Ageing Research Reviews 121 (2026) 103245

Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Review article

Brain health across the lifespan and the impact of nutrition, exercise, microbiota, and sleep

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ARTICLE INFO

Keywords:
Brain
Diet
Aging
Physical exercise
Plasticity
Neurodegenerative disease
Health

ABSTRACT

Dietary strategies that support long-term cognitive health and resilience against neurodegenerative diseases are important with aging and senescence. Brain aging is a consequence of intricate biological changes that occur over the lifespan. The process of aging involves the decline in metabolic and physiologic functions, and changes in anatomical structure. However, our lifestyle practices, including diets and nutrient intakes, physical exercise, sleep quality, and cognitive activity can help to minimize the aging effects on the brain. Furthermore, neurodegenerative diseases often have detrimental effects on brain neurons, that show gradual damage leading to compromised cognitive function and impaired body movement. Our review describes the biochemical and physiological changes in brain with advancing age. We introduce several aspects of nutrients (lipids, glucose, vitamins, and protein), dietary factors (flavonoids), and diet practices that afford benefits to reduce the effects of aging on the brain. In addition, many aspects of metabolic dysregulation of macronutrients are described in brain aging. Vital to the lifestyle factors that improve brain health and reduce or delay the negative effects on brain aging are physical exercise and sleep. The importance of brain-derived neurotrophic factors, exerkines, and endocannabinoids are described. Herein is a concise overview of the aging brain, role of nutrition in brain health, importance of nutrition in aging and senescence of the brain, and the systemic actions of physical exercise on brain plasticity and health. Original research with models, clinical studies, and landmark reviews on the topic are cited in our novel and comprehensive approach to nutrition the aging brain.

1. Introduction overview of brain aging, neurodegeneration, and nutrition

We live in the era of scientific and medical advancements that have helped promote healthier lives and longevity. Current lifespan in countries ranges from 79 to 85 years of age and 61–75 years in developing countries, an increase of 15 years from the average life expectancy 50 years ago(Worldometer, 2025). However, as we live longer, we are more susceptible to the consequences of brain aging. Aging and senescence are associated with the prevalence of cardiometabolic diseases [metabolic dysfunction-associated fatty liver disease (MAFLD)], kidney disease, heart diseases, obesity, and type 2 diabetes (T2D). These chronic diseases are on an increasing trajectory and risk for accelerating brain aging and promoting neurodegeneration.

Brain aging refers to physiological and natural changes that occur in a person's brain as a function of age. The multifaceted process of brain

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https://doi.org/10.1016/j.arr.2026.103245
Received 9 December 2025; Received in revised form 26 June 2026; Accepted 4 July 2026
Available online 7 July 2026

aging involves gradual alterations in the brain biochemistry and structure as one gets older. The process in brain is characterized by reduced synaptic connectivity and myelination, lower neurotransmission, decreased cerebral blood flow, neuronal loss, cortical atrophy, and enlarged ventricles, among other events(Blinkouskaya et al., 2021). Collectively older adults demonstrate a decline in cognitive, motor, and autonomic function that slowly disrupts their learning and memory, decision-making, and alter physiological systems such as those related to immunity and energy balance. The troubling fact is that there is an ever-increasing prevalence of accelerated and pathological brain aging we call neurodegeneration which is evident throughout the world.

Multiple biological factors linked to metabolic and physiological functions contribute to the aging brain and the development of neurodegenerative diseases like Alzheimer's disease (AD) and Parkinson's disease (PD) (Fig. 1). Hence research that targets these changes in the aging brain will likely explain mechanisms at the molecular and cellular levels responsible for organ decline and could serve to help protect and conserve brain function and perhaps delay the progression of neurodegenerative disorders.

Neurodegenerative diseases can be defined as brain conditions in which neurons progressively become damaged and die that result in severely impaired critical thinking, memory, and movement(Gadhave et al., 2024). Although brain aging and neurodegenerative diseases share key cellular and anatomical abnormalities, the latter is differentiated by the severity and the accelerated pathological features. AD that causes dementia is the most common neurodegenerative disease followed by PD. Other major types of neurodegenerative diseases include amyloid lateral sclerosis (ALS), multiple sclerosis (MS), Huntington's disease, and dementia disorders like vascular dementia, Lewy Body dementia, and Frontotemporal dementia(Wilson et al., 2023). Most of these neurodegenerative diseases are progressive and irreversible without any cures. About 57 million individuals worldwide were diagnosed with dementia in 2021 and the number is projected to triple by 2050 with trillions of dollars on healthcare expenditures (Organization, 2025). This is an immense burden on the healthcare system around the world. The quality of life of older individuals with dementia is severely impacted by memory loss, and they are unable to care for themselves and rely on assisted living and the support of caregivers and family members. While aging is the most significant non-modifiable risk factor for dementia, especially AD, a host of disease-modifiable risk factors such as obesity, diabetes, diet, hypertension, alcohol consumption, and smoking are known to substantially impact vulnerability as well as resistance to neurodegeneration and dementia(Livingston et al., 2020).

An important aspect of human biology is the dynamic nature of response to lifestyle factors that can reduce disease and importantly conserve the physiology of systems and organs. The lifestyle factors that can improve brain health are diet, nutrients, physical exercise, and sleep (Mattson and Arumugam, 2018; Puri et al., 2023). Moreover, Flanagan and colleagues (Flanagan et al., 2020) described several benefits of dietary factors and exercise on the ageing brain. They report that some B vitamins and certain omega−3 PUFA afford improvements in cognitive function of older adults.

Our review goes beyond the content presented by Flanagan and others(Flanagan et al., 2020) and delves deeper into the human and animal model research regarding diet types, nutrients, and flavonoids, that support brain health. Furthermore, the role of exercise, sleep, gut microbiota, and actions of exerkines, endocannabinoids, and oxylipins in the brain are discussed. A recent review on multivitamin and mineral (MVM) supplements on ageing reports inconclusive findings(Wang et al., 2025). This is not a surprise because the individual essential nutrients have specific metabolic and/or physiological functions and would be difficult to ascertain in a MVM product(Wang et al., 2025). Therefore, we describe the current understanding of the actions of

