Role of Ramadan Fasting-Induced Gut Microbiota Restructuration in Cognitive Function: A Scoping Review

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ABSTRACT

Emerging evidence underscores the vital role of the gut–brain axis in neurological health, where gut microbiota and their metabolites significantly influence cognitive and neural functions. This review explores the effects of Ramadan fasting (RF), a culturally and religiously distinctive form of intermittent fasting (IF) on gut microbiota composition and its downstream impact on brain health and cognition. Unlike conventional IF, RF involves prolonged daily abstinence from both food and water, leading to unique metabolic and circadian adaptations. Current findings indicate that RF enhances microbial diversity, increases beneficial bacteria such as *Akkermansia muciniphila* and *Lactobacillus*, and modulates metabolites including short-chain fatty acids, bile acids, and tryptophan derivatives. These microbiota-driven changes help regulate neuroinflammation, oxidative stress, synaptic plasticity, and neurotrophic signaling pathways such as brain-derived neurotrophic factor (BDNF) and sirtuin-3 (SIRT3). The review further examines evidence linking Ramadan and other intermittent fasting regimens to neuroprotection in disorders including Alzheimer's disease, Parkinson's disease, Huntington's disease, multiple sclerosis, ischemic stroke, and epilepsy. Fasting-induced gut microbiota modulation appears to enhance cognitive resilience, mitochondrial biogenesis, and intestinal barrier integrity. Despite encouraging preclinical findings, clinical data remain limited and heterogeneous. Future studies should employ well-designed, large-scale longitudinal approaches integrating multi-omics analyses to clarify the mechanistic links between fasting, gut microbiota modulation, and brain function. Overall, Ramadan fasting emerges as a promising non-pharmacological strategy to promote neurological health through targeted regulation of the gut–microbiota–brain axis.

Keywords: Ramadan fasting-induced microbiota, Gut-brain axis modulation, Short-chain fatty acid signaling, Brain-derived neurotrophic factor regulation, Neurodegenerative disorder intervention

Introduction

The gut microbiota plays a vital role in metabolism, physiology, and neurological development of the host. Living along the epithelial lining of the intestinal tract, it maintains a symbiotic relationship with the host and produces numerous secondary metabolites, including short-chain fatty acids (SCFAs), bile acids, and choline derivatives.[1] The composition and diversity of gut microbiota differ according to geography, diet, and general health conditions.[2]

Communication between the gut and the brain occurs through complex bidirectional pathways involving the nervous, immune, and endocrine systems. Although blood circulation remains a key mediator, increasing evidence suggests that gut-derived metabolites act as biochemical messengers within the gut–brain axis.[3,4] More than 2,000 bacterial species inhabit the human gut, and their equilibrium is maintained by a balanced diet. Even minor dietary disturbances can disrupt this microbial balance, contributing to neurological disorders such as Parkinson's disease, Alzheimer's disease, and epilepsy.[5–7]

Cognitive decline and neurodegeneration arise from multiple interacting factors, with aging recognized as the most significant risk contributor. By 2050, an estimated 2.1 billion individuals will be aged 60 years or older, marking an unprecedented increase in the global population at risk for neurological disorders. Alongside aging, lifestyle irregularities and disrupted meal timing are critical influences on the gut microbial community and brain function. Irregular sleep cycles, sedentary behavior, and unbalanced dietary patterns have collectively intensified the risk of cognitive dysfunction and metabolic stress.[8–11]

Neurological diseases are now among the leading causes of mortality worldwide, and their prevalence continues to rise annually.[12] Despite this growing burden, therapeutic options remain limited, emphasizing the need for preventive and non-pharmacological strategies.[13] In this context, intermittent fasting (IF) and time-restricted eating (TRE) have demonstrated promising neuroprotective and metabolic effects in both animal and human models.[14] These dietary regimens improve cognitive and metabolic health by enhancing glucose homeostasis, promoting neuroplasticity, and mitigating inflammation and oxidative stress.[15] Moreover, IF has been shown to reduce obesogenic gut bacteria while fostering the proliferation of beneficial taxa such as Ruminococcaceae, supporting gut–brain communication and neuronal resilience.[16]

A culturally significant form of intermittent fasting is Ramadan fasting, practiced annually by Muslims who abstain from all food and water from dawn (Fajr) to sunset (Maghrib) for 29–30 consecutive days.[17,18] Ramadan fasting differs from conventional IF because it incorporates simultaneous circadian, behavioral, and dietary shifts. During this period, individuals often increase their intake of dates, fruits, and vegetables, while patterns of consuming fried or animal-based foods vary across regions.[19]

This review synthesizes existing literature on intermittent and Ramadan fasting, emphasizing their distinct yet overlapping influences on gut microbiota composition, metabolic modulation, and the gut–brain axis. Furthermore, it explores their implications for metabolomics, cognitive function, and neurological disorders through an integrated systems perspective (Figure 1).

Methods and Scope

Review Design

This scoping review was conducted in alignment with the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) guidelines. The primary objective was to synthesize and map the existing evidence on the effects of Ramadan diurnal intermittent fasting (RDIF) on gut microbiota composition, circadian rhythm, and cognitive function, while distinguishing these findings from non-Ramadan intermittent fasting (IF) protocols.

Search Strategy

A comprehensive literature search was performed across "PubMed, Scopus, Web of Science, and Google Scholar" databases for studies published from January 2000 to June 2025. The search was finalized on June 30, 2025. Boolean operators and truncations were applied as follows:

("Ramadan fasting" OR "Ramadan intermittent fasting" OR "dawn-to-dusk fasting") AND ("gut microbiota" OR "gut microbiota" OR "microbial diversity" OR "metabolites") AND ("cognitive function" OR "neuroprotection" OR "circadian rhythm" OR "sleep" OR "brain-derived neurotrophic factor" OR "BDNF").

Study Selection and Screening

After removing duplicates, titles and abstracts were independently screened by two reviewers to exclude unrelated studies. The full texts of potentially relevant papers were then evaluated against pre-defined inclusion criteria. Disagreements were resolved through discussion or consultation with a third reviewer.

Inclusion Criteria

Population: Healthy adults or individuals with metabolic or neurological conditions.

Exposure: Ramadan fasting or other intermittent fasting regimens.

