REVIEW ARTICLE

CONTENTS

The impact of intermittent fasting on cognitive function and neuroprotection: A literature review

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ABSTRACT

Aim: To summarise current knowledge on the effects of intermittent fasting on cognitive functions and neuroprotective mechanisms, with particular attention to Alzheimer's disease and Parkinson's disease.

Materials and Methods: A narrative review based on twelve peer-reviewed publications on the effects of intermittent fasting on cognitive function, neuroprotection, and circadian rhythms.

Preclinical data and selected clinical studies indicate that intermittent fasting improves memory, attention, and executive functions, which is associated with activation of autophagy, reduction of oxidative stress, improved mitochondrial function, and increased levels of brain-derived neurotrophic factor. In Parkinson's disease, intermittent fasting limits alpha-synuclein aggregation and protects dopaminergic neurons, whereas in Alzheimer's disease it reduces beta-amyloid deposition and enhances synaptic plasticity. Intermittent fasting also influences the gut–brain axis and circadian rhythm alignment, which may further support neuroprotection.

Conclusions: Intermittent fasting is a promising adjunct strategy in the management of neurodegenerative diseases. However, well-designed, randomised clinical trials are needed to confirm its effectiveness and safety.

KEY WORDS: Alzheimer's disease, Parkinson's disease, intermittent fasting, cognitive function, neuroprotection.

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INTRODUCTION

Neurodegenerative diseases such as Parkinson's disease (PD) and Alzheimer's disease (AD) represent a growing public health challenge in aging populations. Current treatment options remain limited in efficacy, prompting increased interest in preventive and supportive therapeutic strategies, including lifestyle modifications and dietary interventions. One such promising approach is intermittent fasting (IF), which has gained attention for its potential benefits on cognitive performance and neuroprotection.

Evidence from both preclinical and some clinical studies indicates that IF may improve memory, attention, and executive function. These cognitive improvements are thought to be mediated by multiple biological mechanisms, including the activation of autophagy, upregulation of brain-derived neurotrophic factor (BDNF), reduction in oxidative stress and neuroinflammation, and enhanced mitochondrial efficiency. In animal models, IF has been associated with reduced alpha-synuclein aggregation and preservation of dopaminergic neurons, suggesting therapeutic potential in PD. In the context of AD, IF has shown benefits in promoting synaptic plasticity and decreasing amyloid-beta deposition.

The aim of this literature review is to assess the current evidence on the effects of intermittent fasting on cognitive function and neuroprotective mechanisms, with a particular focus on its role in Parkinson's and Alzheimer's diseases.

MATERIALS AND METHODS

This narrative literature review aimed to identify and synthesize evidence on the effects of intermittent fasting (IF) on cognitive function and neuroprotective mechanisms, with a focus on Alzheimer's disease (AD) and Parkinson's disease (PD).

The search strategy utilized keywords such as "intermittent fasting,""cognitive function,""neuroprotection," "Parkinson's disease," and "Alzheimer's disease".

Twelve eligible peer-reviewed articles were included in the synthesis.

REVIEW AND DISCUSSION

EFFECTS OF INTERMITTENT FASTING ON COGNITIVE PERFORMANCE

Intermittent fasting (IF) refers to a dietary pattern characterized by alternating periods of energy restriction and normal feeding. The most common protocols include alternate-day fasting, time-restricted eating (TRE), and the 5:2 regimen, in which calorie intake is significantly reduced on two non-consecutive days per week [4, 10, 11]. Unlike chronic caloric restriction, IF aims to induce metabolic and cellular adaptations without continuous energy deficit [6].

Several studies have examined the impact of IF on cognitive performance across different populations and experimental models. In a three-year longitudinal study involving older adults with mild cognitive impairment (MCI), Ooi et al. observed that an IF-based nutritional intervention led to significant improvements in global cognition, memory recall, and executive functioning compared to the control group [5]. Similarly, Alkurd et al. reported in their systematic review that intermittent fasting regimens were associated with increased levels of brain-derived neurotrophic factor (BDNF) and improved cognitive outcomes in both healthy individuals and those at risk of neurodegeneration [6].

