lose it: Food Overabundance, Suboptimal Cognition, and the Shrinking Brain

An understanding of how food scarcity-based adaptations drove human brain evolution provides insight into how removal of this environmental challenge affects cognition and cellular neuroplasticity. One clue comes from data showing that the overall brain size of domesticated animals is reduced compared with the wild species from which they originated, including farm animals raised for meat production (chickens, pigs, and cattle) and pets (dogs and cats) [26–28]. A common environmental factor that might account for the reduction in brain size is that domesticated animals no longer have to devote cognitive and physical exertion to acquire food. Therefore, it would be of interest to compare cognitive capabilities of different breeds within a species of domesticated animals in relation to their *ad libitum* food intake. However, factors other than, or in addition to, living in a food-replete environment may also have contributed to the reduced brain size of domesticated animals, perhaps including selection for docility. Nevertheless, empirical evidence from human cross-sectional studies and human and animal interventional studies, which is summarized below, demonstrates that excessive energy intake reduces, while intermittent energy restriction increases, neuroplasticity, cognitive performance in multiple domains, and brain regional gray matter volumes. Similar evidence linking other traits of domesticated animals (docility, floppy ears, fur features, etc.) to cognition is lacking.

Remarkably, measurements of cranial volumes suggest that there has been a ~10% reduction in brain volume in humans during the past 10 000 years, which corresponds to the time period after the agricultural revolution and the development of effort-sparing technologies [29]. It has been suggested that humans have undergone '**self-domestication**', a process of cultural evolution that selected for the trait of cooperativity in food acquisition, processing, and distribution [30]. Moreover, whereas being fluent in both spoken and written language is a requirement for essentially all occupations in modern societies, being adept at critical decision-making while moving through complex physical environments is largely unnecessary. Although we cannot know for certain because intact brains are lacking from humans who died before 10 000 years ago, it might be expected that brain regions previously used extensively on a day-to-day basis for navigation and associated cognitive processing required for foraging and hunting (motor cortex, and temporal and frontal lobes) have decreased, whereas those regions used for language and abstract thought have increased in size and/or synaptic complexity. Consistent with the latter possibility, cross-sectional MRI-based studies of children and adolescents have shown that temporal and frontal cortex volumes are positively correlated with performance intelligence quotient (IQ), but not with verbal IQ [31].

Removal of a major driving force for brain evolution from modern societies might be expected to influence brain development and plasticity within an individual, as well as in their descendants. Data from brain-imaging studies of humans and interventional studies of laboratory animals support the latter possibility. Obesity and insulin resistance increase the risk for cognitive impairment and Alzheimer's disease as individuals transit their 6th to 8th decades of life [32]. Moreover, chronic excessive energy intake is associated with impaired cognition, reduced temporal lobe gray matter volume, and poorer clinical outcomes in patients with major psychiatric disorders, including depression [33]. Abdominal obesity is associated with lower total gray matter volume and reduced hippocampal volume in adults with type 2 diabetes [34].

Of particular concern is the negative impact of metabolic morbidity resulting from overindulgent sedentary lifestyles on the brains of children. Young children and adolescents who are obese exhibit impaired cognitive function in multiple domains, and have poorer academic and occupational achievement compared with their normal-weight classmates [35–39]. In the USA, the states with the highest prevalence of childhood obesity also have the lowest percentages of high school and college graduates. Interestingly, emerging evidence suggests that a chronic positive energy balance has contributed to the recent increase in the incidence of autism. The increase in childhood obesity during the past 40 years tracks remarkably closely with the increase in autism incidence. Moreover, obesity reduces **brain-derived neurotrophic factor** (BDNF) production, and children with a genetic reduction (haploinsufficiency) of BDNF expression scored lower on tests of cognition and exhibited more autistic behaviors compared with age-matched children with two functional *BDNF* genes [40]. Exercise is effective in reducing behavioral symptoms and improving academic performance in children with autism [41,42].