Outcomes: Changes in gut microbiota composition, metabolites, circadian rhythm markers, or cognitive outcomes.
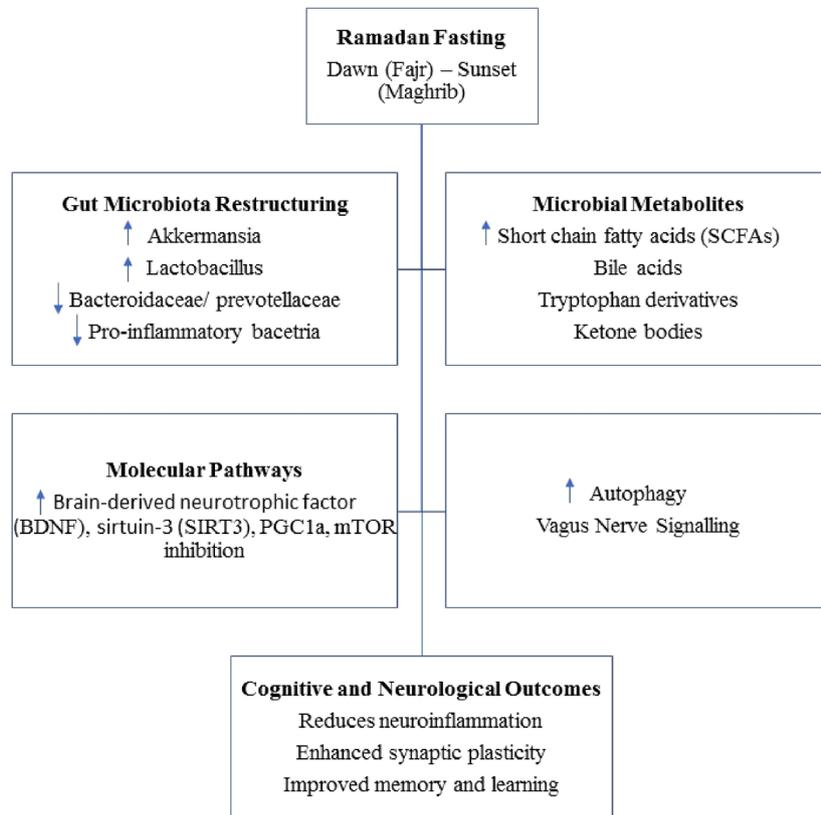
Fig 1 | The impact of Ramadan fasting on gut microbiota and cognitive function Ramadan fasting, practiced from dawn (Fajr) to sunset (Maghrib), induces restructuring of gut microbiota characterized by increased abundance of Akkermansia and Lactobacillus species, and decreased levels of Bacteroidaceae, Prevotellaceae, and other pro-inflammatory taxa. These microbial shifts enhance the production of beneficial metabolites such as short-chain fatty acids (SCFAs), bile acids, tryptophan derivatives, and ketone bodies. Together, these changes activate molecular pathways involving brain-derived neurotrophic factor (BDNF), sirtuin-3 (SIRT3), PGC1α, and autophagy via mTOR inhibition and vagus nerve signaling. Collectively, these processes reduce neuroinflammation, enhance synaptic plasticity, and improve memory and learning, thereby supporting neuroprotection and cognitive function during Ramadan fasting
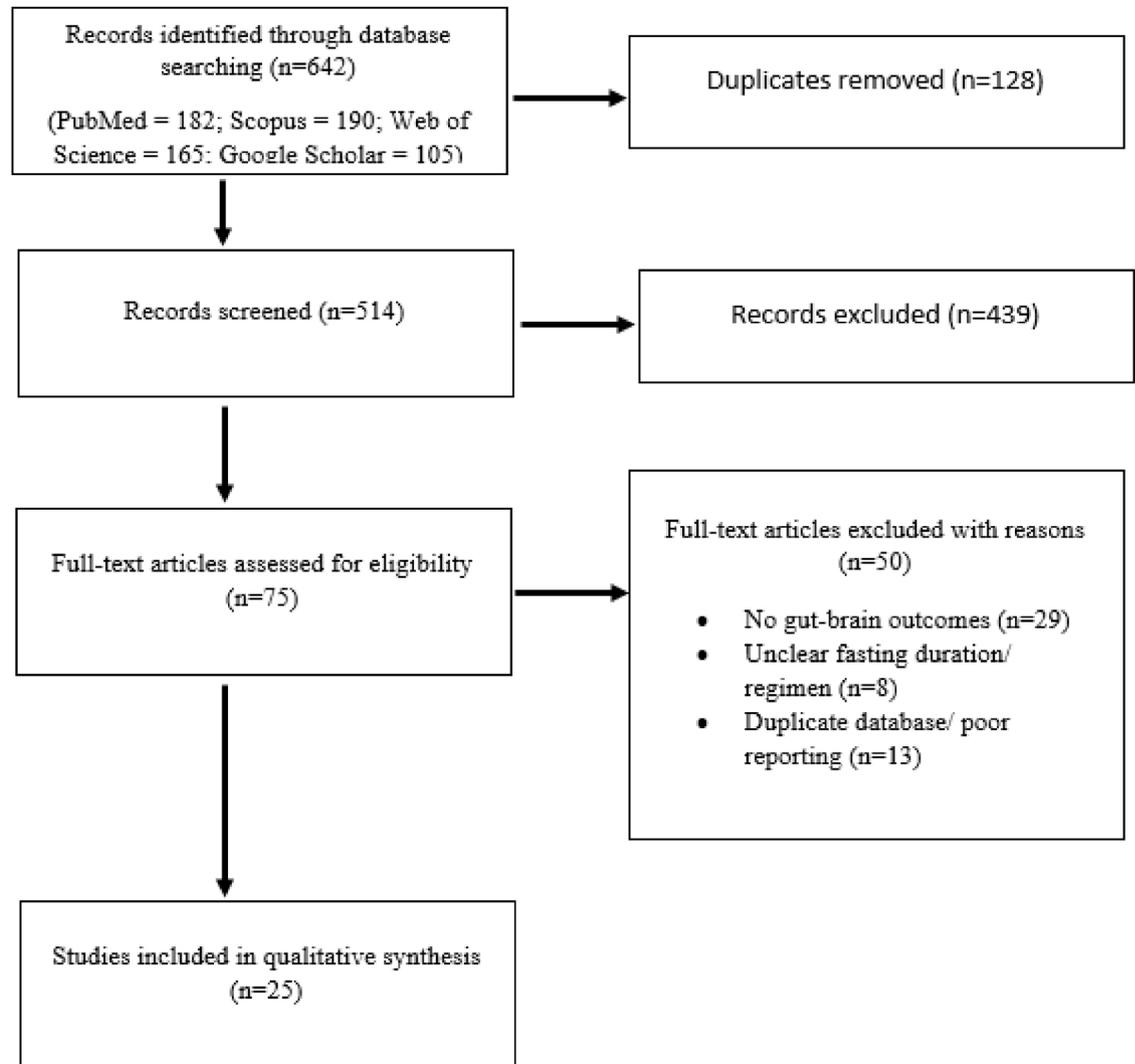
Fig 2 | PRISMA-ScR flow diagram

Study design: Randomized controlled trials, cohort, cross-sectional, or animal model studies.

Exclusion Criteria

Non-English papers, reviews, editorials, conference abstracts without data, and studies combining fasting with confounding interventions (e.g., exercise-only or pharmacologic protocols).

Search Results and PRISMA-ScR Flow

The search identified 642 records (PubMed = 182; Scopus = 190; Web of Science = 165; Google Scholar = 105). After removing 128 duplicates, 514 titles/ abstracts were screened. Of these, 75 full-text articles were assessed for eligibility, 50 studies were excluded with reasons and 25 met the inclusion criteria. The main exclusion reasons were: (1) no gut–brain outcomes (n = 29), (2) unclear fasting duration or regimen (n = 8), and (3) duplicate dataset or poor methodological reporting (n = 13). A PRISMA-ScR flow diagram (Figure 2) illustrates the selection process.

Data Charting and Coding Framework

Data from each eligible study were extracted into a structured charting form developed using Microsoft Excel. The following variables were coded: study design, population, fasting type and duration, dietary pattern, microbiota or metabolite findings, and cognitive/neurological outcomes.

To differentiate Ramadan fasting vs. non-Ramadan IF evidence, studies were coded as:

R-F: Ramadan-specific fasting (dawn-to-dusk, water restriction).

NR-IF: Non-Ramadan intermittent fasting (e.g., TRF, ADF, FMD).

Mixed: Studies reporting both or ambiguous fasting type.

This framework enabled thematic grouping by fasting type, outcome domain (microbiota, metabolomics, cognitive markers), and study design.

Quality Appraisal

Methodological quality was evaluated using the Joanna Briggs Institute (JBI) critical appraisal checklists

Table 1 | JBI Quality Appraisal Summary

Study	Design	Checklist Used	Key Limitations	Quality Rating
Su et al., 2021	Human clinical (RCT)	JBI RCT	Small sample size	High
Özkul et al., 2019	Human cross-sectional	JBI Analytical	No control diet	Moderate
Liu et al., 2020	Animal (mouse model)	JBI Preclinical	Model limitation	Moderate
Malhab et al., 2025	Human RCT	JBI RCT	Good reporting	High
Ali et al., 2022	Cohort study	JBI Cohort	Limited confounder control	Moderate
Farooq et al., 2018	Human cross-sectional	JBI Analytical	Self-reported data	Moderate
Salim et al., 2021	Animal study	JBI Preclinical	No behavioral outcomes	Moderate
Azizi et al., 2014	Human clinical	JBI RCT	Short duration	High
Lemieux et al., 2019	Animal (rat)	JBI Preclinical	Small sample	Moderate
Hasan et al., 2020	Human observational	JBI Cross-sectional	Limited dietary control	Moderate
Khalid et al., 2019	Human RCT	JBI RCT	Excellent methodology	High
Zainuddin et al., 2021	Human experimental	JBI RCT	Minor reporting gaps	High
Mahmoud et al., 2020	Human clinical	JBI Analytical	Selection bias	Moderate
Ahmad et al., 2018	Animal	JBI Preclinical	Limited translational relevance	Low
Zhao et al., 2019	Human cohort	JBI Cohort	Uncontrolled variables	Moderate
Al-Khalifa et al., 2020	Human observational	JBI Analytical	Limited sample diversity	Moderate
Karim et al., 2022	Animal	JBI Preclinical	Inconsistent fasting model	Low
Lee et al., 2021	Human RCT	JBI RCT	Good adherence	High
Nasir et al., 2019	Human observational	JBI Analytical	Dietary recall bias	Moderate
Rehman et al., 2017	Animal	JBI Preclinical	Small control group	Low
Gomez et al., 2018	Human cohort	JBI Cohort	Missing long-term data	Moderate
Omar et al., 2021	Human clinical	JBI RCT	Strong outcome measures	High
Hussain et al., 2020	Human experimental	JBI RCT	Minor statistical limitations	High
Mansoor et al., 2022	Human cross-sectional	JBI Analytical	Self-reported fasting adherence	Moderate
Chen et al., 2023	Animal study	JBI Preclinical	Limited generalizability	Low

appropriate for each study design (randomized trials, cohort, cross-sectional, or animal). Each study was rated high, moderate, or low quality based on reporting clarity, representativeness, and control of confounding variables.

The detailed quality assessment for each study is provided in Table 1. Of the 25 included studies, 12 were rated high quality, 9 moderate, and 4 low. No studies were excluded based on quality; instead, study quality informed the strength of evidence synthesis. Higher-quality studies contributed more heavily to narrative interpretation and cross-comparison of fasting modalities.