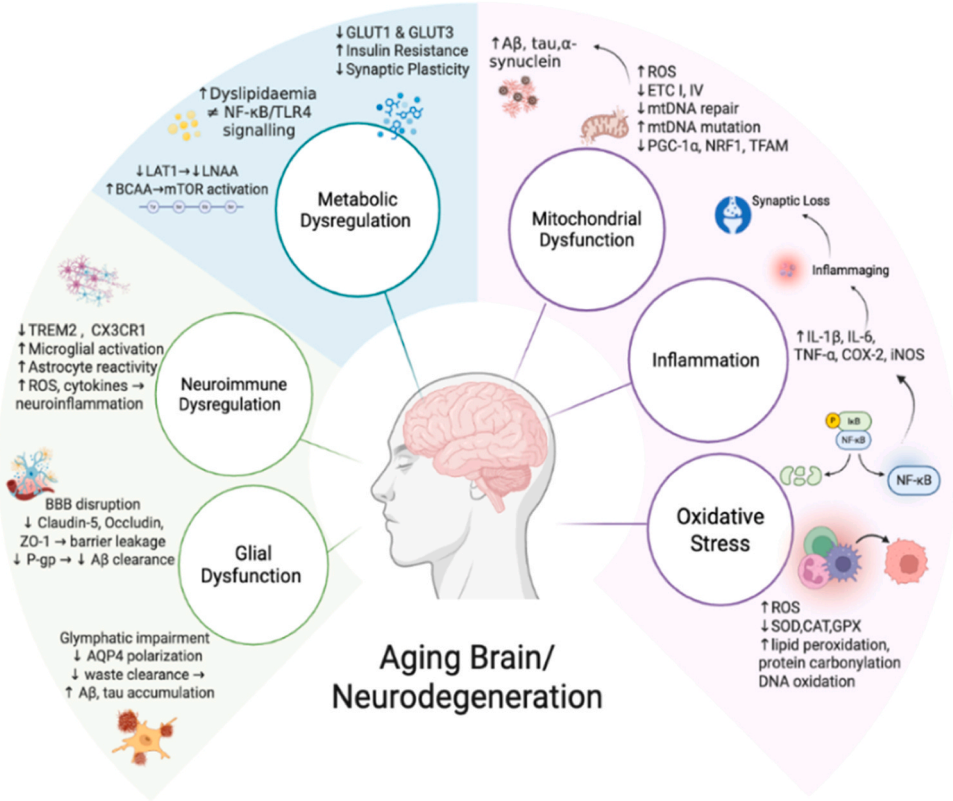

Fig. 1. Pathological changes in aging brain and neurodegeneration. Several interdependent central nervous system (CNS) dysfunctions are observed in the aging brain and are exaggerated in neurodegenerative disorders such as AD. Multiple pathological changes are temporally overlapping during the neurodegenerative progression, and currently the exact chronological order of each pathology or dysregulation is unclear.

nutrition in supporting brain health and delay of disease as a guide to begin comprehensive investigations of diets, nutrients, and plant bioactive factors, following lifestyle factors in a targeted approach for neurodegenerative disease.

In contrast to other reviews on nutrients and diets, we have integrated the metabolism and lifestyle factors that influence the health of the brain and how they delay the consequences on cognitive health and improve well-being. We introduce several aspects of nutrients (lipids, glucose, vitamins, and protein), dietary factors (flavonoids), and diet practices that afford benefits to reduce the effects of aging on the brain (Fig. 2). Many types of food support brain health, cognitive function (Puri et al., 2023), neuroprotection/neurophysiology(Ekstrand et al., 2021), and possess anti-inflammatory benefits(Watkins et al., 2025). Flavonoids have emerged as powerful anti-inflammatory factors in food to lower oxidative stress exerting actions in the gut microbiome and in vivo as well as support of the gut-brain axis(Chu et al., 2024; Taherkhani et al., 2025; Zhan et al., 2024). The findings on physical exercise and exerkine actions on brain are presented (Watkins et al., 2024). In addition, information on physical exercise actions on exerkines and their role in inter-organ communications on brain physiology are described (Watkins et al., 2024). Aspects of metabolic dysregulation of macronutrients are described in brain aging. Further, the importance of brain-derived neurotrophic factors, exerkines, and endocannabinoids are presented. Our objective is a concise overview of the aging brain, role of nutrition in brain health, importance of nutrition in aging and senescence of the brain, and the systemic actions of physical exercise on brain plasticity and health. Throughout we cite original research with models, clinical studies, and landmark reviews on the topics.

2. Rationale for focusing on nutrition as an important modifiable factor

Although aging of the body and brain is inexorable(von Bernhardi et al., 2015), the development of neurodegenerative disease is not a feature of the standard aging process. Many risk and protective factors for neurodegeneration exist, but the most unequivocal predictor is age itself(Niccoli and Partridge, 2012; Walters et al., 2016). Chronological age is a non-modifiable risk factor for neurodegenerative diseases (e.g., dementia), along with sex, ethnicity, and genetic predisposition (Armstrong et al., 2019; Burmistrov et al., 2024; Kuzma et al., 2018; Murphy et al., 1996; Wong et al., 2019). However, emerging evidence increasingly supports biological age as a more reliable risk factor for neurodegeneration than chronological age(Marseglia et al., 2025). Biological age and senescence is dynamically influenced by metabolic health status, metabolic demands such as physiological state and physical exercise(Watkins et al., 2024), nutrient intake, body composition, and energy balance(Liu et al., 2023; Mattson et al., 2018).

Body composition is the net reflection of dynamic nutrient intake, accretion, and energy expenditure(Chow and Hall, 2008), enabling the body to robustly modulate metabolic health status and link favorably with brain metabolism(Boa Sorte Silva et al., 2024; Haas et al., 2025; Samuelsson et al., 2025). However, in the case of exercise, inducing change across these domains of body constituents of substantial magnitude to benefit brain function is a slow and cumulative process, often requiring months or years of structured consistency, which is not always conducive to an aging population (Boa Sorte Silva et al., 2024; Hayden et al., 2018; Rapp et al., 2017). In contrast, there is potential to capture a detectable acute effect of macronutrient diet manipulation or bioactive compound exposure on markers of brain aging before downstream alterations in body composition or metabolic health status occur (Yassine et al., 2023). For instance, lipids play a particularly fundamental role in brain as major membrane components, lipids and fatty acids remodel plasma membrane and polyunsaturated fatty acid (PUFA) influence the types of oxylipins and endocannabinoids biosynthesized and thus their functions as signaling molecules(Watkins, 2018). Moreover, throughout life plasticity of the brain depends often on rapid changes in membrane lipids for adapting to learning and memory involving neuronal structure and function(Vaughen et al., 2023). These points underscore the utility of nutrition status as a paramount modifiable factor and target of intervention for new research to attenuate brain aging and modify neurodegenerative disease risk.

In older adults, good evidence indicates that folates are associated with reduced AD and dementia(Lefevre-Arbogast et al., 2016) and higher levels of homocysteine associated with cognitive decline and dementia (Smith and Refsum, 2016). Another aspect of nutrients is the findings of higher omega−3 PUFA eicosapentaenoic acid (EPA) in blood but not for docosahexaenoic acid (DHA) were associated with lower dementia risk(Neuffer et al., 2022; Samieri et al., 2008). However, randomized controlled trials (RCT) with omega−3 PUFA have yet to demonstrate omega−3 benefits on cognitive performance in older adults or those with cognitive impairment especially in cases of brain pathology(Yassine and Schneider, 2017). Future research in humans and in animal models should examine potential mechanisms where nutrients alter metabolism and physiology at the cell and tissue level.