The association of obesity with poorer cognitive outcomes in humans begs the question of whether food overconsumption is sufficient to impair cognition. Studies of rodents support this possibility. Hippocampal volume is reduced in overfed sedentary rodents, in part by reductions in **neurogenesis**, dendritic arborization, and synaptic density [43]. Mice genetically engineered to eat excessively (leptin receptor-mutant mice) exhibited impaired hippocampus-dependent spatial learning and memory, and impaired recall of novel objects [43]. Their cognitive deficits were associated with impaired long-term potentiation at performant path–hippocampal dentate granule neuron synapses, and reduced hippocampal neurogenesis. The mechanisms by which excessive energy intake and being overweight compromise cognition and neuroplasticity have been elucidated in animal studies (Figure 1). As reviewed in detail elsewhere, these mechanisms include: accumulation of oxidative damage to proteins, lipids, and DNA in brain cells; inflammation (microglial activation and proinflammatory cytokine production); impaired mitochondrial function; impaired synaptic plasticity; reduced neurogenesis; impaired autophagy; and reduced cellular stress resistance [2,32]. Cell membrane-associated oxidative stress impairs neuronal ion-motive ATPases ($Na^+$ and $Ca^{2+}$ pumps) and glucose transport [44], which likely contribute to the dysregulation of neuronal network activity and reduced neuronal glucose utilization observed in overweight humans [45]. Chronic overeating also impairs signaling pathways involved in synaptic plasticity and learning memory. Notably, BDNF expression is reduced in the hippocampus and cerebral cortex of overfed and diabetic laboratory animals [2,46]. The mechanism involves glucocorticoid-mediated suppression of BDNF expression [47,48]. In addition, diet-induced obesity was reported to cause synaptic stripping by microglia, consistent with a role for abnormal activation of the innate immune system [49].

While the impact of sedentary overindulgent lifestyles on brain development and cognitive trajectories in children is clearly an issue of great concern, so too are emerging findings suggesting that the offspring of overnourished mothers and fathers are predisposed to obesity and poorer cognitive outcomes (Box 1). The underlying molecular mechanisms involve **epigenetic modifications**, such as DNA methylation and histone acetylation, that alter the expression of genes involved in neuroplasticity (Box 1 and Figure 2). An analysis of demographic data from the Centers for Disease Control [50] revealed a significant positive correlation between childhood obesity and academic achievement among different states in the USA. While socioeconomic factors undoubtedly influence academic performance, it should also be considered that being overweight and sedentary contribute to suboptimal cognition in those children. Indeed, as demonstrated in interventional studies, regular exercise and dietary counseling can improve academic outcomes [51].