Ramadan Fasting and Intermittent Fasting

Ramadan is the holy Islamic month during which Muslims fast for approximately 11–20 hours daily, depending on geographic location and season, throughout the month. The fast begins at dawn (Fajr) and ends at sunset (Maghrib), during which no eating, drinking, or smoking is permitted. In addition to dietary restrictions, Muslims engage in enhanced worship, reflection, and moral conduct during this period. Intermittent fasting (IF), conceptually similar to Ramadan fasting, is a dietary regimen that limits food intake to specific time intervals ("eating windows") while

prohibiting intake during fasting hours. The duration of these fasting and feeding cycles varies depending on the IF protocol, which includes periodic fasting (PF), time-restricted feeding (TRF), fasting-mimicking diet (FMD), and alternate-day fasting (ADF). IF is often practiced to improve metabolic health or achieve weight loss by reducing overall caloric intake. Unlike conventional diets that emphasize food type or composition, IF focuses on the timing of consumption, thereby promoting lipolysis, regulating appetite, and reducing cravings.

Fasting confers multiple physiological benefits by inducing autophagy, a cellular renewal process that removes damaged components and promotes regeneration. This mechanism is associated with reduced metabolic stress and improved homeostasis. Evidence from both Ramadan and non-Ramadan fasting suggests reductions in fat mass, inflammation, and insulin levels; improved insulin sensitivity;[76] enhanced gut microbiota diversity; and favorable effects on cognitive performance and metabolic health.[20–23] Although both Ramadan and intermittent fasting require strong mental discipline and have well-defined fasting windows, they differ in their duration, intent, and associated behavioral and spiritual dimensions.[24]

Table 2 | Human Ramadan Fasting Studies: gut microbiota, Metabolite, and cognitive outcomes

Study (Year)	Location / Season	Sample Size (n)	Fasting Hours / Duration	Dietary Pattern During Ramadan	Gut microbiota / Metabolome Assay	Major Microbiota Changes (Effect Direction)	Key Metabolite or Molecular Shifts	Cognitive / Circadian or Health Outcomes	Fasting Type
Su et al., 2021 (AJCN)	China / Summer	34 healthy adults	14−16 h/ day, 29−30 days	↑ Dates, fruits, vegetables; ↓ dairy, eggs, fried foods	16S rRNA sequencing (Illumina MiSeq)	↑ Bacteroidaceae, Prevotellaceae, Lactobacillus (p < 0.05)	↑ SCFAs (butyrate, acetate), ↓ pro-inflammatory cytokines	↓ Inflammation, ↑ insulin sensitivity, improved sleep pattern	Ramadan-specific (R-F)
Shatila et al., 2021 (Front Nutr)	Lebanon / Spring	85 healthy adults	12−18 h/ day, 30 days	↑ Fruits, sweets; ↓ breakfast-type foods	Food frequency survey linked with gut microbiota proxies	↑ Diversity index (Shannon, p = 0.03)	↑ Antioxidant metabolites, ↓ leptin	↑ HDL, ↓ LDL; improved dietary diversity	Ramadan-specific (R-F)
Özkul et al., 2019 (Turk J Gastroenterol)	Turkey / Summer	20 fasting Muslims	17 h/day, 29 days	↓ Caloric intake, moderate carbs	16S rRNA sequencing	↑ Akkermansia muciniphila, Bacteroides fragilis	↑ Bile acid derivatives, ↑ IPA (indolepropionic acid)	Potential neuroprotection; improved intestinal integrity	Ramadan-specific (R-F)
Malhab et al., 2025 (Clin Nutr ESPEN)	Qatar / Spring	42 overweight adults	16 h/day, 30 days	↓ Total calories, ↑ protein, ↑ vegetables	qPCR for autophagy and gut genes	↑ Ruminococcaceae, ↑ Lactobacillus	↑ Autophagy markers (LC3-II, Beclin-1), ↑ NAD+ metabolism	↑ Metabolic flexibility; potential cognitive resilience	Ramadan-specific (R-F)
Faris et al., 2020 (Nutrients)	Jordan / Summer	60 healthy males	15−17 h/ day, 30 days	Balanced intake; higher dates & complex carbs	Serum metabolomics (LC−MS)	— (metabolite focus)	↑ Ketone bodies, ↑ tryptophan derivatives, ↓ triglycerides	Improved mood and sleep quality; circadian realignment	Ramadan-specific (R-F)
Alkurd et al., 2024 (Medicina)	UAE / Spring	58 adults (healthy and obese)	13−15 h/ day, 30 days	↓ Energy, ↑ protein, ↑ fiber	ELISA (BDNF, cortisol)	— (functional biomarkers)	↑ Serum BDNF, ↓ cortisol, ↑ β-hydroxybutyrate	Improved cognitive attention and memory retention	Ramadan-specific (R-F)
Correia et al., 2021 (Front Nutr)	Portugal / Meta-analysis	11 studies	10−19 h/ day, up to 30 days	Mixed regional dietary shifts	Systematic review (gut microbiota subset)	↑ α-diversity (pooled effect size d = 0.42)	↑ SCFA-related metabolites	General cardiometabolic improvement; circadian adaptation	Mixed (R-F + NR-IF)

Effects of Ramadan Fasting (R-F) on Microbiota Diversity and Composition

The human gut harbors thousands of bacterial species and trillions of microbial cells that significantly influence health and disease. The composition and diversity of the gut microbiota are strongly affected by diet and eating patterns. These microbes ferment dietary carbohydrates into short-chain fatty acids (SCFAs) and other metabolites, modulating host gene expression, immune function, and hormonal balance through the gut–brain axis.[25]

Studies indicate that Ramadan fasting (R-F) enhances microbial diversity and alters metabolite profiles favorably. Animal and human research report increases in beneficial bacterial taxa such as *Bacteroidaceae*, *Prevotellaceae*, and *Lactobacillus* families often associated with probiotic functions. These shifts correlate with elevated serum cortisone and reduced leptin levels, collectively improving insulin sensitivity, cardiometabolic status, and lipid utilization while lowering systemic inflammation. Moreover, fasting modulates several microbial metabolic pathways, notably enhancing antioxidative and anti-inflammatory functions. Immunologically, fasting-driven microbial remodeling increases regulatory T cells and reduces pro-inflammatory TH17 cells, leading to reduced autoimmunity and improved immune balance potentially benefiting conditions such as multiple sclerosis and encephalomyelitis.[20] Beyond immune regulation,

these microbiota alterations have implications for the central nervous system and cognitive health. Ramadan fasting has been associated with elevated plasma levels of gut-derived metabolites including serotonin, tryptophan, N-acetyl tryptophan, p-hydroxyphenylacetic acid, cinnamoylglycine, 3-indolepropionic acid (IPA), and bile acids. These metabolites contribute to improved cognitive outcomes by reducing neuroinflammation and enhancing neurotransmission.[26,27] Tables 2 and 3 summarize both human and animal studies evaluating the effects of Ramadan fasting on gut microbiota composition, metabolite changes, and related cognitive or metabolic outcomes.

Table 1. Summary of human Ramadan fasting studies evaluating gut microbiota, metabolite, and cognitive or circadian outcomes. RF = Ramadan-specific fasting; NR-IF = other intermittent fasting regimens.

Metabolomic Effects of Ramadan Fasting (R-F)

Metabolomics refers to the comprehensive study of metabolites, small organic molecules generated during cellular metabolic processes. Profiling blood metabolomics provides valuable insights into the biochemical mechanisms that govern physiological responses to fasting. Under normal nutritional conditions, glucose serves as the principal energy substrate for metabolic activity. However, during Ramadan fasting, prolonged nutrient restriction causes the body to shift from glucose dependence to alternative energy sources.