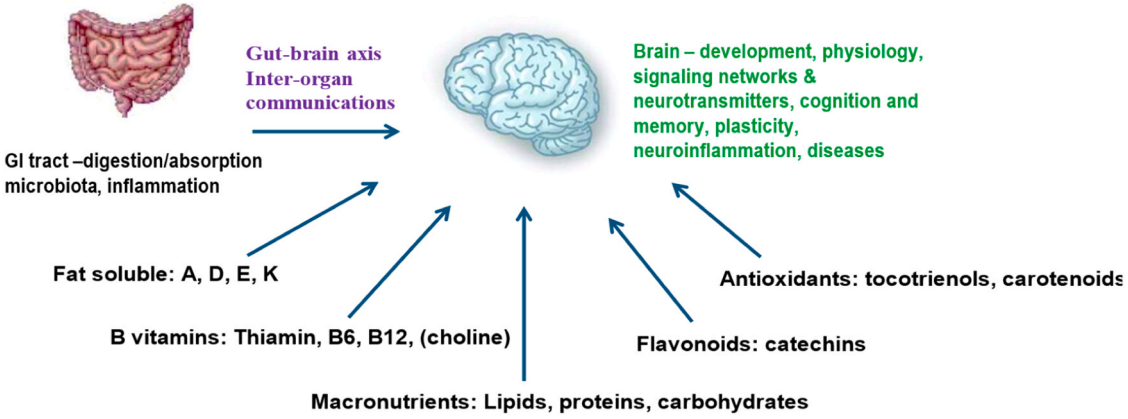

Fig. 2. Dietary nutrients and plant bioactives support brain metabolism and physiology throughout the lifespan for healthy aging. Antioxidant nutrients such as tocopherols, ascorbic acid, and many flavonoids are known antioxidants or possess antioxidant activity. Moreover, Cu and Zn also serve some role in antioxidant reactions to quench free radicals or regenerate antioxidant capacity. In addition, many of these nutrients and bioactives act as anti-inflammatory agents that lower neuroinflammation. In general, many B vitamins serve as co-enzymes supporting metabolic pathways, intermediary metabolism, and ATP production from the generation of reducing equivalents via mitochondrial processes for brain and inter-organ communications. The role of diet and nutrients to support the brain and protect against neurological disease is becoming of great research interest especially in older adults.

3. Mechanisms for brain aging and neurodegeneration: Impact of nutrition

3.1. Changes in brain plasticity during aging and the potential support by nutrition

The human brain maintains its ability to change and adapt in a process called plasticity throughout every stage of life instead of experiencing fixed deterioration(Faraji and Metz, 2024; Navakkode and Kennedy, 2024). Neural development happens through excessive growth, refinement, stabilization and reorganization, with synaptogenesis leading to synaptic pruning regulated by brain-derived neurotrophic factor (BDNF), PI3K/Akt, and MAPK/ERK signaling(Faraji and Metz, 2024; Navakkode and Kennedy, 2024). At an early stage of life rapid myelination increases signal transmission for better cognitive and motor functions. Synaptic elimination and prefrontal cortex maturation enable better executive function while maintaining high adaptability in adolescent brain(Navakkode and Kennedy, 2024). In adulthood, localized plasticity persists through synaptic modification, hippocampal neurogenesis, and BDNF-dependent network remodeling(Faraji and Metz, 2024). Aerobic exercise, enriched environments and metabolic optimization enhance BDNF signaling and maintain redox equilibrium (Navakkode and Kennedy, 2024). DHA also improves BDNF function in brain (Sugasini et al., 2019). Despite these adaptive mechanisms, aging shifts cellular equilibrium toward increased vulnerability. Neuroplasticity-supporting mechanisms become dysregulated with aging causing oxidative stress, mitochondrial breakdown, chronic neuroinflammation, and impaired bioenergetics(Lopez-Otin et al., 2013; Mattson and Arumugam, 2018). Antioxidant nutrients and anti-inflammatory dietary components may attenuate these damaging effects on the brain(Watkins et al., 2025). Many specific nutrient and diet actions on brain aging are presented in Table 1.

Table 1
Mechanisms underlying brain aging/neurodegeneration and the impact of nutrition.

Target	Nutrients/Diets	Human Pre/Clinical Findings	Animal Model Findings	References
Brain plasticity	Omega−3 PUFAs (DHA) Polyphenols (resveratrol, curcumin, flavonoids) Intermittent fasting B vitamins	↑ Circulating BDNF and cognitive scores with polyphenol nutraceutical (RCT) ↑ Vascular function and cognition in older adults (65–80 yr) with blueberry polyphenols (RCT) ↓ Brain atrophy by 30% with B-vitamin supplementation in elevated homocysteine (VITACOG RCT)	↑ Hippocampal BDNF via CREB signaling with intermittent fasting ↑ BDNF-TrkB signaling in aged hippocampus with DHA ↑ Nrf2 antioxidant defenses ↓ NF-κB inflammatory signaling with polyphenols	Wood et al., (2023); Carrillo et al., 2025; Alkurd et al., (2024); Mattson and Arumugam, (2018); Wen et al., (2024); Jalouli et al., (2025); Puri et al., (2022); Smith et al., (2010); Douaud et al., (2013)
Oxidative stress	Curcumin Resveratrol EGCG (green tea) Vitamins C & E Flavonoids Trace elements (Cu, Zn)	↓ Urinary CNS lipid peroxidation markers and ↑ episodic memory with 12-wk wild blueberry consumption (RCT)	↓ Hippocampal lipid peroxidation with curcumin in rats ↓ Protein carbonylation in PD models with resveratrol ↑ SOD and catalase activity via Nrf2 translocation with EGCG in neuronal cultures	Wood et al., (2023); Plascencia-Villa and Perry, (2023); Khan et al., (2010); Hao et al., (2024); Tang et al., 2025; Butterfield and Halliwell, (2019)
Neuroinflammation	Polyphenols (resveratrol, EGCG) Omega−3 PUFAs Melatonin	↑ Vascular function and cognition in older adults with blueberry (poly) phenols (RCT; anti-inflammatory component)	↓ Microglial activation and pro-inflammatory cytokines via Keap1/Nrf2/ARE with polyphenols ↑ Aβ clearance through glymphatic pathways and ↑ BBB integrity with omega−3 PUFAs Melatonin regulates glymphatic function during sleep	Jalouli et al., (2025); Norden and Godbout, (2013); Franceschi and Campisi, (2014); Heneka et al., (2013); Ren et al., (2017); Wen et al., (2024); Chen et al., (2025)
Mitochondrial function	Antioxidant vitamins (C, E, tocotrienols) Flavonoids Trace elements (Cu, Zn)	(Primarily supported by preclinical evidence; antioxidant vitamins and trace elements that support SOD protect against mitochondrial oxidative damage)	Aging weakens ETC complexes I and IV, reducing ATP and increasing ROS Antioxidant vitamins (C, E, tocotrienols) and Cu/Zn support SOD to protect against ETC-derived ROS ↓ PGC−1α, NRF1, TFAM with aging reduces biogenesis; impaired mitophagy allows damaged mitochondria to persist	Ng et al., 2025; López-Otín et al., 2023; Kerr et al., (2017); Watkins et al., (2025); Chu et al., (2016); Polis and Samson, (2024)
Glial cell function / Neuronal cell function	Omega−3 PUFAs (DHA) Melatonin Polyphenols	(Clinical evidence primarily indirect; dietary omega−3 and polyphenol intake associated with reduced neurodegeneration risk in cohort studies)	Omega−3 PUFAs promote Aβ clearance via glymphatic pathways and support BBB integrity Melatonin regulates AQP4-dependent glymphatic clearance during sleep ↓ Neurotoxic A1 astrocyte conversion with anti-inflammatory nutrients	Liddelow et al., (2017); Knox et al., (2022); Deo et al., (2014); Hablitz and Nedergaard, (2021); Mestre et al., (2022); Ren et al., (2017); Wen et al., (2024); Chen et al., (2025); Corbali and Levey, (2025)
Metabolic dysregulation	Mediterranean diet Ketogenic diet Omega−3 PUFAs (DHA) Olive oil, nuts, blueberry, curcumin B vitamins	↑ Insulin sensitivity and ↓ AD biomarkers with Mediterranean diet adherence 36% ↓ AD risk with high fish intake (meta-analysis) ↑ Circulating BDNF with polyphenol-rich nutraceutical (RCT) ↓ Brain atrophy by 30% with B-vitamin supplementation (VITACOG RCT)	Ketone bodies bypass impaired glucose transport in aging brain ↑ BDNF in brain with DHA supplementation ↑ BDNF in brain with olive oil, nuts, blueberry, and curcumin	Grammatikopoulou et al., (2020); Norwitz et al., (2019); Zhang et al., (2016); Sugasini et al., (2019); Carrillo et al., 2025; Smith et al., (2010); Douaud et al., (2013)