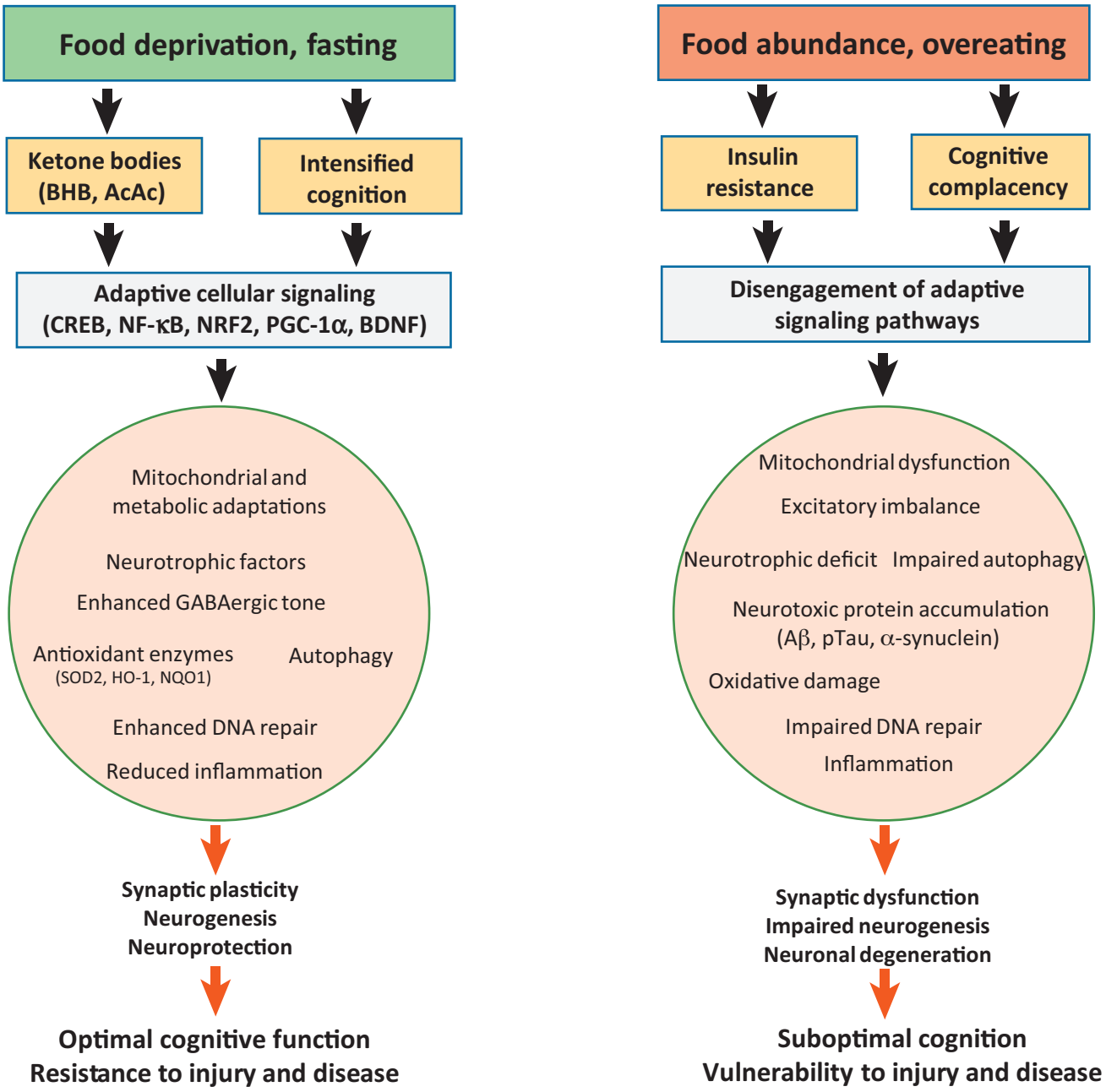


Figure 1. Cellular and Molecular Mechanisms by which Food Intake Impacts Neuroplasticity and Cognition. (A) Adaptive responses of neuronal networks to intermittent food deprivation or fasting. Extended periods with no or little energy intake trigger a metabolic shift from utilization of liver glycogen-derived glucose to adipose cell-derived fatty acids and ketone bodies (BHB, β-hydroxybutyrate; AcAc, acetoacetate) generated therefrom. In addition to serving as a source of acetyl CoA for mitochondrial ATP production, ketone bodies can activate signaling pathways involved in synaptic plasticity and cellular stress resistance, including those involving the transcription factors cAMP response element-binding protein (CREB) and nuclear factor kappa B (NF-κB), and neurotrophic factors, such as brain-derived neurotrophic factor (BDNF). The increased activity in neuronal networks involved in cognitive processing during food seeking (navigation, decision-making, etc.) engages adaptive signaling pathways that bolster mitochondrial function and upregulate neurotrophic factors, GABAergic tone, antioxidant defenses, and DNA repair, while suppressing inflammation. These adaptive responses promote synaptic plasticity, neurogenesis, and cellular stress resistance, which, in turn enhance cognition and resistance of the brain to injury and disease. (B) Excessive food intake as occurs in laboratory animals fed *ad libitum* and most humans in modernized countries