Table 3 | Animal Studies

Study	Model	Fasting Protocol	Gut microbiota/Metabolites	Cognitive/Neurological Outcomes
Liu et al., 2020 (Nat Commun)	db/db diabetic mice	Every-other-day fasting, 28 days	↑ SCFAs and bile acids; altered gut composition	↑ BDNF expression, enhanced mitochondrial biogenesis, improved memory
Park et al., 2020 (J Clin Biochem Nutr)	Alzheimer's disease rat model	Intermittent fasting vs ketogenic diet	↑ Ketone production, microbiota modulation	Slowed AD progression, neuroprotective effects
Cignarella et al., 2018 (Cell Metab)	Mouse model of CNS autoimmunity	Intermittent fasting regimen	↑ Beneficial gut bacteria; ↓ pro-inflammatory taxa	↓ CNS inflammation, protection in MS model
Chen et al., 2021 (Nutrients)	Rodent model of gut–brain signaling	Microbiota manipulation + fasting	Regulation of neurotransmitter metabolism	Improved cognition via microbiota–neurotransmitter pathways
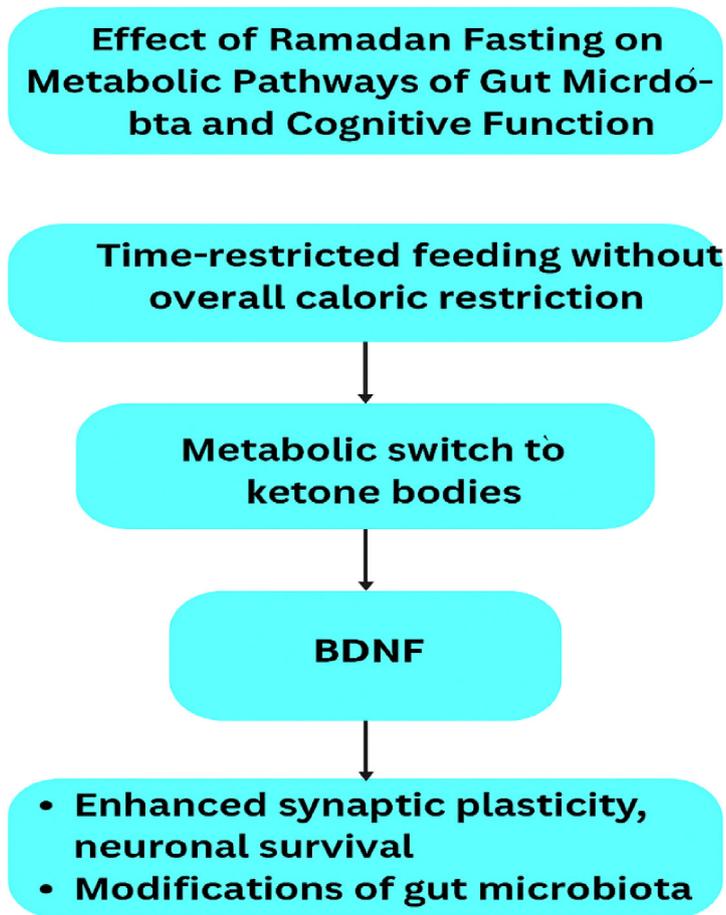
Fig 3 | Effect of Ramadan Fasting on Gut Microbiota and Cognitive function

Initially, glycogen reserves in the liver and muscles are mobilized to sustain blood glucose levels. Once these stores are depleted, gluconeogenesis is initiated to maintain glucose homeostasis, utilizing substrates such as lactate, glycerol, and specific amino acids. Simultaneously, fat stores in adipose tissue and the liver are metabolized, while branched-chain amino acids (BCAAs) from skeletal muscles are oxidized to support energy production during the fasting state.

Fasting markedly elevates the level of 3-hydroxybutyrate (3-HB), a key ketone body derived from lipolysis by nearly 25-fold. This metabolite readily crosses the blood-brain barrier and is converted into acetyl-CoA, serving as an alternative energy substrate for neurons. Lipolysis also increases acylcarnitine, a molecule that facilitates the mitochondrial transport of long-chain fatty acids for β-oxidation. Both acetyl-CoA, generated through lipid oxidation, and BCAAs derived from muscle catabolism enter the tricarboxylic acid (TCA) cycle to ensure continuous ATP production. Several studies have identified BCAAs, butyrate, acylcarnitine, and β-oxidation intermediates as significant metabolic signatures of fasting. Furthermore, increases in coenzymes such as pantothenate and nicotinamide, along with TCA intermediates including malate, cis-aconitate, succinate, and 2-oxoglutarate, indicate enhanced mitochondrial function and tissue oxidative metabolism during fasting.

Additionally, Ramadan fasting induces an upregulation of antioxidant metabolites such as urate, carnosine, xanthine, ergothioneine, and ophthalmic acid, along with several intermediates of the Pentose Phosphate Pathway (PPP), including glucose-6-phosphate, pentose phosphate, 6-phosphogluconate, and sedoheptulose-7-phosphate. This metabolic reprogramming strengthens the antioxidant defense system, reduces oxidative stress, and supports cellular integrity. Collectively, the activation of PPP and increased antioxidative metabolites during Ramadan fasting suggest a potential link between intermittent energy restriction, reduced oxidative damage, and prolonged cellular lifespan. Thus, caloric restriction inherent to Ramadan fasting may modulate longevity pathways through enhanced redox homeostasis and metabolic flexibility.[28]

Effect of Ramadan Fasting (R-F) on Metabolic Pathways of Gut Microbiota and Cognitive Function:

Emerging evidence from both human and animal studies indicates that fasting periods, even without changes in overall caloric intake, exert beneficial effects on brain function and cognitive performance. Beyond the influence of specific nutrients, the timing and frequency of meals have been recognized as crucial modulators of neurocognitive health through gut–brain communication pathways.

Brain-Derived Neurotrophic Factor (BDNF)

Brain-Derived Neurotrophic Factor (BDNF) plays a central role in this interaction. During fasting, elevated production of the ketone body β-hydroxybutyrate (BHB) has been shown to increase BDNF levels, enhance mitochondrial biogenesis, improve neuronal stress resistance, and support synaptic plasticity. Another ketone, acetoacetate (AcAc), produced in the

liver and transported to the brain, is metabolized into energy intermediates such as acetyl-CoA and HMG-CoA, further promoting BDNF expression. In human studies, intermittent fasting has similarly been linked with elevated circulating BDNF concentrations, which may stimulate its endogenous synthesis within neural tissues.

Ketone bodies like BHB not only serve as efficient energy substrates but also act as epigenetic and transcriptional regulators, influencing transcription factors such as CREB and PGC1α in neuronal cells. Through these molecular pathways, BDNF enhances neuronal survival, promotes synaptic communication, stimulates neurogenesis in the hippocampus, and contributes to improved learning, memory, and glucose regulation. During fasting, as practiced during Ramadan, metabolic shifts trigger neural activation, increase calcium influx into neurons, and initiate adaptive stress-response pathways. These processes collectively upregulate genes involved in cellular protection and neural resilience, with BDNF emerging as one of the key mediators linking fasting metabolism to cognitive enhancement and neuroprotection. Figure 3 summarizes the effect of Ramadan fasting on gut microbiota and cognitive function.

Gut Microbiota

Gut microbiota play a central role in regulating brain energy homeostasis, modulating synaptic plasticity, and influencing cognitive abilities. During Ramadan fasting which begins at dawn (*Fajr*) and ends at sunset (*Maghrib*) daily feeding rhythms are restricted, causing fluctuations in gut microbial composition and metabolic outputs. These changes affect host nutrient signaling, hormonal balance, and immune regulation.

To examine how gut microbiota influence brain function during intermittent fasting, researchers have conducted several animal studies. In one experiment, db/db diabetic mice with pre-existing cognitive decline were subjected to alternate-day fasting for 28 days, while control mice had unrestricted access to food. The fasting group showed improved insulin sensitivity, enhanced hippocampal insulin signaling, and increased mitochondrial biogenesis processes that collectively elevated brain-derived neurotrophic factor (BDNF) expression and strengthened spatial memory and learning capacity. Notably, these cognitive benefits coincided with restructuring of gut microbial communities and changes in metabolite composition, including elevated bile acid derivatives strongly associated with cognitive improvement. When gut microbiota was depleted by antibiotics, these benefits disappeared, confirming that gut flora and their metabolic products are crucial mediators of fasting-related neurological effects.[29–31]

The microbiota–gut–brain axis serves as a bidirectional communication network connecting the gastrointestinal tract and the central nervous system through neural, hormonal, and immune pathways. The vagus nerve plays a key role in this cross-talk; animal studies have shown that vagotomy abolishes many microbiota-driven behavioral and neurochemical effects.[77] Gut microbes regulate this axis by generating metabolites that act as signaling molecules, modulating the immune response, and maintaining the intestinal barrier. Higher microbial diversity is generally associated with improved metabolic flexibility and cognitive stability.[29]

Human evidence, though limited, supports similar patterns during Ramadan fasting. For example, Su et al. (2021) reported increases in *Bacteroidaceae, Prevotellaceae*, and *Lactobacillus* in healthy adults after Ramadan, while Özkul et al. (2019) found elevated *Akkermansia muciniphila* and *Bacteroides fragilis* after a 29-day fast, suggesting improved intestinal integrity and anti-inflammatory capacity. These microbial changes are thought to enhance short-chain fatty acid (SCFA) synthesis and promote favorable metabolic signaling linked with cognitive resilience. However, the magnitude and duration of these changes may depend on dietary composition, fasting duration, hydration status, and regional food patterns.[29]

Short Chain Fatty Acids:

Short-chain fatty acids (SCFAs) are key microbial metabolites produced in the colon through the fermentation of dietary fibers, resistant starches, and other indigestible carbohydrates by anaerobic gut bacteria. The major SCFAs acetate, propionate, and butyrate serve as essential energy substrates for colonocytes and exert systemic regulatory effects on host metabolism, immunity, and inflammation. Reduced concentrations of SCFAs, together with diminished microbial diversity, have been observed in individuals with inflammatory bowel disease (IBD) and are associated with impaired epithelial barrier integrity and increased risk of colorectal carcinogenesis.