A randomized controlled trial (RCT) showed that polyphenols improved vascular function and cognition in adults aged 65–80(Wood et al., 2023). A polyphenol-rich nutraceutical significantly increased circulating BDNF and cognitive scores in healthy adults (Carrillo et al., 2025). Intermittent fasting upregulated hippocampal BDNF via CREB signaling in mice(Alkurd et al., 2024; Mattson and Arumugam, 2018), while DHA enhanced BDNF-TrkB signaling in aged mouse hippocampus (Wen et al., 2024). Dietary polyphenols such as resveratrol, curcumin, and flavonoids can partially counteract age-related oxidative stress and neuroinflammation, engaging Nrf2 antioxidant defenses while down-regulating NF-κB-driven inflammatory signaling(Jalouli et al., 2025; Puri et al., 2022).

3.2. Oxidative stress, neuroinflammation, and mitochondrial dysfunction

The brain consumes 20% of total body oxygen despite comprising only 2% of body mass, making it highly susceptible to oxidative stress (Butterfield and Halliwell, 2019). Mitochondrial oxidative phosphorylation produces reactive oxygen species (ROS) neutralized by superoxide dismutase (SOD), catalase, and glutathione peroxidase. Aging weakens these antioxidant defenses by increasing ROS, causing lipid peroxidation, protein carbonylation, and DNA oxidation(Butterfield and Halliwell, 2019). The hippocampus shows vulnerability, with elevated 4-hydroxynonenal (HNE) and 8-hydroxy−2′-deoxyguanosine (8-OhdG) (Dhapola et al., 2024). NF-κB activation links oxidative damage to neuroinflammation through IL-1β, IL-6, TNF-α, COX−2, and iNOS upregulation(Dhapola et al., 2024).

Dietary antioxidant vitamins and flavonoids protect against free radical damage in both central and peripheral nervous systems, supporting cognitive function and reducing neurodegeneration(Puri et al., 2022). Wild blueberry consumption for 12-week reduced urinary CNS lipid peroxidation markers and improved episodic memory in older adults(Wood et al., 2023). Curcumin suppressed hippocampal lipid peroxidation in rats(Plascencia-Villa and Perry, 2023), while resveratrol reduced protein carbonylation in PD models(Khan et al., 2010). Epigallocatechin gallate (EGCG) from green tea enhanced SOD and catalase activity via Nrf2 translocation in neuronal cultures (Hao et al., 2024; Tang et al., 2025).

Aging transforms microglia into a primed state with elevated cytokine production(Norden and Godbout, 2013), establishing “inflammaging” that damages synapses and impairs neurogenesis(Franceschi and Campisi, 2014). DAMPs from damaged mitochondria activate TLRs and the NLRP3 inflammasome(Heneka et al., 2013). Polyphenols including resveratrol and EGCG inhibit microglial activation and suppress pro-inflammatory cytokines through Keap1/Nrf2/ARE pathway activation(Jalouli et al., 2025).

Mitochondrial dysfunction exacerbates oxidative stress and inflammation. Aging weakens ETC complexes I and IV, reducing ATP and increasing ROS(Baars et al., 2022). Mitochondrial DNA mutations accumulate(Ng et al., 2025), while decreased PGC−1α, NRF1, and TFAM reduces biogenesis and impaired mitophagy allows damaged mitochondria to persist(Kerr et al., 2017; Lopez-Otin et al., 2013). Dysfunctional mitochondria release pro-apoptotic signals promoting Aβ, tau and α-synuclein aggregation. The protective role of antioxidant pathways in neurons is clear. Antioxidant vitamins (C, E, tocotrienols), flavonoids, and trace elements (Cu, Zn) that support SOD protect against this oxidative damage(Chu et al., 2016; Polis and Samson, 2024).

3.3. Neuroimmune dysregulation and glial dysfunction

Neuroimmune homeostasis undergoes fundamental changes as people age(Andronie-Cioara et al., 2023). Senescent microglia produce excessive cytokines losing their phagocytic capacity, with reduced TREM2 and CX3CR1 decreasing neuroprotection(Hickman et al., 2013; Keren-Shaul et al., 2017). Microglial IL-1α, TNF, and C1q trigger astrocyte to convert into neurotoxic A1 phenotypes that impair glutamate uptake and promote neuronal death(Liddelow et al., 2017). Loss of tight junction proteins (claudin−5, occludin, ZO−1), pericyte depletion, and increased peripheral infiltration cause blood-brain barrier (BBB) deterioration(Knox et al., 2022). Reduced P-glycoprotein (P-gp) function decreases Aβ clearance and increases amyloid accumulation(Deo et al., 2014). Astrocytic aquaporin−4 (AQP4)-dependent glymphatic system becomes damaged with aging through AQP4 depolarization, vascular stiffening, and sleep disruption(Hablitz and Nedergaard, 2021; Mestre et al., 2022), accelerating protein aggregation and neurodegeneration in AD, PD, and ALS(Corbali and Levey, 2025). Omega−3 PUFAs promote Aβ clearance through glymphatic pathways and support BBB integrity(Ren et al., 2017; Wen et al., 2024), while melatonin regulates glymphatic function during sleep(Chen et al., 2025).

