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Assessing causality in the association between neurocognitive gains and fasting

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Abstract. **Fasting is associated with improvements in cognitive function, and triggers weight loss in human and animal models. In recent years, the connection between fasting, brain health, and cognitive function has increasingly proven deserving of attention from researchers. The objective of this review work is to highlight evidence supporting a positive association between fasting and enhanced cognition.**

We looked at the following database sources "The Cochrane Library, PubMed, EMBASE, Web of Science and Google Scholar" for present review article. All the studies based on the key words "impact of fasting", or "cognitive function" or "brain stimulation".

Much of this evidence demonstrates that fasting results in enhanced performance in cognitive tests of memory and visuospatial processing, which rely heavily on hippocampal function. The mechanisms responsible for the cognitive improvements associated with fasting are not fully understood, although current evidence suggests neuroplasticity plays an important role.

Maintaining the health and the functionality of neurologically and cognitively impaired individuals can be extremely costly. Higher life expectancy and ageing populations globally is anticipated to increase the prevalence of many non-communicable, chronic, progressive conditions including neurological disorders.

Key Words:
tDCS (transcranial Direct Current Stimulation), Ramadan, Fasting, Cognitive function.

Introduction

One of the lifestyle choices that has garnered significant attention is fasting, which is accessible to everyone and is not dependant on money or access to technology. The premise underlying research interest in fasting is that it may help maintain, or even enhance, neurocognitive function[1]. Fasting is practiced differently in various religions. Fasting in Ramadan requires that all Muslim people abstain from food and beverages from the sunrise to sunset for 30 days in the 9th lunar month of each year. Fasting during Ramadan leads to alterations in circadian rhythms and change to endocrine and metabolic functions as well as a measurable reduction in physical and cognitive performance[2].

The homeostatic influences on hormonal and physiological processes from an endocrine-metabolic perspective have drawn considerable attention and research interest in the field over recent decades. Up to date findings suggest that factors affecting the brain-to-behavior spectrum may also contribute to the long-term gains following fasting. These influences, when examined within the scope and boundaries of psychology and neuroscience, may determine how well a subject is able to adhere to dietary requirements and the other lifestyle behavior adjustments that are needed after fasting. Additionally, performance in cognitive tasks related to attention, executive function, and memory, which are known to support and facilitate behavioral change appear to improve with fasting[3]. Complementing this evidence, recent study[3] involving functional neuroimaging suggest brain mechanisms can be also improved. These studies have examined changes in brain activation in response to images of food before and after fasting and found reorganization of brain circuitry when processing both cognitive as well as reward/motivational information related to food and eating behavior[4]. Specifically, during fasting there was decreased activation of the brain regions related to reward and motiva-

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tion, such as the parahippocampus, medial prefrontal cortex, and the insula and inferior frontal gyrus, as well as an increase in the anterior prefrontal cortex, a region involved in cognitive control and inhibition[4].

Much of the evidence available regarding the assessment of reward/motivational aspects associated with fasting and eating behavior relies largely on interviews and self-report. There is need for objective measures to assess the status of the brain circuitry involved in these processes in a way that could be naturalistic and relevant to real-world situations.

Connections between caloric restriction and brain function have been investigated substantially in previous studies[4-10]. According to research[6] conducted by Current Opinion in Clinical Nutrition and Metabolic Care in 2008, reducing calorific intake improves neurogenesis as a result of several mechanisms. For example, it reduces inflammation, neuronal oxidative stress and enhances synaptic plasticity. Furthermore, caloric restriction could potentially promote healthy brain aging[6]. This can be explained by the fact that it is associated with increasing synthesis of neurotrophins, which play an essential role in age-related brain diseases. Neurotrophins can also improve neuronal survival and stress resistance. In addition, reducing calorie intake antagonizes the negative impact of aging on the expression of genes involved in synaptic transmission leading to better memory consolidation[6]. In 2017, an article[11] in the journal of neuroendocrinology demonstrated that mild caloric restriction reduces both the incidence of age-related neurodegenerative disease and depressive symptoms.

Fasting and Cognitive Function (Enhanced Cognition Associated with Fasting)

For several decades, researchers have been reviewing the effects of fasting on brain and cognitive function. Ramadan fasting has been found to increase resilience and accuracy, reduce impulsivity, and performance on tasks requiring sustained rapid responses[12]. In a study[12] conducted involving older adults with mild cognitive impairment (MCI), intermittent fasting (IF) was proven to significantly enhance cognitive performance in a variety of domains. These domains were global functions, including orientation, memory, registration, calculation, attention, and language[12]. Furthermore, IF was found to reduce addiction behaviors and improve self-control[13]. Interestingly, fasting can modify emotional memory by activating emotion-related brain regions, such as the amygdala, orbitofrontal cortex, and hippocampus, thereby triggering hunger-induced enhancement of memory in humans. This can help with managing both post-traumatic disorders and fear related disorders[13]. In addition, a study[14] aimed at examining the protective effect of IF on brain function was performed using young mice. The mice were subjected to IF and a high-fat diet for 11 months, and memory and learning were measured by fear conditioning and the Barnes maze[14]. The findings reported that mice in the IF group had increased thickness of the pyramidal cell layer of the hippocampal CA1 region and experienced an increase in a dendritic protein called drebrin in the cerebral cortex and hippocampus. This thereby suggests that IF improves brain function in the context of memory and learning[15].