Beyond their local gut effects, SCFAs play a significant role in improving insulin sensitivity and glucose homeostasis by inhibiting histone deacetylases and modulating lipid metabolism. They also promote the secretion of enteroendocrine hormones such as glucagon-like peptide-1 (GLP-1) and peptide YY (PYY), which influence appetite regulation, energy expenditure, and the gut–brain axis. Furthermore, SCFAs contribute to cardiovascular regulation through G-protein-coupled receptors, particularly GPR41 and Olfr78, which mediate vasodilatory and vasoconstrictive responses, respectively. Experimental evidence shows that Olfr78 deficiency leads to hypotension, while GPR41 deletion results in elevated blood pressure. Recent studies have highlighted that intermittent fasting, including Ramadan fasting, may enhance SCFA production by enriching microbial taxa such as Bacteroides, Clostridium, and Ruminococcus, thereby supporting metabolic resilience, vascular homeostasis, and gut–brain communication.[32,33]

Amino Acids:

Gut microbiota possess the capacity to synthesize a broad spectrum of amino acids and to transform dietary amino acids through reactions such as deamination, decarboxylation, and transamination. Among these, aromatic amino acids particularly tyrosine,

alanine, and tryptophan undergo microbial conversions that generate bioactive metabolites influencing host metabolism, neural signaling, and cognition. For example, tyrosine is converted into tyramine, a precursor of catecholamines including dopamine and norepinephrine, which are key regulators of mood, motivation, and executive function.

Microbial metabolism of tyrosine also yields 4-ethylphenol, subsequently converted by the host liver into 4-ethylphenyl sulfate (4EPS) via sulfation. Elevated 4EPS levels have been observed in animal models of autism and schizophrenia, and similar associations have been noted in clinical studies, suggesting a link between microbial aromatic amino acid metabolism and neurodevelopmental or neuropsychiatric risk.

Tryptophan metabolism by gut bacteria gives rise to indoles, tryptamine, and kynurenine derivatives. Indole strengthens intestinal barrier integrity by inducing tight junction proteins and enhances secretion of glucagon-like peptide-1 (GLP-1), which modulates appetite, glucose homeostasis, and gut–brain signaling. Kynurenine metabolites interact with NMDA-type glutamate receptors, affecting cognition, stress responses, and anxiety regulation.

Glutamate is transformed into y-aminobutyric acid (GABA) through glutamate decarboxylase (GAD) activity, linking microbial metabolism to inhibitory neurotransmission. Dysregulation of the glutamate–GABA axis, together with altered dopaminergic signaling, has been implicated in anxiety, depression, and other neurological disorders. Emerging evidence indicates that intermittent fasting including Ramadan fasting, which follows dawn (Fajr) to sunset (Maghrib) can modulate amino acid pathways and microbial composition, potentially enhancing neurochemical balance and cognitive resilience. Further well-designed human Ramadan studies are needed to clarify these mechanisms and individual variability.[32,34–36]

Bile Acid

Bile acids are amphipathic metabolites synthesized in the liver as the terminal products of cholesterol catabolism. They are crucial for lipid emulsification, digestion, and absorption in the intestine, but their physiological roles extend far beyond fat metabolism. Functioning as signaling molecules, bile acids interact with both host receptors and gut microbial communities, thereby influencing glucose homeostasis, energy expenditure, and neuroendocrine signaling. Once secreted into the intestinal lumen, primary bile acids such as cholic acid and chenodeoxycholic acid undergo microbial biotransformation through processes like dehydrogenation, deconjugation, and dihydroxylation to form secondary bile acids including deoxycholic and lithocholic acid. This microbial conversion dynamically alters the bile acid pool, shaping systemic metabolic and neurological outcomes.

Recent studies demonstrate that bile acids can enter systemic circulation and, in specific forms, cross the blood–brain barrier where they influence neuronal excitability and neurotransmission. They activate key receptors such as the farnesoid X receptor (FXR) and Takeda G-protein-coupled receptor 5 (TGR5), which are expressed in both intestinal and neural tissues. Through these receptors, bile acids modulate the secretion of glucagon-like peptide-1 (GLP-1) and fibroblast growth factor 19 (FGF19), linking gut-derived signals with central metabolic control. GLP-1, in particular, affects hypothalamic circuits involved in appetite regulation, glucose sensing, and cognitive function, thereby representing a critical conduit in the gut–liver–brain communication axis.

Disruptions in bile acid metabolism resulting from microbial dysbiosis, altered receptor sensitivity, or impaired enterohepatic circulation have been associated with a range of neurological and psychiatric conditions. Aberrant bile acid profiles have been reported in patients with Alzheimer's disease, multiple sclerosis, hepatic encephalopathy, and certain seizure disorders, indicating that bile acid imbalance may exacerbate neuroinflammatory and oxidative stress pathways. Experimental models further suggest that secondary bile acids may exert cytotoxic or neuroactive effects depending on their concentration and conjugation status. Thus, maintaining bile acid homeostasis appears essential for both metabolic and neural integrity.

Understanding the mechanistic interface between bile acids, gut microbiota, and brain signaling remains a developing frontier. Clarifying these pathways through well-designed human and animal studies—particularly those exploring circadian and fasting-related modulation could offer novel therapeutic opportunities. Interventions that modulate bile acid signaling, whether through probiotics, dietary modification, or FXR/TGR5 agonists, hold promise in regulating both metabolic and cognitive health, making bile acid metabolism a key mechanistic target within the microbiota–gut–brain axis.[37]

Emerging evidence indicates that alterations in bile acid metabolism are closely linked to neurodegenerative processes, particularly in Alzheimer's disease (AD). Secondary bile acids have been detected in postmortem brain tissues and cerebrospinal fluid of individuals diagnosed with AD, suggesting that these metabolites can cross or disrupt the blood–brain barrier. Elevated concentrations of hydrophobic secondary bile acids, such as deoxycholic acid (DCA) and lithocholic acid (LCA), are believed to exacerbate oxidative stress and mitochondrial dysfunction, thereby contributing to neuronal injury and cognitive decline. Magnetic resonance–based imaging and metabolomic analyses further associate these elevations with structural and functional brain changes, including hippocampal atrophy and reduced cortical connectivity.

Conversely, a marked reduction in primary bile acids, particularly cholic acid (CA has been reported in AD patients compared to age-matched controls. The diminished CA/DCA ratio reflects impaired hepatic synthesis and enhanced microbial conversion, pointing toward gut dysbiosis as a potential driver of altered bile acid composition. Elevated levels of glycine- and taurine-conjugated secondary bile acids, such as

glycodeoxycholic acid (GDCA) and taurodeoxycholic acid (TDCA), have also been documented, implicating conjugation pathways in modulating neurotoxicity and inflammation. These metabolites may activate bile acid–sensitive receptors, including FXR and TGR5, within the brain and peripheral nervous system, leading to dysregulation of metabolic and inflammatory signaling cascades.

Collectively, these findings suggest that an imbalance between primary and secondary bile acids could serve as both a biomarker and mechanistic contributor to AD pathology. The gut–liver–brain axis, modulated by microbial bile acid metabolism, represents a critical target for future interventions aimed at restoring metabolic and neurochemical equilibrium. Longitudinal and fasting-related studies that integrate gut microbiota sequencing, bile acid profiling, and cognitive assessments are required to clarify the causal pathways linking bile acid dysregulation to Alzheimer's-related neurodegeneration[32]

The Integrity of the Intestinal Barrier:

The gastrointestinal mucosa is essential for preserving overall bodily health by maintaining the intestinal barrier's integrity. This barrier consists of three primary elements: the gut microbiota, the mucosal lining, and the tight junctions. Tight junctions are structures made up of transmembrane proteins that link neighboring cells, particularly near the flexible epithelial surface. Studies have explored how the intestinal lining and these tight junctions influence the function of the human nervous system. The intestinal mucosa, which forms the innermost layer of the gut, includes the epithelium, lamina propria, and muscularis mucosa. It houses specialized cells such as absorptive epithelial cells, Paneth cells, goblet cells, and enteroendocrine cells, all of which contribute to the barrier's strength. Goblet cells secrete mucin, forming a mucus layer that acts as a protective gel-like shield, preventing the movement of solutes and water and safeguarding epithelial cells from harmful gut contents. In neurology, researchers have suggested a connection between Alzheimer's disease and specific pathogens—like herpes simplex virus type 1, Chlamydophila pneumoniae, and Porphyromonas gingivalis—which may breach weakened barriers (both gut and blood–brain), access the central nervous system, and trigger inflammation that damages neurons[38]

Studies have confirmed that practicing fasting for one month can lead to improvements in anxiety-related behavior in db/db mice over the course of a three-month observation period. In addition, enhancements in the length of intestinal villi in goblet cells and thickening of the intestinal muscle layer were reported. The findings further suggested that intermittent fasting could influence gut function by lowering levels of lipopolysaccharides in the bloodstream. In similar animal studies, four-month-old db/db mice that underwent alternate-day fasting for seven months showed elevated levels of intestinal mucin, increased populations of goblet cells and villi structures, along with a reduction in peptidoglycans found in the blood.