3.4. Metabolic dysregulation

Brain metabolic adaptability deteriorates with aging(Lopez-Otin et al., 2023). Glucose transport declines as GLUT1/GLUT3 decrease and insulin resistance develops(Talbot et al., 2012). Impaired PI3K-Akt signaling suppresses plasticity promoting tau hyperphosphorylation via GSK−3β(Bomfim et al., 2012; Talbot et al., 2012). Human FDG-PET studies confirm decreased parietal and temporal glucose uptake in both aging and AD brains(Mosconi et al., 2008). Aging brains accumulating oxidized lipoproteins and ceramides trigger ROS production and apoptosis(Yin, 2023). Decreased phosphatidylcholine, phosphatidylethanolamine, and plasmalogens occur alongside increased ceramides and oxysterols, activating NF-κB and TLR4 pathways(Yin, 2023). APP cleavage through lipid rafts links dysfunctional lipid catabolism to Aβ formation(Lazar et al., 2022; Wang et al., 2021). Elevated plasma BCAAs activate mTOR signaling and compete with neurotransmitter precursors (tryptophan, tyrosine, phenylalanine) uptake in brain impairing insulin function and monoamine synthesis(Siddik et al., 2022; Yang et al., 2024). Chronic neuroinflammation further diverts tryptophan to neurotoxic quinolinic acid promoting excitotoxic neuronal death (Schwarcz et al., 2012).

Several studies have shown that nutritional strategies can address these metabolic deficits. For example, adherence to the Mediterranean diet improves insulin sensitivity and reduces AD biomarkers in human cohorts(Grammatikopoulou et al., 2020), while ketogenic diets supply ketone bodies that bypass impaired glucose transport(Norwitz et al., 2019). Omega−3 PUFAs, particularly DHA, help restore membrane phospholipid composition, with meta-analysis showing 36% lower AD risk with high fish intake(Zhang et al., 2016). DHA, olive oil, nuts, blueberry, and curcumin each been shown to increase BDNF levels in brain or circulation in both human trials and animal models(Carrillo et al., 2025; Sugasini et al., 2019), and the VITACOG (VITAmins and COGnition) RCT demonstrated that vitamin B supplementation slowed brain atrophy by 30% in older adults with elevated homocysteine (Douaud et al., 2013; Smith et al., 2010).

4. Exercise and the brain

Physical exercise and proper food to sustain the body are vital for lifelong health. A balanced diet and adequate caloric intake support optimal metabolism and physiology. Intermediary metabolism and cell biochemistry are integrated in the inter-organ exchange between muscle, gut, adipose, liver, and brain. Exerkines (both metabolic and physiologic) include metabolites, hormones, and cytokines in the inter-organ communications of the brain with other organs and tissues during exercise(Watkins et al., 2024). The exerkines are elaborated by muscle, adipose, and liver, to support brain metabolism, its caloric needs, and physiological processes(Watkins et al., 2024). In addition to exerkines, brain production of endocannabinoids (eCB) biosynthesized from arachidonic acid are released from brain during exercise(Watkins, 2018). The binding of eCB to their receptor CB1 in brain activates

food intake and supports energy metabolism(Watkins et al., 2024). It is important to note that exercise and all the motor skills associated with movement and balance involve the cognitive aspects of the brain and new movements such as those associated with learning Tai Chi induce brain plasticity(Puri et al., 2023).

Exercise (running and strenuous walking) in both humans and animals has been reported to enhance neuroplasticity and lower neurodegenerative disease(Muller et al., 2021; Park and Watkins, 2022; Watkins, 2018). Running (and cycling) especially increases the eCB anandamide (AEA) in brain and blood compared to walking in humans and cursorial mammals(Raichlen et al., 2012). The exercise component associated changes in eCB appear to improve mood responses in adults (Brellenthin et al., 2017; Matei et al., 2023; Meyer et al., 2019). Moderate levels of exercise intensity are less effective in raising AEA and little work has been done on exercise and other eCB, especially those derived from EPA (N-eicosapentaenoyl ethanolamine, EPEA) and DHA (N-docosahexaenoyl ethanolamine, DHEA).

Evidence of physical activity or structured exercise confers many benefits on the brain and the endocannabinoid system fine-tunes factors to improve metabolism and reduce mental health issues. In this regard, Tai Chi affords benefits of well-being and pain reduction but the effects on blood levels of eCB are not well known (Watkins, 2018). Further, the mind-body aspect of Tai Chi is a reasonable result where brain and muscle work in conjunction with eCB biosynthesis to facilitate the inter-organ communications to improve well-being. Moreover, exercise can confer benefits to control neuroinflammation in aging(Barad et al., 2023). Likely, no exercise or sedentary lifestyle may lead to an absence of exercise-derived beneficial mediators and dysregulated inter-organ communications, impaired glucose metabolism, and dyshomeostasis of the CNS(Barad et al., 2023). Other exercise types like walking had less effects on circulating eCB in humans compared to running or strenuous exercise(Siebers et al., 2021).

In some regards, the eCB would seem to be likely candidate exerkines because they exert actions on the brain and intermediary metabolism (Park and Watkins, 2022). For example, exercise effects on eCB and the elaborated exerkines, the neurotrophin BDNF, exerts protective actions on the CNS that are likely in combination with other exerkines(Watkins et al., 2024). Illustrated in Fig. 3 are the actions of exercise on the brain resulting in plasticity and elaboration of exerkines that support inter-organ communications. The eCB and oxylipins also influence inflammatory processes in the brain and peripheral nervous system.

Another critical factor acting on brain metabolism during exercise is irisin which appears to be neuroprotective(Zhang et al., 2026). Irisin is a myokine (also an exerkine) elaborated by muscle during exercise but also promotes secretion of BDNF, activation of AMPK signaling, and improves glucose metabolism, and modulates autophagy for cellular cleanup(Zhang et al., 2026). The complementary relationships of irisin and BDNF are shown in Fig. 3.