In preclinical studies, IF has demonstrated the ability to reverse diet-induced cognitive deficits. Lee et al. showed that mice fed a high-fat diet exhibited impaired spatial memory and increased neuroinflammatory markers, both of which were ameliorated by alternate-day fasting. The intervention downregulated proinflammatory proteins such as lipocalin-2 and galectin-3, suggesting a mechanistic link between IF and reduced neuroinflammation [3].

Although evidence from human trials remains limited, current findings suggest that IF may exert beneficial effects on attention, learning, and memory, particularly in aging populations or individuals with early cognitive decline. Further large-scale randomized controlled trials are needed to validate these findings and to determine optimal fasting protocols for cognitive enhancement.

Beyond short-term improvements in cognitive domains, some studies suggest that IF may exert long-term effects on brain plasticity and resilience to age-related decline. Elias et al. [4] reported in their scoping review that IF was consistently associated with enhanced learning, better processing speed, and attention in both healthy and cognitively impaired populations. These effects were hypothesized to arise from modulations in insulin sensitivity, increased synaptic activity, and enhanced neuronal survival pathways.

Interestingly, Mayor [9] highlighted the neurotrophic effects of intermittent fasting, calorie restriction, and exercise, suggesting that different interventions may exert varying influences on cognition and mood. However, specific comparisons between TRE and the 5:2 protocol remain limited. Although mechanistic explanations remain under investigation, these findings point to differential neural adaptations triggered by specific fasting regimens.

Importantly, cognitive benefits of IF may also be mediated by better circadian alignment, reduced systemic inflammation, and modulation of the gut–brain axis, which has been implicated in regulating mood and cognition. These multidimensional effects highlight the potential of IF not only as a metabolic strategy, but also as a holistic approach to preserving cognitive function across the lifespan [10].

NEUROPROTECTIVE MECHANISMS OF INTERMITTENT FASTING

The neuroprotective potential of intermittent fasting (IF) has been increasingly recognized across multiple models of aging and neurodegeneration. Several studies have highlighted the biological pathways through which IF exerts its beneficial effects on the central nervous system (CNS), including autophagy activation, modulation of oxidative stress, mitochondrial biogenesis, neurotrophic factor upregulation, and gut–brain axis regulation.

One of the most consistently reported mechanisms is the stimulation of autophagy, a cellular recycling process essential for the clearance of damaged proteins and organelles. Dong et al. observed that IF significantly enhanced autophagic activity in aged rodent brains, which correlated with improved neuronal survival and synaptic integrity [7]. This finding is particularly relevant in the context of Alzheimer's and Parkinson's diseases, where defective autophagy contributes to protein aggregation and neuronal death.

Oxidative stress reduction is another critical neuroprotective mechanism associated with IF. Hein et al. reported that preclinical studies indicate that intermittent energy restriction modulates the activity of antioxidant enzymes, including superoxide dismutase and catalase, thereby lowering reactive oxygen species (ROS) levels in the brain [10]. These effects may counteract age-re-

lated mitochondrial dysfunction and support redox homeostasis.

IF has also been shown to improve mitochondrial function and stimulate mitochondrial biogenesis via pathways involving AMP-activated protein kinase (AMPK) and sirtuin-1 (SIRT1). These enzymes not only support energy homeostasis but also enhance neuronal plasticity and delay the progression of neurodegenerative pathology [10].

Neurotrophic factor regulation plays a complementary role in the neuroprotective profile of IF. Multiple studies have demonstrated that IF increases brain-derived neurotrophic factor (BDNF) levels, which promote neurogenesis, dendritic growth, and synaptic remodeling [6, 9]. The upregulation of BDNF is believed to underlie improvements in learning and memory observed in both human and animal models.

An emerging area of interest is the interaction between intermittent fasting and the gut–brain axis. Hein et al. suggested that IF influences the composition of gut microbiota, which in turn modulates systemic inflammation, short-chain fatty acid (SCFA) production, and microglial activation in the CNS [10]. These changes may support brain health and reduce neuroinflammatory responses implicated in Alzheimer's and Parkinson's diseases.