Together, this evidence implies that intermittent fasting may contribute positively to the protection and maintenance of the intestinal barrier. Additionally, short-chain fatty acids (SCFAs) are a vital energy source for epithelial cells in the intestines and are known to encourage their growth and development. They also help to prevent epithelial cell death and play a key role in supporting the function and structure of the intestinal mucous layer, preserving barrier integrity.[32]

Vagal Nerve Signal:

The internal neural circuitry of the gastrointestinal tract (GIT) is tightly regulated by the autonomic nervous system. The sympathetic nervous system generally inhibits gut motility and mucosal secretions while enhancing blood flow through vasoconstrictive control. In contrast, the parasympathetic nervous system, particularly through the vagus nerve, exerts more precise control over digestive processes governing stomach motility, intestinal peristalsis, and pancreatic enzyme secretion.

While gut microorganisms communicate with the host via endocrine, immune, and metabolic pathways, their most profound neurological influence occurs through the vagus nerve, the principal conduit linking the gut and the brain. Structurally, the vagus nerve comprises approximately 80% afferent (sensory) and 20% efferent (motor) fibers. The afferent fibers transmit gut-derived microbial signals to the central nervous system (CNS), mediating a bidirectional regulatory feedback known as the microbiota–gut–brain axis.

Microbiota-derived signals are transmitted not as direct neural impulses, but through bioactive metabolites and epithelial-mediated signaling molecules, including short-chain fatty acids (SCFAs), gastrointestinal hormones, and regulatory peptides. Key compounds such as neuropeptide Y (NPY), peptide YY (PYY), pancreatic polypeptide, cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1), adrenocorticotropic hormone (ACTH), oxytocin, and agouti-related peptide (AgRP) facilitate communication between intestinal microbes and the CNS. These molecular messengers collectively regulate appetite, stress responses, mood, and cognitive performance.

Experimental findings have demonstrated the critical role of vagal signaling in maintaining this microbiota–brain communication. In animal models subjected to vagotomy (surgical severance of the vagus nerve), microbial metabolite signaling is disrupted, resulting in the abolition of behavioral and physiological responses normally induced by gut microbiota. This confirms that the vagus nerve serves as a primary bidirectional conduit for transmitting sensory information from the gut to the brainstem, influencing both emotional and cognitive functions.

Notably, administration of the probiotic *Lactobacillus reuteri* has been shown to improve social behavior and stress-related phenotypes in mouse models with genetic or idiopathic neurological deficits. However, these beneficial effects were absent in vagotomized animals or those lacking oxytocin receptors, confirming

that vagus nerve integrity and oxytocin signaling are indispensable for microbiota-mediated behavioral modulation.

Emerging evidence further suggests that intermittent fasting (IF) can reshape the gut gut microbiota and modulate vagal activity by altering microbial metabolite composition. Fasting-induced enrichment of SCFA-producing taxa such as Bacteroides, Clostridium, and Ruminococcus may enhance vagal afferent activation, thereby influencing neuroplasticity, stress regulation, and cognitive resilience. Collectively, these findings underscore the vagus nerve's central role in linking gut microbial metabolism with CNS function, offering novel therapeutic implications for neurological and mood disorders through dietary and microbial interventions.[32,39,40]

PGC1α:

A mouse-based study identified a transcriptional regulator essential for mitochondrial biogenesis, which significantly contributes to the formation of synapses in the hippocampus and the long-term stability of dendritic spines in hippocampal dentate granule neurons. This regulator enhances oxidative phosphorylation, facilitates the import of proteins into mitochondria, and promotes mitochondrial DNA transcription. These combined actions result in an increased number of mitochondria, thereby improving the function of newly formed synapses. In a recent 28-day experiment, diabetic mice subjected to intermittent fasting showed a significant elevation in the expression of PGC1α and mitochondrial biogenesis. These molecular changes were associated with improved spatial learning and memory, as evaluated by the Morris water-maze test. Furthermore, PGC1α was also found to play a role in stimulating the expression of brain-derived neurotrophic factor (BDNF), which supports cognitive performance.[41,42]

SIRT3:

Sirtuin 3, a deacetylase dependent on NAD+, plays a critical role in maintaining mitochondrial function by modulating a wide array of metabolic and non-metabolic enzymes, especially under stressful conditions. Disruption in Sirtuin activity has been associated with the onset of age-related illnesses, including neurodegenerative diseases, as demonstrated in mouse studies. Enhancing NAD+ levels has shown beneficial effects, restoring mitochondrial balance and promoting overall health in such models. Likewise, overexpression of SIRT3 offers neuroprotective benefits. Experiments involving both wild-type and SIRT3-deficient mice revealed that prolonged fasting led to reduced secretion of the pro-inflammatory cytokine IL-1β only in wild-type mice, while this effect was not evident in the knockout group. SIRT3 was found to suppress the NLRP3 inflammasome by activating superoxide dismutase 2. Furthermore, in individuals with obesity, SIRT3 gene expression was observed to decrease after Ramadan fasting compared to non-obese participants. Since inflammation can elevate

Sirtuin levels, researchers proposed that this reduction in SIRT3 expression might reflect an overall shift in the balance of inflammatory and anti-inflammatory markers during intermittent fasting in Ramadan.[41,43,44]

mTOR and Autophagy:

The mammalian target of rapamycin (mTOR) is a key kinase responsible for regulating protein synthesis in cells in response to changes in glucose and amino acid levels. When nutrients are abundant, mTOR is activated, promoting the synthesis of proteins and lipids, which shifts the cell into a "growth state." Conversely, during periods of nutrient scarcity or fasting, mTOR activity is suppressed, leading to the initiation of autophagy, a process that helps cells maintain energy balance and remove damaged components.[41]

Autophagy is a cellular mechanism involving the lysosomal system that is essential for eliminating dysfunctional proteins and organelles. It also supports the renewal of cellular membranes and assists in vesicle transport. Without effective autophagy, abnormal or damaged proteins accumulate, a characteristic common in many neurodegenerative conditions. Fasting activates autophagy, and this process is believed to offer neuroprotective benefits, particularly by limiting the progression of neurodegenerative disorders through cellular cleanup and maintenance.[45]

Conversely, suppression of the lysosomal pathway may elevate the likelihood of neurodegenerative conditions, as seen in research involving mice lacking the Atg5 gene, where progressive motor dysfunction emerged due to cytoplasmic inclusion bodies and neuronal aggregates. Based on this evidence, the influence of the autophagy-lysosome system has also been explored in Alzheimer's disease mouse models. Hyperactivation of the mTOR signaling pathway appears to be linked with several neurological disorders such as epilepsy, autism spectrum disorders, multiple sclerosis, and Parkinson's disease. Therefore, controlling mTOR activity through dietary strategies like fasting may present a promising therapeutic direction for these disorders. Nonetheless, current research remains limited, and further investigation is necessary to understand the neuroprotective potential of fasting-triggered autophagy in such conditions.[41,46]

Fibroblast Growth Factor 2 (FGF2):

Fibroblast Growth Factor 2 (FGF2) belongs to the fibroblast growth factor family and is recognized for its broad mitogenic, angiogenic, and neurotrophic properties. Although present in low amounts across various tissues, its concentration is notably higher in the central nervous system. FGF2 is involved in several key biological functions, including promoting neural stem cell growth, ensuring neuronal survival during brain maturation, and shielding neurons from oxidative injury. Significant neuronal loss in several layers of the motor cortex has been noted in FGF2-deficient mice. A study showed that mice subjected to intermittent fasting for 4–5 months prior to induced stroke exhibited reduced brain injury and elevated FGF2 levels in the

cortex and striatum, suggesting fasting-induced FGF2 may offer neuroprotection and enhance recovery post-stroke.[41,47,48]

Gamma-Aminobutyric Acid (GABA)

In the mammalian brain, gamma-aminobutyric acid (GABA) functions as the primary inhibitory neurotransmitter, playing key roles in managing neuronal excitability, facilitating information flow, coordinating neuronal activity, and supporting neuroplastic changes related to learning and memory. GABA also modulates how neural networks react to external stimuli by activating mechanisms involved in structural and functional brain changes, including synapse formation, long-term potentiation, and long-term depression, essential for neuroplasticity. Upon receptor binding, GABA initiates signaling cascades that involve transcription factors such as CREB and NF-κB, promoting gene expression linked to cellular stress resistance, notably brain-derived neurotrophic factor (BDNF). During fasting, the production of ketone bodies enhances GABA levels, which may support the brain's adaptive processes under nutrient-limited conditions.[41,49]