*(See figure legend on the bottom of the next page.)*

### Box 1. Transgenerational Epigenetic Impact of Excessive Food Intake on Cognition

Findings from recent animal studies in which food intake and exercise were precisely controlled, and associational data from studies of humans, provide evidence that the metabolic status of parents can influence their offspring's risk for obesity and impaired glucose regulation. When female mice maintained on a high-fat diet to induce obesity and insulin resistance were mated with healthy males, their offspring exhibited insulin resistance and obesity, and this phenotype persisted through at least a second generation in both maternal and paternal lineages [82]. The adverse effect of maternal obesity on the metabolic phenotype of offspring in mice and rats is associated with impaired cognition in the offspring in reference memory and associative learning [83–85]. Spatial learning and memory deficits in male offspring of obese dams can be reversed when the offspring exercise (run) regularly [84]. Interestingly, moderate food restriction and/or daily IF of nursing dams that were obese during pregnancy can ameliorate behavioral deficits caused by the maternal obesity, suggesting that the early postnatal metabolic state of the mother influences cognitive trajectories of offspring [86]. Several studies have reported that hippocampal BDNF expression is reduced in offspring of over-nourished dams, suggesting one underlying abnormality in gene expression [84,87]. However, starvation in humans has been reported to adversely affect the metabolic outcomes of offspring [65]. Thus, moderate levels of intermittent energy restriction and physical activity may best promote healthy transgenerational metabolic phenotypes.

The adverse impact of overweight and obesity in parents on metabolic outcomes of their descendants is believed to result from epigenetic molecular changes occurring *in utero* that are then propagated transgenerationally (reviewed in [88]). The *in utero* environment can have enduring effects on the regulation of gene expression resulting from epigenetic molecular mechanisms, which encompass heritable modifications of the genome without changes in the DNA sequence. Prominent among such genome modifications are DNA methylation, post-translational modifications of chromatin and/or histone proteins (acetylation, methylation, phosphorylation, and ubiquitination), and miRNA alterations [88]. It has been reported that offspring of obese females exhibited DNA hypomethylation in gene promoters including those encoding proteins involved in dopamine uptake, and serotonergic and opioid signaling [89,90]. The proximate cause of such epigenetic modifications in brain cells of the developing embryo may include hyperglycemia, insulin resistance, and a proinflammatory lipotoxic environment [86,91,92].

*In utero* epigenetic modifications could predispose the offspring of obese mothers to some developmental brain disorders. Multiple studies have revealed a negative association of prepregnancy maternal obesity and child IQ [93–95]. Children born to obese mothers perform more poorly on reading and math tests than children born to normal-weight mothers [96]. Children born to women who are obese and/or diabetic may be at increased risk for autism spectrum disorder and attention deficit hyperactivity disorder [97–100]. Although not yet conclusive, increasing evidence suggests that maternal obesity increases the risk of several psychiatric disorders in adulthood, including depression, anxiety disorders, and schizophrenia [101]. Consistent with the latter, animal studies have shown that pups born to obese dams exhibited heightened anxiety and depression-like behaviors [102]. Paternal obesity may also adversely impact cognitive and behavioral outcomes in offspring by epigenetic mechanisms [103,104]. Collectively, the emerging data suggest that overconsumption of high-energy foods by conceiving mothers and fathers increases the risk of poor or suboptimal cognitive outcomes of their offspring.

The correlations between obesity and cognitive outcomes in humans, together with the evidence that excessive food intake impairs synaptic plasticity and cognition in animal models, suggests that a return to more evolutionarily normal intermittent eating patterns might enhance neuroplasticity and cognition. Recent findings support this possibility.

## Intermittent Metabolic Challenges Enhance Cognition and Neuroplasticity

The typical eating pattern in modern societies of three meals plus snacks every day belies the fact that humans have adapted over millions of years of evolutionary history to sporadic eating patterns. The evolutionary pressure of food scarcity resulted in selection for individuals whose cognitive capabilities were heightened in a food-deprived state, suggesting that cognition of modern-day humans is enhanced by a change from eating three meals plus snacks every day to an IF eating pattern. IF eating patterns incorporate periods of time with little or no food intake

impairs neuroplasticity. Consumption of food throughout the waking hours results in little or no metabolic switching, which can result in insulin resistance and a relative lack of engagement of neuronal networks involved in navigation and critical decision-making. As a consequence, signaling pathways that promote neuroplasticity and resilience are disengaged, with the result being suboptimal cognitive abilities and vulnerability of the brain to stress and neurodegenerative disorders. Animal studies have shown that high-energy diets and diabetes accelerate cognitive decline and motor dysfunction in models of Alzheimer's disease (AD) and Parkinson's disease (PD), respectively. Excessive energy intake accelerates the underlying accumulation of amyloid β-peptide (Aβ) and hyperphosphorylated Tau (pTau) in the brain in AD, and α-synuclein in PD. Abbreviations: NRF2, nuclear regulatory factor 2; PGC-1α, peroxisome proliferator-activated receptor γ coactivator 1α.