Finally, fasting-induced elevation of ketone bodies - particularly beta-hydroxybutyrate (BHB) - has been shown to provide alternative energy substrates for neurons and to exhibit signaling properties that promote neuronal resilience. Szegő et al. reported that BHB supplementation mimicked several beneficial effects of IF in a Parkinson's disease mouse model, including improved synaptic function and reduced alpha-synuclein aggregation [1].

Collectively, these mechanisms suggest that intermittent fasting exerts a multimodal neuroprotective effect, targeting metabolic, inflammatory, and regenerative pathways. Understanding these mechanisms may help develop dietary strategies tailored to prevent or slow neurodegeneration.

INTERMITTENT FASTING AND PARKINSON'S DISEASE

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by dopaminergic neuronal loss in the substantia nigra, aggregation of alpha-synuclein (α-syn) into Lewy bodies, and a broad spectrum of motor and non-motor symptoms. Although dopaminergic therapies remain the standard of care, they primarily provide symptomatic relief, and effective disease-modifying treatments are lacking. Recent experimental studies have suggested that intermittent fasting (IF) may offer neuroprotective benefits through metabolic, anti-inflammatory, and regenerative mechanisms [2].

In a pivotal study by Szegő et al. [1], alternate-day fasting was applied in a transgenic mouse model overexpressing human alpha-synuclein, which mimics key pathological features of PD, including dopaminergic neuronal loss and motor dysfunction. IF significantly reduced α-syn pathology, preserved substantia nigra neurons, and improved striatal synaptic activity. Behavioral analysis also demonstrated enhanced motor coordination and exploratory behavior. Mechanistically, these outcomes were linked to increased autophagic flux and upregulation of genes involved in synaptic plasticity and mitochondrial dynamics.

A review by Neth et al. [2] highlighted several converging mechanisms by which IF may exert neuroprotective effects in PD models. These include reduced oxidative stress, enhanced mitochondrial biogenesis via AMPK/SIRT1 signaling, and increased expression of brain-derived neurotrophic factor (BDNF), all of which promote neuronal survival and delay dopaminergic degeneration. The authors also emphasized IF's potential to modulate brain glucose metabolism and improve synaptic resilience.

Lei and Chen [8] further discussed the relevance of gut-brain axis dysfunction in PD pathogenesis and how IF may act to restore intestinal microbiota, reduce systemic inflammation, and prevent aberrant α-syn propagation from the gut to the brain. This emerging area supports the hypothesis that IF may interrupt early, peripheral drivers of neurodegeneration.

Another mechanism of interest is the elevation of ketone bodies during fasting, particularly beta-hydroxybutyrate (BHB). BHB serves not only as an energy substrate but also as an epigenetic regulator and anti-inflammatory molecule. In the study by Szegő et al. [1], exogenous BHB supplementation in a PD mouse model mimicked several benefits of intermittent fasting, including improved synaptic function and reduced α-synuclein aggregation.

While preclinical findings are promising, clinical evidence remains sparse. To date, no large-scale randomized controlled trials have evaluated the efficacy of IF in patients with Parkinson's disease. The potential clinical utility of IF in PD is therefore hypothetical, and future studies are needed to assess feasibility, safety, and possible interactions with pharmacological treatment regimens [1, 2, 8, 10].

INTERMITTENT FASTING AND ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder globally, characterized by

progressive memory loss, cognitive decline, and behavioral changes. The neuropathological hallmarks of AD include extracellular deposition of amyloid-beta (Aβ) plaques, intracellular neurofibrillary tangles of hyperphosphorylated tau protein, synaptic loss, and widespread neuroinflammation. Despite decades of research, therapeutic strategies capable of halting or reversing AD progression remain elusive. Recent literature suggests that intermittent fasting (IF) may offer neuroprotective benefits by modulating several of the key pathophysiological processes underlying AD [4-6, 10].