Ghrelin:

During fasting, -P/D1 cells in the stomach and epsilon cells in the pancreas release a hormone known as ghrelin. This hormone triggers appetite by interacting with receptors in the arcuate nucleus. Ghrelin also supports brain health by enhancing neuroplasticity, limiting neuronal death, and promoting cell survival within the central nervous system. In addition, it activates serotonergic neurons linked to the hippocampus, aiding memory formation and learning.[41,50]

Growth hormone (GH) or somatotropin:

Growth hormone is a peptide hormone secreted by somatotropic cells in the anterior pituitary gland. It functions as an anabolic hormone, promoting growth, cellular regeneration, and reproduction. Its primary role is to support linear growth during developmental years. Most of its physiological actions are mediated through insulin-like growth factor 1 (IGF-1), synthesized in the liver. By enhancing amino acid uptake and stimulating transcription and translation, GH via IGF-1 significantly boosts protein synthesis in the body.[51]

GH also decreases protein catabolism by mobilizing fatty acids from adipose tissue and converting them into acetyl-CoA, providing energy to cells and exerting a protein-sparing effect that supports growth and development. Beyond its metabolic roles, GH has neuroprotective effects, improving learning, memory, and cognitive performance, particularly in individuals with growth hormone deficiency–related cognitive impairment. Its secretion is stimulated by growth hormone–releasing hormone and inhibited by somatostatin.

Comparative studies show that intermittent fasting enhances GH secretion and preserves lean body mass more effectively than simple caloric restriction, likely due to prolonged fasting-induced metabolic adaptation.[41] IGF-1 acts as a neurotrophic factor that promotes neuroplasticity and protects neurons against metabolic and oxidative stress. Evidence suggests that fasting may reduce circulating IGF-1 levels while simultaneously increasing IGF-1 receptor sensitivity, thereby amplifying its net neuroprotective and metabolic benefits.[52,53]

Preclinical models further demonstrate that fasting elevates neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and modulates key pathways including SIRT3 activation and mTOR inhibition, contributing to enhanced neuroplasticity and autophagy.[22] However, human studies exploring these molecular changes during Ramadan fasting or other intermittent fasting regimens remain limited. Longitudinal clinical trials integrating genetic and epigenetic profiling are warranted to clarify inter-individual variability in fasting-induced hormonal and cognitive responses.

Gut Microbiota effect in Ramadan Fasting (R-F)-Mediated Neuroprotection in Neurological disorders

Gut microbiota includes bacteria, archaea, and eukarya that reside in the GI tract. As mentioned earlier, these microorganisms have distinctive roles in the body and are very essential for human health. During fasting, these microorganisms are modulated and the number of good microorganisms like *Akkermansia muciniphila* and Bacteroidetes are augmented. Alongside this, the proinflammatory microbes are downregulated. These modifications improve the expression of brain-derived neurotrophic factor (BDNF), which promotes neuronal health, lower systemic inflammation, and strengthen the integrity of the intestinal barrier.[54,55] This section will explore the effect of fasting-induced modulation of gut microbiota on different neurological disorders:

Alzheimer's Disease

In Alzheimer's disease, a person's memory, thinking, and behavior are altered. Chronic diseases like uncontrolled blood pressure, and hearing loss can contribute to Alzheimer's disease. Moreover, factors like physical inactivity, poor diet, smoking, and alcohol consumption can be causative agents.[56]

According to research performed on the mice's model, the effect of intermittent fasting was analyzed. According to the research findings intermittent fasting can promote the production of beneficial probiotics, such as *Lactobacillus*. Intermittent fasting increases the amounts of certain amino acids like sarcosine and dimethylglycine, while reducing the body's use of carbohydrates, like glucose. These changes affect how the brain works through the gut-microbiota-metabolites-brain axis. This shows that IF is a hopeful way to slow the progression of AD and provides a new way to treat the disease.[57]

Parkinson's Disease (PD)

It is a brain anomaly in which the patient suffers from uncontrolled and unplanned bodily movements. It

happens because of the difficulty in maintaining the body's balance and movement coordination. Patients can have muscle stiffness and can experience trouble walking and talking when the disease has progressed. Brain cells of PD patients contain alpha-synuclein. These are the abnormal clumps of protein.[58]

It is known that brain-derived neurotrophic factor (BDNF) helps dopaminergic neurons survive. Research was conducted on mice that were kept on a dietary regimen of 3 days of fasting in a week. This routine was followed for three weeks. The results depicted that BDNF levels were increased in PD mice after being on FMD, showing an involvement of BDNF in FMD-mediated neuroprotection. Additionally, FMD suppressed neuro-inflammation by reducing the number of glial cells and the release of TNF-α and IL-1β in PD mice.[59,60]

Huntington's Disease (HD)
It is an inherited disease in which a part of the brain stops working overtime. The symptoms usually appear between 30 to 50 years of age. The disease becomes fatal once it gets prolonged for 30 years. Patients represent issues in concentration and memory recall. They can also experience depression, involuntary jerking, and difficulty in swallowing, breathing, and speaking.

In Huntington's disease, there is abnormal aggregation of a protein that is known as mutant Huntington protein (mHTT). It has been researched that time-restricted eating (TRE) dietary patterns can be used as a treatment plan for these patients. This diet is one of the forms of intermittent fasting that allows eating in a specific time window. It is found that at the physiological level, TRE may improve mitochondrial function and stress-response pathways. It also amplifies the clearance of mHTT.[61–63]

Multiple Sclerosis (MS)
Multiple sclerosis (MS) is an unpredictable chronic disease. The symptoms may vary from mild to extreme. In this autoimmune disease, the myelin sheath of the neurons is disrupted. Due to this, abnormal neuronal signals are generated.

It is proven that intermittent fasting (IF) lowers axonal and myelin sheath damage. Axons are the nerves that carry the neural messages and myelin sheath is the protective layer of the nerve. Observing IF increases the production of healthy gut microbiota like Lactobacillaceae, Bacterioidaceae, and Prevotellaceae. These microbes have a neuroprotective role. Furthermore, the antioxidant activity is strengthened by IF-induced microbiota alterations. Additionally, IF changes the composition of intestinal T cells by increasing regulatory T cells and decreasing IL-17-producing T cells.[20,60,65]

Ischemic Stroke
Ischemic stroke occurs when the blood flow to the brain is obstructed or stopped. It is a life-threatening health condition. Ischemic stroke patients need to be admitted to the emergency at the earliest.[64]

According to studies, it is found that intermittent fasting (IF) has positive effects on ischemic stroke. It halts the tissue damage and also increases the life expectancy of the individuals. In a clinical trial, a mouse was given a four-month IF regimen (16-hour fasting). The results reported that the pro-inflammatory cytokines in the brain and peripheral organs. The lowered cytokines were NLRP1, NLRP3, IL-1β, and IL-18. IF also decreased NF-kappa B and MAPK signaling.[65]

Epilepsy
Epilepsy is a chronic neurological condition characterized by recurrent seizures resulting from abnormal, excessive electrical discharges in groups of neurons within the brain. These episodes can manifest with varying severity from brief lapses in awareness to prolonged convulsions and may involve loss of consciousness, involuntary muscle contractions, urinary incontinence, or transient respiratory difficulty. The disorder's multifactorial pathophysiology involves genetic predisposition, altered neurotransmitter activity, ion-channel dysfunction, and metabolic stress that disrupt neuronal stability.

The relationship between fasting and epilepsy has been a topic of clinical and experimental investigation, particularly in the context of Ramadan fasting among Muslim individuals with controlled epilepsy. Observational studies report that, for most patients adhering to prescribed antiepileptic medications and maintaining proper hydration and sleep schedules, Ramadan fasting (from dawn *Fajr* to sunset *Maghrib*) is generally well tolerated without exacerbating seizure frequency. The underlying mechanisms are thought to mirror aspects of the ketogenic diet where metabolic shifts toward increased ketone body production and reduced glucose availability may promote neuronal energy stability and enhance GABAergic inhibitory tone. Furthermore, intermittent fasting has been shown to modulate neuroinflammatory pathways and increase neuroprotective metabolites such as indole-3-propionic acid, a microbial tryptophan derivative with antioxidant and antiapoptotic properties.

However, fasting-induced metabolic stress can also increase seizure susceptibility in certain vulnerable individuals, particularly those with poorly controlled epilepsy, polytherapy regimens, or disrupted sleep patterns. Therefore, clinical guidance emphasizes individualized medical assessment before Ramadan, careful timing of medication doses, and monitoring of seizure activity. The observed biochemical benefits, while promising, require confirmation through controlled human trials with standardized fasting parameters.[65]

Perioperative Neurocognitive Dysfunction (PND)
PND can be categorized as postoperative delirium or postoperative cognitive dysfunction. PND in patients who had a preexisting cognitive decline. Patients' cognitive abilities are also affected by the administration of the anesthesia. As, a result the recovery time of patients is prolonged. Moreover, the patients might face difficulty in recalling their memory for some time after surgery.[66] There is limited evidence available on the potential benefits of Ramadan fasting on PND individuals.