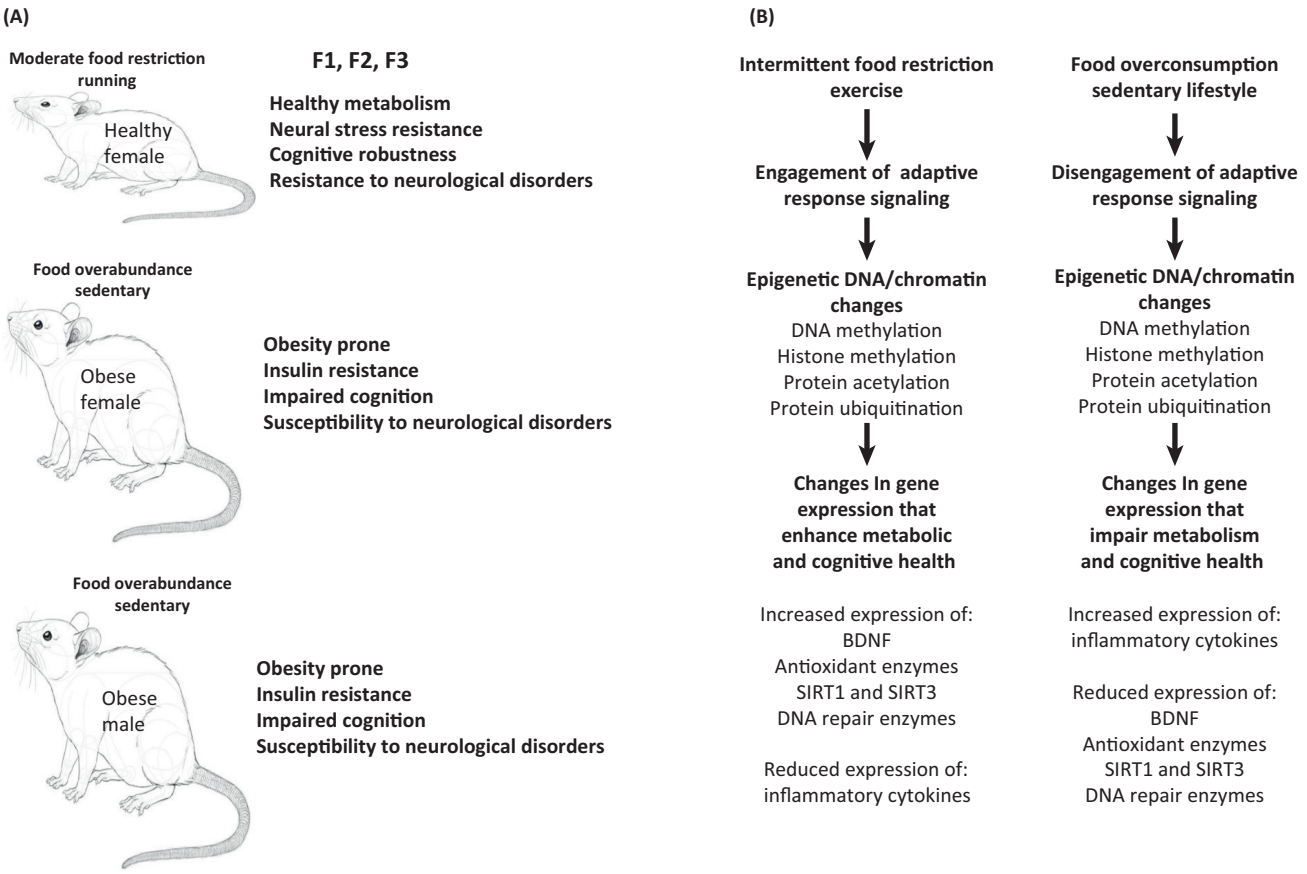


Figure 2. Epigenetic Impact of Food Overabundance and a Sedentary Lifestyle on the Metabolism and Cognitive Outcomes of Offspring. (A) Under conditions of moderate intermittent food intake and regular physical activity, female mice give birth to offspring that inherit epigenetic DNA and chromatin modifications that result in gene expression profiles that promote a healthy metabolic phenotype, stress resistance, optimal cognitive function, and resistance to neurological disorders. Conversely, females and males that are obese as the result of overconsumption of food and a sedentary lifestyle generate offspring that inherit epigenetic DNA and chromatin modifications and gene expression profiles that render them prone to insulin resistance and obesity, stress susceptibility, impaired cognitive function, and vulnerability to neurological disorders. (B) Intermittent food restriction and exercise promote epigenetic DNA and chromatin modifications (DNA and histone methylation and chromatin protein acetylation and ubiquitination) that induce the expression of genes encoding proteins that enhance neuroplasticity and neuronal stress resistance [e.g., neurotrophic factors such as brain-derived neurotrophic factor (BDNF), antioxidant enzymes, protein deacetylases, such as SIRT1 and SIRT3, and DNA repair enzymes, such as APE1]. Proinflammatory gene expression is suppressed by intermittent energy restriction and exercise. Food overconsumption and a sedentary lifestyle shift epigenetic modifications and consequent changes in gene expression in a manner that impairs neuroplasticity and increases vulnerability of the brain to stress. See Box 1 in the main text and [1,32,81] for further details.

that typically range from 16 h to 48 h with a frequency of the fasting period ranging from daily to once weekly [52,53]. From physiological and neurobiological perspectives, such fasting periods are of sufficient length to deplete liver glycogen (glucose) stores. When liver glycogen stores are depleted, fatty acids are released from adipose cells into the circulation, and the fatty acids are then metabolized to ketone bodies in the liver. The two ketones