Fasting is known to be a stress-inducing environment for the human body. Stress is one of the multifactorial environmental causes of cognition in the long term, due to the well-known stress hormone corticosterone. Several studies[16,17] have reported that IF has a great impact on brain function in stress situations, particularly due to the mechanism of inflammatory response pathway regulation. Estrogen is known to protect memory, down-regulate neuroinflammation, and prevent β-amyloid deposition. Interestingly, a study[17] of Alzheimer's disease-induced estrogen-deficient rats demonstrated that IF served as an effective intervention protecting against deterioration of the cognitive function and improving memory by potentiating the insulin signaling in the hippocampus, which inhibits β-amyloid deposition. Fasting for 48 hours was associated with improved prefrontal-cortex-cognitive functions, such as cognitive flexibility and set shifting. The same study found no change to cognitive functions in the hippocampus[18].

On the other hand, a study showed[19] that fasting during Ramadan in a non-Muslim environment adversely effected the academic performance of Muslim students. More specifically, a reduction by 10% in standard deviation in the final grade in one subject upon exposure to one additional week of Ramadan. The explanation for this fall in academic achievement was attributed to the suggestion that fasting lowers concentration, activity, and desire to study[19]. Overnight and morning fasting were found to slow stimulus discrimination, increase errors, and impair recall[20]. Islamic fasting was also found to impair spatial memory, visual memory and attention in youngsters[21].

A systematic review[22] of evidence collected between 2013 and 2020 showed no conclusive evidence as to whether the impact of voluntary fasting on cognition was positive or negative. The conclusion reached was that the impact is influenced by a variety of psychosocial and demographic factors. Other evidence suggests fasting during Ramadan has a heterogeneous effect on cognitive domains. Indeed, an experiment[23] involving Muslim athletes who underwent a computerized neuropsychological test showed that performance was better in the morning and declined in the late afternoon, especially with regard to psychomotor function, memory and learning ability. More recently, IF particularly has broad health benefits, improving cognition in multiple domains, including associative memory, working memory, and spatial memory[24]. Speculation concerning the cause of these effects includes that a high BMI may adversely affect the structure and function of the brain, by reducing the prefrontal metabolism causing temporal lobe atrophy. Furthermore, the switch between glucose and ketones bodies has been shown to lead to enhance performance in cognition, mood, motor and autonomic nervous system function[25]. IF and calorie restriction, connected to the release of the brain derived neurotrophic factor and associated with neurogenesis and neuron protection, bolsters the growth and survival of serotonin neurons[26].

Reduction in Cognitive Decline Associated with Fasting

More recently, a study by Jamshed et al[27] involving 43 participants with central obesity aged 35-75 years, showed that time-restricted feeding early in the day tended to increase their brain-derived neurotrophic factor, as well as having a potential anti-aging effect by increasing gene expression of longevity genes SIRT1 and MTOR[27]. It has been suggested that young newborn neurons within the dentate gyrus may be responsible for mediating pattern separation and that as they age may mediate the ability to trigger “pattern completion-mediated recall”, i.e., recognition memory[22]. Moreover, caloric restriction was also found to increase the activity of certain enzymes, including the DNA-repairing enzymes. Thus, it was expected to maintain the cognitive function of older adults by reducing DNA damage events[8].

Regular and constant IF can assist in reversing mild cognitive impairment. Specifically, one study[8] found that 30% of individuals aged between 50 and 80 years old showed improved verbal memory, possibly due to lower insulin and CRP levels. Furthermore, obese older adults with MCI who practiced caloric restriction for 12 months showed improvements in verbal memory, verbal fluency, executive function, and global cognition[26]. These findings were similar to those in a previous study[28] testing Ramadan fasting and cognition.

In addition, high blood pressure resulted in blood-brain barrier dysfunction, causing the penetration of proteins from the blood into brain tissue. Proteins entering the brain can interact with neurons or synapses and induce the accumulation of amyloid- β in the brain. Individuals who practice regular IF exhibit lower blood pressure, which prevents or improves cognitive impairment[25]. Another known effect of IF is that it lowers blood glucose and as a result reduces blood insulin levels. Insulin has been proven to increase the deposition of amyloid-β, a neurotoxic material that causes an acute memory-inhibiting effect[21].

IF increases the concentration of ketone bodies, which have a neuroprotective effect, raising adenosine triphosphate (ATP) levels and reducing reactive oxygen species (ROS) production through enhanced nicotinamide adenine dinucleotide (NADH) oxidation, and the inhibition of mitochondrial permeability transition[29]. However, this effect is feasible only while IF continues, as it disappears once the ketonoegenesis stops[30].