5. Diet and nutrients for brain health

The macronutrients carbohydrates, protein, and fats are vital for the brain. The World Health Organization recommends a balance of macronutrients to supply glucose, essential amino acids, and fatty acids for the brain(Kromhout et al., 1982; Organization, 2009). Fig. 4 illustrates the contribution of macronutrients to healthy brain aging. However, many people do not consume adequate nutrition, which can be detrimental to healthy aging in older age(Fallon and Karlawish, 2019; Imamura et al., 2015). Inadequate dietary intake is linked to neurodegeneration(Cohen et al., 2009; Sanchez-Morate et al., 2020). Nutritional imbalances are associated with depression and cognitive decline (Duc et al., 2021; Ngandu et al., 2015). Meal timing and nutrient manipulation can also impact mental health(Dye et al., 2000; Gopinath et al., 2016; Wilson et al., 2020). Understanding the underlying mechanisms of macronutrients and their impact on healthy aging is an important research goal.

5.1. *Carbohydrates and healthy brain aging*

Carbohydrates are simple (i.e., sugar) and complex (i.e., starches and fibers). Simple carbohydrates provide immediate energy for the brain; however, they may also cause rapid fluctuations in blood glucose, leading to inflammation, oxidative stress, hormonal imbalance, and neurological disruption impacting psychological and emotional functioning(de Sousa Rodrigues et al., 2017). The serotonergic system uses serotonin to regulate mood and cognition(Jenkins et al., 2016). Carbohydrates influence serotonin availability, and if not balanced, could lead to mood disturbances of neurological disease(Markus, 2008; Naghshi et al., 2024). Diets high in simple carbohydrates are associated with deleterious effects on cognitive aging(Al-Sabah et al., 2020; Chong et al., 2019; Fado et al., 2022). Additionally, a high glycemic diet has been shown to increase AD risk and cognitive decline(Roberts et al., 2012;

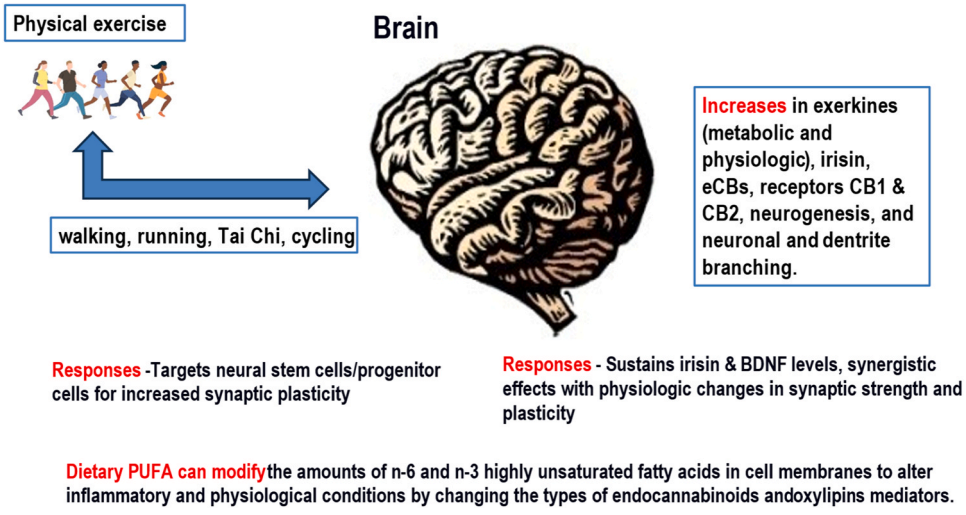

Fig. 3. Impact of exercise is shown on brain metabolism and physiology. Inter-organ communications with muscle and brain increase to support heightened intermediary metabolism of fatty acids, carbohydrates, and glucose. The response in brain up-regulates the production and release of metabolic and physiologic exerkines, irisin, and endocannabinoids. Euphoric state is recently supported by the interactions of endocannabinoids and exerkines. Dietary PUFA such as increases of n−3 PUFA DHA and EPA can lower arachidonic acid (n−6 PUFA) in tissues and likely increase the biosynthesis of endocannabinoid-like products DHEA and EPEA in brain and nervous tissues.

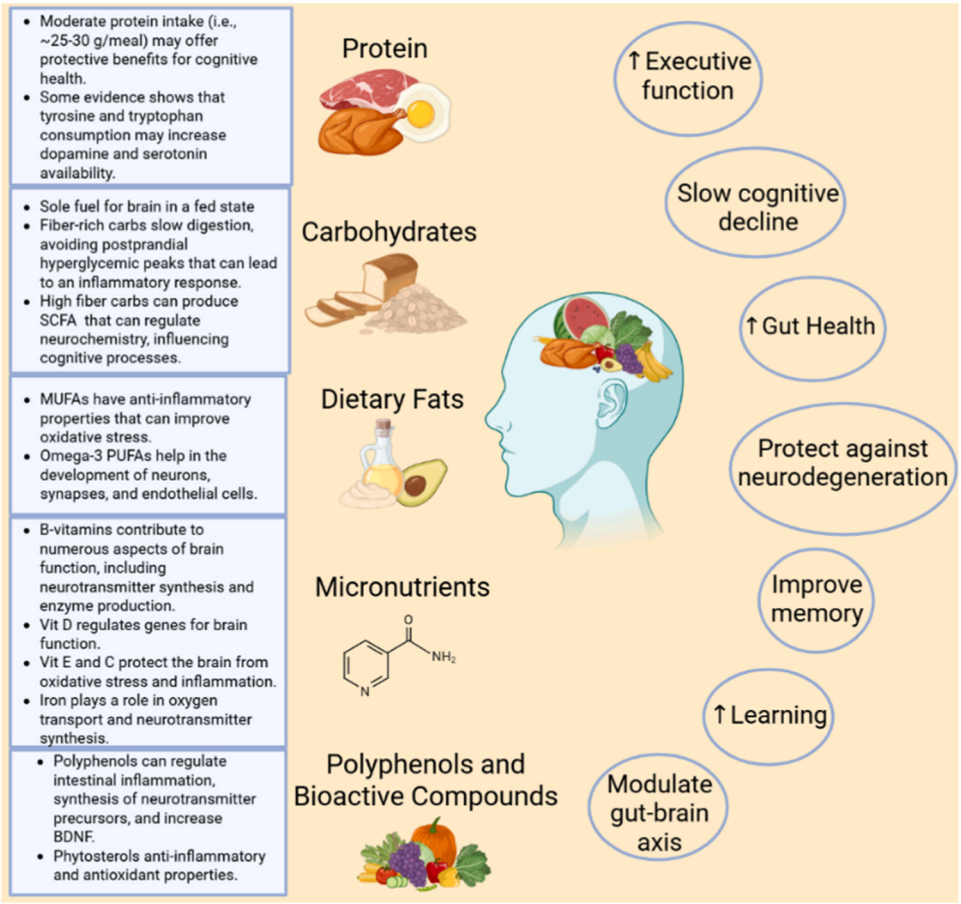

Fig. 4. Contribution of nutrients in protecting the gut-brain axis for healthy brain aging. Each nutrient plays a vital role in neuroprotection, gut health, and influences the cognitive processes. Insufficiency of many of these nutrients are associated with oxidative stress, inflammation, and cognitive decline. MUFA=monounsaturated fatty acid; PUFA=polyunsaturated fatty acid; SCFA=short-chain fatty acid; BDNF=brain-derived neurotrophic factor.