produced, β-hydroxybutyrate (BHB) and acetoacetate, are then transported into the brain, where they provide an energy source for neurons. An elevation of circulating ketones provides evidence that the metabolic switch from glucose to ketones has occurred. It typically takes at least 12 h to deplete liver glycogen stores in someone who is relatively sedentary. However, vigorous exercise can accelerate the onset of ketogenesis and can increase the magnitude of ketone production when the exercise is initiated after the metabolic switch has occurred [54]. As

reviewed elsewhere [2], multiple signaling pathways are engaged by intermittent switching between fasted and fed states that together enhance neuroplasticity, cognition, and neuronal resilience.

Studies of rodents have shown that IF and running enhance cognition and motor system function by mechanisms involving structural and functional synaptic plasticity, and activation of signaling pathways that bolster neuronal bioenergetics and cellular stress resistance (Box 2) [2,55,56]. Learning and remembering previously traveled routes to a food source are associated with structural changes in neuronal circuits, most notably the formation of new synapses and neurogenesis in the hippocampus [57,58]. Both IF and running enhance spatial learning and memory, which is associated with an increased density of dendritic spines in hippocampal dentate granule neurons and increased expression of BDNF [43,46,59]. Running and IF also stimulate hippocampal neurogenesis, resulting in the production of new granule neurons that integrate into the existing hippocampal circuitry [59,60]. This overlap in the cellular and molecular mechanisms by which exercise and IF enhance neuroplasticity and neuronal resilience likely stems from the fact that they are both bioenergetic challenges that occur coincidently in food-sparse environments. Both cognitive and physical exertion in the food-deprived and/or fasted state were required for survival. The findings from animal studies suggest that neuroplasticity is enhanced by exposure to conditions that mimic an environment with sparse food sources and the need to travel considerable distances to acquire the food.