A study[26] contrasting intermittent and continuous energy restriction concluded that regardless of the pattern of restriction it possibly influences memory function through modulating adult human neurogenesis, with the potential to be used as an intervention to prevent or boost cognitive decline. Normal aging induces structural changes in the human brain, which can then be detected by using different neuroimaging modalities. In a longitudinal study[31] designed to evaluate changes in intracranial volume (ICV) across an adult’s lifespan, it was concluded that ICV increases until the fourth decade and then gradually decreases thereafter.

These changes were identified in a group of studies involving MRI data, which demonstrated reduced brain tissue volume, cortical thinning, leukoaraiosis (i.e., white matter hyper-intensities on T2weighted MRI), altered white matter microstructure, changes in structural and functional connectivity, reduced cerebral perfusion, micro-bleeds, and greater blood-brain barrier permeability[32-38]. PET has been used to show reduced cerebral metabolism, as well as the deposition of beta-amyloid and signs of neuron-inflammation[37]. Moreover, arterial spin labeling (ASL) perfusion MRI showed a drop in overall cerebral blood flow (CBF), which was more pronounced in the frontal lobe[39].

Based on measurements from various image modalities, researchers have discovered that the majority of brain regions follow a linear decline in their grey matter volume (GMV) as a consequence of normal aging, while nonlinear age trajectories have been observed in some regions (e.g., the medial temporal lobe), indicating preservation of GMV during the early adult lifespan[40].

Increased Grey Matter in the Brain Associated with Fasting

A 12-week program of caloric restriction assigned to obese, postmenopausal women beside the functional improvement in recognition memory found increased grey matter volume in the hippocampal formation[23].

Moreover, when compared to overweight and normal individuals, obese subjects have shown a reduction in overall brain volume and grey matter. Thus, it is important to ascertain whether IF can inhibit this reduction by lowering BMI[8,31]. A high BMI has been shown to be associated with regional alterations in the brain structure in the left lateral occipital cortex and right ventromedial prefrontal cortex. Previous neuroimaging studies[32-36] have highlighted the crucial role of the hunger and satiety centers, and brain locations in the hypothalamus, insula, amygdala, middle temporal cortex, thalamus, and medial prefrontal cortex in relation to emotional regulation deficits. There is also evidence that the left amygdala increases in size and has a linear relationship with spatial working memory[35].

Fasting and Non-Invasive Brain Stimulation

Transcranial direct current stimulation (tDCS) is a form of non-invasive brain stimulation, wherein direct and low amplitude electric current is conducted into the brain *via* electrodes placed on the scalp[41,42]. tDCS is used in research to determine specific tasks in specific brain regions, or to evaluate the therapeutic effect in some neurological and psychiatric disorders[37]. Minor side effects are associated with tDCS, such as nausea, headaches, dizziness, skin irritation, and itching under the site of the electrode[42,43]. There are limited studies regarding the impact of performing tDCS while fasting. However, one study[42] reported that tDCS is safe and can be used in fasting healthy adults. Moreover, another study[44] about chronic pain found evidence supporting the benefits of both non-invasive brain stimulation and IF for preventing maladaptive plasticity in chronic neuropathic painful conditions. So, potentially, combining brain stimulation and fasting could be used to achieve adaptive neuroplasticity changes[40].

Observational Relationships Between Physical Activity, Cardiovascular Fitness, Neurocognitive and Neuroimaging in Fasting

It has been demonstrated that certain aspects of physical performance and mental health, such as coping and decision-making strategies, can be negatively affected by daylight fasting[45]. In a study[46] evaluating the effect of fasting on brain imaging using MRI, diffusion tensor imaging (DTI) and diffusion-weighted imaging (DWI), the FA values of the amygdala, middle temporal cortex, thalamus, and medial prefrontal cortex during the fasting period were found to be lower than FA values during satiety. This suggests micro-structural changes, mainly arising from a loss of functional and structural integrity in these locations.

In contrast, recent findings[47] have revealed that IF may inform the relationship between cytokine expression in the brain and cognitive deficits, including memory deficits. Particularly, IF protects neurons against dysfunction and degeneration by improving levels of antioxidant defenses and anti-inflammatory IL-10, and increasing the expression of BDNF and protein chaperones such as the heat shock protein (HSP-70), and reducing levels of the circulating pro-inflammatory IL1b, IL-6, and TNF-a[5]. A similar effect has been linked to exercise as it increases brain-derived factors, thus increasing brain activity[5]. It primarily affects the hippocampus, the cerebellum, and areas of medial/superior frontal cortex[47]. The effect of exercise on brain function can be summarized as follows: activation of the secretion of IGF-I to support synaptic plasticity[6], neurotransmitter synthesis and release, and[6] cognitive function[45].

Conclusions

Evidence related to fasting during Ramadan found enhancements in certain cognitive functions associated with resilience, mind shifting, sustained speed reaction, and non-speed related accuracy, but impairments to visuo-spatial memory, and attention. The effect of fasting on brain and cognitive function is controversial, domain specific, and depends on the stage of fasting, the age of the subjects, and their overall physical fitness and nutritional status. Further studies on a larger population size would shed more light on impact of Ramadan fasting on cognitive function.

Informed Consent

Not applicable.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Ethics Approval

Not required.

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