Taylor et al., 2017). However, fructose is associated with enhancements in cognitive function(Chong et al., 2019; Overby et al., 2013). Fiber-rich diets have a positive impact on cognition and healthy aging(Gopinath et al., 2016). Through slowing down gastric emptying, intestinal transit time and absorption, complex carbohydrates can stabilize blood glucose levels to improve cognitive performance and memory. Additionally, fiber-rich carbohydrates promote gut health that can lead to healthy brain aging(Arshad et al., 2025). Intestinal health is linked to the immune system and the digestion and absorption of nutrients that play pivotal roles in optimal brain function(Aziz et al., 2024). Thus, the effect of carbohydrates on brain function varies depending on the type and quality(Arshad et al., 2025).

5.2. *Dietary fatty acids and healthy brain aging*

Dietary fats have different effects on the brain. Consumption of MUFAs could improve metabolic regulation of neural stem cells by supporting neurogenesis and lowering cognitive decline(Assmann et al., 2018; Kandel et al., 2022). Both omega−3 and omega−6 PUFAs have been associated with neuroprotective effects(Oleson et al., 2020; Wang et al., 2018). In contrast, diets high in saturated fatty acids (SFA) and trans-fats have been linked to neurodegenerative disease states(Butler et al., 2023; Laitinen et al., 2006; Ruan et al., 2018). SFA-rich diets can decrease BDNF compromising neuroplasticity(Wu et al., 2004). Trans-fats promote oxidative stress, and diets high in trans-fats may lead to cognitive decline(Golomb and Bui, 2015; Morris et al., 2004). However, some evidence indicates that exercise may reverse some of the oxidative stress caused by high-fat diets that impact neural function (Hinton et al., 2011; Molteni et al., 2004; Park et al., 2019). Conflicting reports on the effects of dietary cholesterol on brain function involves one study showing no cognitive decline with high intakes of cholesterol (Naqvi et al., 2011),while another study shows a cholesterol-rich diet was associated with poor cognitive functioning(Zhang et al., 2006). Oxidized cholesterol can lead to neuroinflammation, but the healthy aging brain has a demand for cholesterol due to age-related cholesterol loss(Chen et al., 2018; Gamba et al., 2015; Martin et al., 2014). A diet enriched with phytosterols as the cholesterol source has been associated with reducing amyloid (Aβ42) levels, a peptide known to increase the risk of developing dementia and AD(Perez-Canamas et al., 2016). Dietary fats affect the brain in different ways. SFA, trans-fats, and cholesterol can be associated with cognitive impairment, while MUFA and PUFA consumption can have neuroprotective benefits(Eskelinen et al., 2008; Handing et al., 2019). The amounts and balance of n−6 and n−3 PUFA influence eCB and oxylipin biosynthesis and their downstream actions on food intake, inflammation, cognition, and mood in the brain(Kelaiditis et al., 2023; Kim and Watkins, 2014; Lust et al., 2025; Watkins et al., 2024).

5.3. *Protein and healthy brain aging*

Proteins are the building blocks for neurotransmitters. The digestion of proteins liberates amino acids (AA), with branch-chain amino acids (BCAAs) having influence on neurotransmitter levels and might impact inflammation leading to neurodegenerative diseases(Contrusciere et al., 2010; Vilela et al., 2017). Moreover, BCAAs are transported into the brain via LAT1 (Large amino acid transporter 1), the same transporter

used for the entry of aromatic amino acids (AAAs). This can lead to competition between BCAAs and AAAs influencing the synthesis of dopamine, norepinephrine, and serotonin in the brain. Maintaining adequate BCAA levels in the blood is imperative for healthy brain aging; however, high levels of BCAAs have negative consequences. Manipulating certain amino acid ratios in the diet has conflicting results. Some research shows BCAAs have beneficial, harmful, or minimal to no effects on aging, making diet recommendations challenging(Cummings et al., 2018; Jewell et al., 2013; Liu and Sabatini, 2020). Encourage quality protein sources and aim for 25–30 gm protein for each meal is suggested (Le Couteur et al., 2020).

5.4. Micronutrients and healthy brain aging

There are beneficial nutrients beyond the macros that protect against cognitive decline. The B-vitamins and iron, antioxidant vitamins, polyphenols, and bioactive compounds are critical for cognitive health (Dangour et al., 2015; Galasko et al., 2012; Kesse-Guyot et al., 2013). As shown in Fig. 5, a "whole diet" approach has the best potential for healthy brain aging. Micronutrients play a role in enzyme, hormone, and other compound production. B-vitamins play a critical role in brain function with deficiency symptoms of confusion, memory loss, neurodegeneration, and more due to their roles in neurotransmitter synthesis and enzyme production for brain metabolism and function(Asha Devi and Manjula, 2014; O'Keeffe et al., 1994; Quadri et al., 2004). Studies demonstrate that consuming above the RDA for most B-vitamins could be an effective and safe strategy because B-vitamins are water soluble (Agnew-Blais et al., 2015; Dangour et al., 2015; MacFarlane et al., 2014; Smithline et al., 2012). Vitamin D deficiency affects various cognitive tests and is linked to dementia(Menant et al., 2012; Navale et al., 2022). Optimizing vitamin D levels may prevent and modulate brain dysfunction(Montero-Odasso et al., 2023; Suzuki et al., 2013). Antioxidants like vitamins E and C intake and their effect on brain health have various outcomes; reduced risk of cognitive decline(Basambombo et al., 2017); no association(Nooyens et al., 2015); or an inverse association(Galasko et al., 2012). Including antioxidant-rich foods has yielded positive outcomes like increased learning and decreased oxidative stress(Gray et al., 2008; Joseph et al., 2009; Shetty et al., 2014; Willis et al., 2009). Iron is critical for biological processes in the brain; however, supplementation is not recommended unless there is an iron deficiency present due to the risk of iron overload that can impair neurophysiological mechanisms (Milward et al., 2010; Schiepers et al., 2010). Maintaining adequate micronutrients through a healthy dietary pattern is essential to good brain health.