Emerging findings suggest that IF enhances neuroplasticity and cognition via signals emanating from the periphery, as well as by activating brain-intrinsic signaling pathways (Figure 1). One

### Box 2. Intermittent Metabolic Challenges Boost the Cellular Engines of Cognition

Studies of rodents have shown that enriched environments, food deprivation, and running result in increased activity in neuronal circuits involved in cognition, including those in the hippocampus [56,57]. Such increases in excitatory synaptic (glutamatergic) activity impose a mild metabolic stress on the neurons as a consequence of $Na^+$ and $Ca^{2+}$ influx, increased mitochondrial metabolism, and the activation of ion-motive ATPases. The $Ca^{2+}$ influx and mitochondrial reactive oxygen species activate transcription factors that induce the expression of genes that encode proteins involved in adaptive cellular stress responses and synaptic plasticity [2,80,105]. Consequently, synapses involved in learning and memory are potentiated, synapse numbers increase, and neurons are better able to cope with a range of environmental challenges, including metabolic, excitatory, and oxidative stress. In response to the systemic bioenergetic challenges of fasting and exercise, peripheral organs produce and release into the circulation molecules that affect neuroplasticity. These include liver-derived ketones, and muscle-derived cathepsin B and irisin [56,106,107]. Interestingly, all three of these peripheral signals stimulate the production of BDNF, which, in turn, stimulates synaptogenesis and neurogenesis [2]. By pathways involving BDNF, the transcription factor PGC-1$\alpha$ and the mitochondrial deacetylase SIRT3, exercise and fasting can increase the numbers of well-functioning stress-resistant mitochondria in hippocampal and cerebral cortical neurons to enhance neuroplasticity and resilience [65,108]. The increased number of healthy mitochondria in neurons is believed to be critical for the enhancement of cognitive performance that occurs in response to fasting and aerobic exercise [2,66].

Human studies have shown that cognition and intellectual achievement can be enhanced by exercise and energy restriction [109]. In a study of over 1000 schoolchildren between the ages of 12 and 16, it was found that those who engaged in physical activity more than 5 h per week had a higher IQ compared with their more sedentary classmates [110]. There was also a positive association of aerobic fitness and cognitive processing speed in preadolescent children [111]. In a birth cohort study, general cognitive ability and processing speed at age 70 were positively associated with physical activity regardless of IQ at age 11 [112]. In a study in which adults were randomly assigned to either aerobic exercise or control (video-watching) groups, only those in the exercise group exhibited improvements in cognitive flexibility and/or creativity [113]. Dietary energy restriction can also improve cognition. Compared with their baseline scores, and to subjects in two different control diet groups, those individuals who reduced their daily calorie intake by 30% for 3 months exhibited significant increases in verbal memory scores [114]. Recognition memory improved, hippocampal and inferior frontal gyrus gray matter volumes increased, and functional connectivity of hippocampal and parietal lobe networks increased in older women during 12 weeks on a very low-calorie diet and/or daily fasting diet [115]. Similarly, improvements in verbal memory and fluency and executive function were improved in response to dietary energy restriction in overweight patients with mild cognitive impairment [116].

prominent peripheral signal produced during fasting is the ketone BHB, which stimulates the production of BDNF by neurons. BDNF has critical roles in learning and memory, synaptic plasticity, and hippocampal neurogenesis, and enhances neuronal stress resistance [61,62]. Mice adapted to IF exhibit improved regulation of neuronal network activity, effectively enhancing GABAergic tone [63,64]. BHB may have a role in the latter effect of IF because ketogenic diets can prevent seizures in patients with epilepsy [65]. IF and running may also bolster neuronal bioenergetics by stimulating mitochondrial biogenesis, resulting in an increased number of healthy mitochondria in neurons [66]. Interestingly, the combination of IF with running wheel exercise resulted in elevations of BDNF expression and enhanced synaptic plasticity by amounts beyond that which occurred with IF or exercise alone [46].

Controlled trials aimed at determining whether IF improves cognition in humans have not yet been reported. However, daily calorie restriction by an amount that triggers the metabolic switch to ketones has been reported to improve several cognitive domains (Box 2). In addition, IF results in significant elevations of circulating BHB levels on the fasting days in humans [67,68]. Assuming that BHB induces cerebral BDNF expression in humans, it would be expected that IF enhances synaptic plasticity and cognition in humans. An ongoing clinical trial of IF (fasting 2 days each week) in subjects at risk for cognitive impairment (obese, insulin-resistant subjects between the ages of 55 and 70) may provide initial answers regarding the translatability of findings in animals described above [69].