Elias et al. [4], in their scoping review, summarized evidence indicating that IF can enhance cognitive performance and delay neurodegenerative progression in individuals at risk of or diagnosed with AD. Animal studies have shown that IF attenuates Aβ plaque accumulation, improves hippocampal synaptic plasticity, and reduces markers of oxidative stress. Similar effects were observed in preclinical models with time-restricted feeding (TRF), which promoted spatial memory retention and long-term potentiation.

Ooi et al. [5], in a progressive three-year study involving older adults with mild cognitive impairment (MCI), reported that IF-based interventions improved memory recall and executive functioning. The authors hypothesized that improved metabolic flexibility and enhanced insulin sensitivity could contribute to reduced central insulin resistance, a condition increasingly recognized in the pathogenesis of AD.

The neuroprotective mechanisms of IF in AD appear to overlap with those identified in Parkinson's disease and include enhanced autophagy, reduction of oxidative and inflammatory damage, increased expression of brain-derived neurotrophic factor (BDNF), and improved mitochondrial function [6,10]. Additionally, IF-induced ketone production, particularly beta-hydroxybutyrate (BHB), provides alternative energy substrates to glucose-hypometabolic regions of the AD brain, thereby preserving neuronal activity and reducing excitotoxicity.

A growing body of evidence supports the role of central insulin resistance in the pathogenesis of AD, often referred to as "type 3 diabetes." Impaired insulin signaling in the brain leads to reduced glucose uptake, mitochondrial dysfunction, and tau hyperphosphorylation. In their longitudinal study, Ooi et al. [5] hypothesized that the cognitive benefits of IF in older adults with MCI may be partly explained by restored insulin sensitivity in the hippocampus and cerebral cortex. Similarly, Hein et al. [10] suggested that intermittent fasting modulates insulin and IGF-1 pathways in the brain, improving neuronal glucose utilization and enhancing energy efficiency under fasting conditions.

Emerging evidence also highlights the role of IF in regulating the gut–brain axis in AD, modulating the intestinal microbiota and decreasing systemic inflammation [10]. Dysbiosis and elevated peripheral inflammation have been linked to amyloid deposition and cognitive dysfunction. IF may counteract these processes by restoring microbial diversity and reinforcing intestinal barrier integrity.

Although promising, most evidence supporting the beneficial effects of IF in AD originates from animal studies and observational data. High-quality randomized controlled trials in patients with early-stage or mild-to-moderate AD are still lacking. Future clinical studies should evaluate the long-term cognitive and functional outcomes of IF and assess its feasibility and safety in vulnerable populations.

CHRONONUTRITION AND CIRCADIAN ALIGNMENT IN INTERMITTENT FASTING

Emerging research highlights the pivotal role of circadian rhythms in mediating the neuroprotective effects of intermittent fasting (IF). The circadian system, governed by a central clock in the suprachiasmatic nucleus and peripheral clocks in various tissues, orchestrates numerous physiological processes, including metabolism, hormone secretion, sleep-wake cycles, and neuronal activity. Disruptions in circadian alignment have been associated with increased risk of cognitive decline, neurodegeneration, and metabolic dysregulation.

Intermittent fasting, particularly time-restricted eating (TRE), has been shown to restore circadian synchrony by aligning feeding-fasting cycles with endogenous biological rhythms. Santos et al. [11] reported that early TRE (eTRE; e.g., 8 a.m. – 4 p.m.) improves insulin sensitivity and reduces oxidative stress, consistent with better circadian alignment.

The gut–brain axis represents a critical mediator of these chronobiological effects. Daas and de Roos [12] reported that IF induces diurnal oscillations in gut microbiota composition and function, notably increasing the abundance of short-chain fatty acid (SCFA) - producing bacteria during the fasting period. These microbial shifts enhance SCFA signaling, improve blood–brain barrier integrity, and modulate microglial activity, thereby promoting anti-inflammatory and neuroprotective responses. Moreover, bile acid metabolism - tightly linked to feeding rhythms - was also shown to be restored under IF regimens, contributing to circadian alignment.