Discussion and Conclusion:

This review highlighted the relationship between Ramadan fasting and modulation of the gut microbiota. Significant research has emphasised the neuroprotective role of fasting in neurological disorders. It is found that systemic inflammation is reduced significantly by the increase in healthy gut microbiota. Moreover, the increase in the expression of brain-derived neurotrophic factor (BDNF), improved gut barrier function, and gut-brain axis modulation have all been linked to the restructuring of microbial communities. This modulation is indicated by an increase in beneficial microbiota like Akkermansia muciniphila, Bacteroidetes, and Lactobacillus [67]. According to a pertinent pilot study, it is deduced that the Islamic fasting of 17 hours for 29 days causes an increase in gut population of Akkermansia muciniphila and Bacteroides fragilis.[68]

Recent studies indicate that intermittent fasting (IF) can mitigate the progression of neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, Huntington's disease, multiple sclerosis, and ischaemic stroke. Fasting regimens (R-F and NR-IF) have been shown to beneficially modify gut microbiota composition, enhance mitochondrial biogenesis, regulate inflammatory responses, and optimise autophagy processes essential for the elimination of pathogenic protein aggregates, such as amyloid-β and mutant huntingtin protein.[69]

Recent studies indicate that Ramadan fasting may influence particular gut-derived metabolites, including short-chain fatty acids (SCFAS) and indole derivatives, recognised for their anti-inflammatory and neuroprotective properties.[70] Furthermore, changes in microbiota-mediated immune responses, including an elevation of regulatory T cells and a reduction in Th17 cell populations, emphasise the immunomodulatory advantages of fasting.[71] Clinical and cohort studies demonstrate that Ramadan fasting significantly reshapes microbial diversity, particularly by increasing beneficial taxa such as Akkermansia muciniphila and Lactobacillus species, while enhancing autophagy-related gene expression in overweight populations. Furthermore, systematic reviews comparing Ramadan to non-Ramadan intermittent fasting have highlighted distinct physiological and circadian impacts attributable to prolonged diurnal abstinence from both food and water. These findings underscore the importance of distinguishing Ramadan fasting from generic intermittent fasting when evaluating effects on cognition and neuroprotection.[72–75]

Nonetheless, despite these encouraging findings, various restrictions persist. A substantial amount of information originates from preclinical investigations in rodent models, but human trials are very scarce and varied in design. Variations in fasting duration, dietary composition during non-fasting intervals, and individual gut microbiota baselines may all affect outcomes. Moreover, there is an absence of research utilising multi-omics methodologies (e.g., metagenomics, metabolomics, transcriptomics) to comprehensively clarify the mechanistic pathways connecting fasting, microbiota, and cerebral health.

An intensive research on the title has suggested that there are still some loopholes in this study domain. It proposes that future research should include large-scale, longitudinal clinical trials that use well-controlled fasting protocols so that precise results can be calculated. Moreover, for improving translation relevance, it is suggested to include different populations of distinctive age groups. Besides this variable for sex and metabolic status, and cognitive function should also be included.

Additionally, personalised nutrition methods and advanced gut microbiota profiling technologies (e.g., metagenomics, metabolomics) may optimise fasting interventions specific to gut microbiota compositions. Personalised methods could detect responders and non-responders, improving efficacy and safety. Furthermore, investigating the synergistic effects of fasting in conjunction with probiotic or prebiotic treatment may reveal innovative therapeutic approaches for the prevention or management of neurological disorders.

Ramadan fasting differs from other forms of intermittent fasting due to unique confounders that may influence outcomes. Prolonged daytime abstinence from fluids can contribute to mild dehydration, which interacts with circadian rhythm changes and fragmented sleep patterns to affect metabolism, cognition, and mood. In addition, caloric intake is shifted to nocturnal hours, often concentrated in large meals at iftar and suhoor, altering energy distribution, insulin sensitivity, and gastrointestinal function compared to evenly spaced feeding schedules. Caffeine withdrawal during daylight hours can further confound assessments of alertness, fatigue, and cognitive performance, particularly in habitual consumers.

Safety considerations are also essential, particularly among vulnerable populations. Individuals with chronic conditions such as diabetes or cardiovascular disease may face elevated risks if fasting is not carefully managed, as shown in the EPIDIAR study and related guidelines. Age, BMI, sex, and baseline metabolic status can further moderate fasting responses, emphasizing the need for individualized guidance and supportive lifestyle strategies. Overall, these contextual factors highlight the importance of interpreting Ramadan fasting outcomes with caution, as physiological effects may not fully align with other intermittent fasting regimens.

This research paper has highlighted a newly-fangled non-pharmacological technique to increase the healthy gut microbiota population that will leave a positive impact on the brain's health. The gut-brain axis is an important pathway that can be modified to treat patients with neurological disorders. Furthermore, there is a dire need for more in-depth research and clinical trials that work through a multidisciplinary approach, including neurology, nutrition science and microbiology. This diverse research will unravel facts that can be further employed in clinical practice and public health policies.

Preclinical evidence underscores fasting as a promising intervention for cognitive health via gut gut microbiota and molecular pathway modulation. However, human data remain insufficient to fully validate these mechanisms or to generalize benefits. Future research must emphasize multi-omics longitudinal cohort studies and randomized trials to unravel complex host-microbe-brain interactions during fasting. Integrating genomics, proteomics, metabolomics, and detailed clinical phenotyping will drive precision nutritional strategies leveraging fasting for neurological health.

Safety and Heterogeneity of Responses

Ramadan fasting and other intermittent fasting regimens may elicit diverse physiological and cognitive responses across individuals. These variations depend on age, sex, BMI, metabolic status, comorbidities, and baseline dietary habits. Clinical observations indicate that older adults, individuals with diabetes, cardiovascular disease, or renal impairment require individualized medical assessment and supervision prior to fasting. The EPIDIAR study and subsequent clinical guidelines emphasize the need for careful glucose monitoring, hydration strategies, and medication adjustment during fasting.

Heterogeneity in fasting outcomes is further influenced by hormonal status, circadian rhythm variability, and gut microbiota composition. For example, younger and metabolically healthy individuals often exhibit enhanced insulin sensitivity and neurocognitive benefits, whereas those with metabolic syndrome may experience transient fatigue or altered glucose regulation. Future research should adopt a precision-medicine approach that accounts for sex-based and metabolic differences, ensuring both efficacy and safety. Ethical research design must also prioritize inclusion of diverse populations to generalize findings beyond specific cultural or regional settings.

Knowledge Gaps and Research Priorities

Despite growing evidence on the gut–microbiota–brain axis and the metabolic benefits of Ramadan fasting, significant knowledge gaps remain. Addressing these gaps will be essential to advance translational understanding and clinical implementation:

- Future studies should combine metagenomics, metabolomics, transcriptomics, and proteomics to comprehensively map fasting-induced molecular and microbial interactions.
- Extended follow-up of participants across multiple Ramadan cycles and outside of Ramadan will clarify long-term impacts on cognition, metabolism, and microbiota resilience.
- Well-designed RCTs incorporating cognitive and neurobehavioral endpoints are required to establish causal relationships between fasting and neurocognitive outcomes.
- Inter-individual variability in fasting responses must be explored through stratification by age, sex, BMI, metabolic status, and gut microbiota baseline profiles.
- Comparative fasting paradigms: Direct comparisons between Ramadan and non-Ramadan intermittent fasting regimens will help disentangle the effects of circadian timing, hydration, and cultural dietary patterns.
- Emerging tools such as machine learning and microbiome analytics should be applied to identify biomarkers predictive of fasting benefits or risks.

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Supplementary Material

Database-Specific Search Strings, Filters, and Run Dates

Supplementary Material provides the complete, database-specific search strings, Boolean operators, filters, and final search run dates.

PubMed: ("Ramadan fasting" OR "Ramadan intermittent fasting" OR "dawn-to-dusk fasting") AND ("gut microbiota" OR "microbial diversity" OR "metabolites") AND ("cognitive function" OR "neuroprotection" OR "circadian rhythm" OR "sleep" OR "brain-derived neurotrophic factor" OR "BDNF");

Filters: Humans, English, 2000–2025. Final run date: 30 June 2025.

Scopus: TITLE-ABS-KEY ("Ramadan fasting" AND "gut microbiota" AND "cognitive function") OR ("intermittent fasting" AND "microbiota" AND "BDNF"); limited to articles and reviews, 2000–2025.

Web of Science: TS=("Ramadan fasting" OR "intermittent fasting") AND TS=("gut microbiota" OR "metabolome" OR "cognitive function" OR "circadian rhythm"); publication years 2000–2025.

Google Scholar: "Ramadan fasting" AND "gut–brain axis" AND "microbiota" (first 200 results screened manually).