While enhancement of neuroplasticity by patchy food sources and physical exertion may enable success in food acquisition, these bioenergetic challenges can also enhance neuronal resilience and protect the brain against injury and disease. As evidence, IF reduced neuronal degeneration and improved functional outcome in rodent models of ischemic stroke, spinal cord injury, and traumatic brain injury [70–74]. In rats, IF lessened hippocampal neuron dysfunction and degeneration, and preserved hippocampus-dependent learning and memory in an experimental model of epilepsy [75]. Rodents maintained on IF exhibited reduced neuronal degeneration and improved functional outcomes in animal models of Alzheimer's, Parkinson's, and Huntington's diseases [76–78]. Daily energy restriction also attenuated the depletion of dopamine and improved functional outcome in a rhesus monkey model of Parkinson's disease [79]. Although controlled trials of IF in humans with or at risk for neurological disorders are as yet lacking, there is evidence that individuals with high energy intakes are at risk for Alzheimer's disease, perhaps because of a relative lack of activation of pathways involved in adaptive neuroplasticity [32]. The potential benefits of IF on cognition, mood, and academic achievement in children who are obese and/or who have autism also remain to be tested.

## Concluding Remarks

It has become clear that being overweight and sedentary adversely affects essentially all organ systems, including the brain. As briefly described above and recently reviewed in detail [32,80], an overarching reason for this is that cells, tissues, and organs become 'complacent' when they are not subjected to intermittent metabolic challenges. Signaling pathways involved in adaptive cellular plasticity are downregulated, organ function becomes impaired, and disease processes are enabled. As briefly reviewed herein, much of the neuronal cytoarchitecture of the brains of animals and humans was 'sculpted' by the evolutionary 'chisel' of competition for limited and sporadic food availability.

A better understanding of the bioenergetic processes and regulatory signaling pathways that mediate the enhancement of cognitive performance in response to dietary energy restriction and exercise will likely lead to the development of novel approaches for promoting optimal

### Outstanding Questions

How might a better understanding of the impact of food scarcity on brain evolution help conceptualize human cognition in general, and spatial learning and memory and decision-making in particular?

Did social intelligence and cooperation within large societies evolve as an adaption to overcome food scarcity as the size of societies increased? Can differences in brain structure and/or functional connectivity between current-day hunter-gatherers and individuals in modern food-replete societies be discerned?

During evolution, intense cognitive processing occurred while animals, including our human ancestors, were moving through their territories. Does running and other types of physical exertion affect cognition? Which domains are affected and by what mechanisms? Does exercise in the fasted state, a condition common during the evolution of many species, amplify the effects of exercise on cognition?

What are the cellular and molecular mechanisms by which intermittent fasting enhances brain resilience in the contexts of aging and vulnerability to neurological disorders that impact cognition? Can prescriptions for intermittent eating patterns be implemented as an approach to promoting brain health?

How will the brain evolve as future generations of humans live in the setting of food overabundance and with sedentary occupations?

To what extent can pharmacological interventions be developed that activate the same cognition-enhancing signaling pathways that are activated by intermittent fasting and exercise?

cognition throughout the life course (see Outstanding Questions). The metabolic shift to ketogenesis is one such evolutionarily ancient adaptation that can enhance cognition [2]. Although there has been a recent flurry of translational research on IF and general health (reviewed in [53]), its impact on brain health in humans remains to be interrogated in randomized controlled trials. The question of what regimens of IF eating patterns and exercise promote optimal cognition might be answered by such trials.

Finally, it is of more than academic interest to consider how living in the food-replete niches of modern societies will impact the future evolution of the human brain. Throughout most of human evolution, critical thinking and decision-making occurred as individuals navigated through a heterogenous environment hunting and foraging in a fasted state. The latter conditions might be expected to engage more brain regions compared with modern-day occupations that are relatively devoid of body movement and multimodal sensory input, and are performed in the fed state. The reduction of the cognitive load required for successful hunting or foraging is likely a major factor in the reduction in overall brain size in domesticated animals, and a similar scenario may be occurring in humans. While increased specialization among and within occupations may enable more rapid progress and efficiency of very large societies, it might also foster, over a period of relatively few generations, a reduction in the cognitive repertoire of each individual person. If and to what extent 'renaissance men and women' bolstered by lifestyles that include IF and exercise will shape our future remains to be determined.

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