Importantly, circadian misalignment - common in aging populations and neurodegenerative diseases

such as Alzheimer's - has been associated with impaired clearance of neurotoxic proteins during sleep and increased neuroinflammation. By promoting synchrony between central and peripheral clocks, IF may support glymphatic clearance, mitochondrial efficiency, and synaptic homeostasis, thereby protecting against cognitive deterioration [10].

Although clinical data remain limited, existing preclinical and translational studies support the hypothesis that IF may exert cognitive benefits not solely through caloric restriction, but by restoring temporal order to metabolic and neural pathways. The integration of chrononutrition principles into fasting regimens may therefore enhance their neuroprotective potential, particularly in individuals at risk of circadian dysregulation.

LIMITATIONS OF CURRENT EVIDENCE

Although the potential cognitive and neuroprotective benefits of intermittent fasting (IF) have been extensively explored in preclinical models and several observational studies, the current body of evidence remains limited in several key aspects. Most of the available data are derived from animal studies, which, although mechanistically informative, may not fully replicate the complexity of human neurodegenerative diseases or dietary adherence in real-world settings [1, 4, 6].

Human trials investigating IF in cognitive decline are relatively few and often involve small sample sizes, short intervention periods, and limited follow-up [5, 10]. Furthermore, the heterogeneity in IF protocols—ranging from alternate-day fasting to time-restricted eating—complicates cross-study comparisons and hampers the identification of an optimal regimen. Many studies also lack proper blinding, standardized neurocognitive assessments, or control for confounding lifestyle variables such as sleep, stress, and physical activity [6, 9].

Another critical gap is the absence of large-scale randomized controlled trials (RCTs) specifically targeting populations with Alzheimer's disease (AD), Parkinson's disease (PD), or mild cognitive impairment (MCI). While promising trends have been noted in early-stage cognitive decline, the generalizability of findings to patients with established neurodegenerative pathology remains uncertain [4, 10].

Additionally, adherence to IF in older adults or those with neurodegenerative conditions may pose practical challenges, including risks of malnutrition, medication timing issues (especially in PD), and potential exacerbation of frailty. Ethical and logistical considerations often preclude long-term fasting interventions in vulnerable populations, further limiting data availability [2, 5].

Taken together, these limitations underscore the need for rigorously designed, adequately powered RCTs to evaluate the cognitive and neuroprotective efficacy of IF. Standardization of protocols, comprehensive outcome measures, and long-term follow-up will be essential to establish clinical guidelines and ensure safe implementation.

CONCLUSIONS

Intermittent fasting (IF) has emerged as a promising non-pharmacological intervention with potential cognitive and neuroprotective benefits. Preclinical and early clinical evidence suggests that IF may attenuate key pathological processes involved in Alzheimer's disease and Parkinson's disease, including oxidative stress, mitochondrial dysfunction, neuroinflammation, and impaired autophagy. Furthermore, IF improves insulin sensitivity in the central nervous system and modulates gut-brain axis signaling - both increasingly recognized as relevant in neurodegenerative disorders.

Recent findings also highlight the importance of circadian alignment as a mediator of the beneficial effects of IF. By restoring synchrony between feeding patterns and endogenous biological rhythms, IF may enhance neuroplasticity, circadian alignment, and metabolic resilience in aging populations.

Although the majority of current evidence is derived from animal models and observational studies, selected human trials - particularly in individuals with mild cognitive impairment - suggest improvements in memory, executive function, and metabolic health. Compared to other dietary strategies, IF appears to exert its effects through dynamic metabolic switching, chrononutritional entrainment, and cellular stress adaptation, which may uniquely enhance neuronal resilience.

Nevertheless, critical gaps remain in the literature. High-quality randomized controlled trials are urgently needed to assess the long-term cognitive and functional outcomes of IF, its optimal implementation protocols, and its safety in older and vulnerable populations. Future research should also explore its synergistic effects with pharmacological therapies and other lifestyle interventions.

In conclusion, IF represents an encouraging avenue for neuroprotection and cognitive preservation. With growing interest in lifestyle-based strategies for brain health, intermittent fasting holds the potential to complement existing approaches in the prevention and management of neurodegenerative disorders [4–6, 10–12].

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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