5.5. Polyphenols, bioactive compounds, and healthy brain aging

Many polyphenols like quercetin and catechins help with healthy brain aging because they act as an antioxidant and reduce senescence (Abdallah et al., 2012; Gueguen et al., 2015). Flavonoids serve in

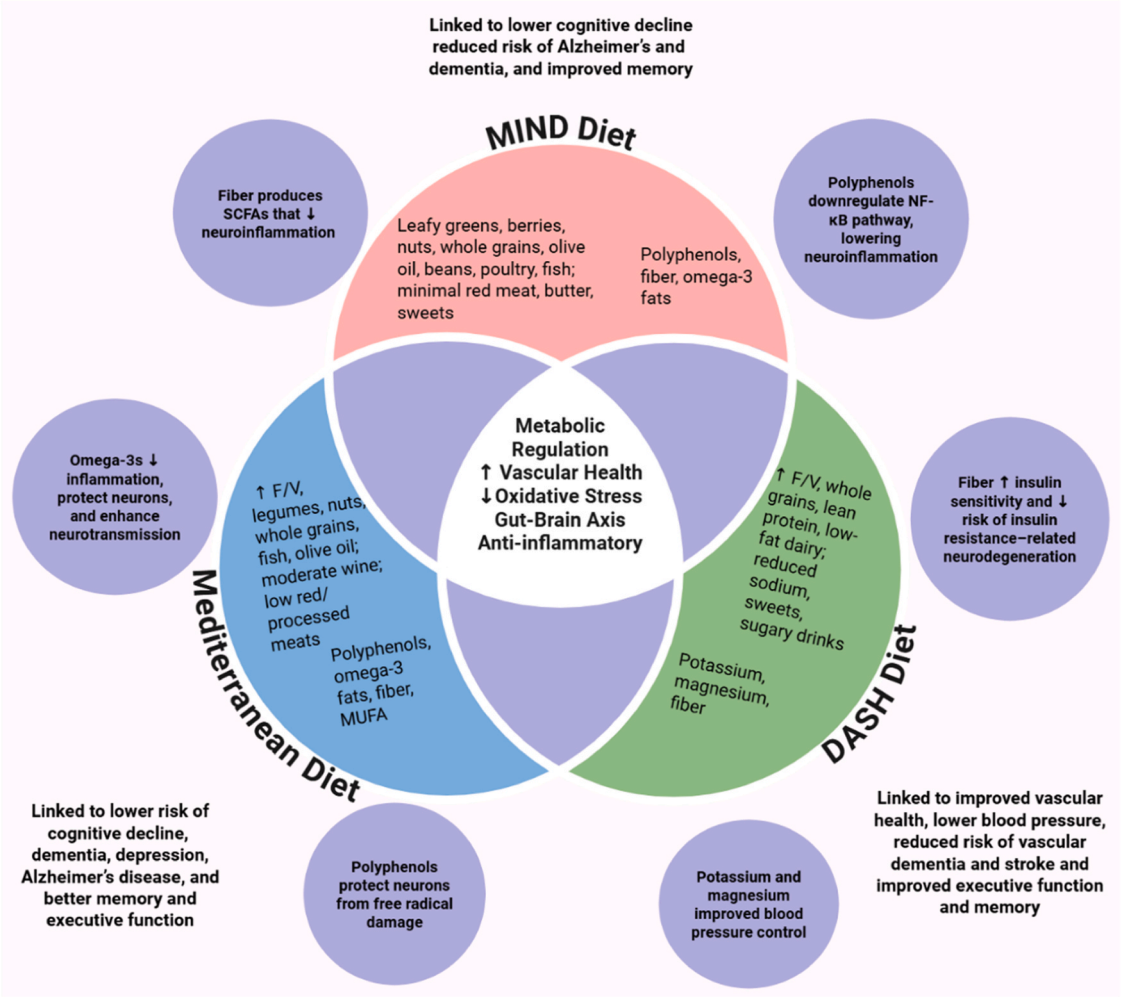

Fig. 5. Diet eating patterns and brain health. These eating patterns are rich in plant-based foods, healthy fats, and lean proteins while limiting food products high in saturated fat and sugars leading to reduce oxidative stress and inflammation that can improve cognitive function and slow cognitive decline. MUFA=monounsaturated fatty acid; F/V=fruits and vegetables; SCFA=short-chain fatty acid.

antioxidant and anti-inflammatory roles in the brain to support health and reduce neurodegenerative diseases(Jennings et al., 2021). Supplementation with flavonoids has yielded positive results, with doses of ~500 mg/day for over 8 weeks showing improvements in cognitive tasks(Brickman et al., 2014; Desideri et al., 2012; Hunt et al., 2024). Additionally, Plant sterol treatment can improve spatial learning and memory in mice(Bogie et al., 2019; Ye et al., 2020). However, intake of 2.5 g/day of plant sterols for 85 weeks did not affect neurocognitive functioning in a human study (Schiepers et al., 2009). Another study examined diet-derived phytosterol levels and found a negative association with cognitive decline, suggesting it as a prevention strategy for cognitive impairment(Clark et al., 2023). Diets containing bioactive compounds found in walnuts have brain health benefits due their anti-inflammatory and antioxidative properties(Arab and Ang, 2015; Muthaiyah et al., 2014). Furthermore, another study found that 67 g/day of soy nuts (rich in phytosterols) may improve cerebrovascular function in adults(Kleinloog et al., 2021). In addition to adequate macronutrient consumption, polyphenols and phytosterols from food sources should be included as part of healthy eating pattern for brain health.

6. Diets and healthy eating patterns for brain health

Dietary patterns are a powerful influence on healthy brain aging. Higher diet quality is recommended to reduce the global burden of cognitive decline(Smyth et al., 2015). Eating patterns are valuable to benefit aging and brain health as shown in Fig. 5 (Kesse-Guyot et al., 2013; Samieri et al., 2013).

6.1. Mediterranean diet (Med diet)

The Med diet is shown to improve cerebrospinal fluid biomarkers, cognition, and cerebral perfusion(Hoscheidt et al., 2022). Another study conducted in nonhuman primates found that Med diets provide anti-inflammatory benefits, reflected in the preserved brain structure and socioemotional behavior(Frye et al., 2024). The Med diet is considered one of the healthiest eating patterns due to varied nutrients, bioactives, and phytochemicals.

6.2. Dietary approaches to stop hypertension (DASH) diet

The DASH diet has shown to benefit cognitive function. In several studies involving the DASH diet among older adults, it showed slower rate of cognitive decline(Berendsen et al., 2017; Tangney et al., 2014; Wengreen et al., 2013). Another study in adults with cognitive impairment the DASH diet was associated with better verbal memory (Blumenthal et al., 2017). However, a study among older women concluded that the DASH diet had no significant association with cognitive decline(Haring et al., 2016). Collectively, there is evidence that the DASH diet can have a positive effect on healthy brain aging.

6.3. Mediterranean-DASH intervention for neurodegenerative delay (MIND) diet

The MIND diet, which is a hybrid of the Med diet and DASH diet, has specific guidelines to benefit brain health. A randomized, controlled trial involving older adults without cognitive impairment revealed no significant difference in changes in cognitive and brain MRI outcomes from baseline to year 3(Barnes et al., 2023). In a prospective study and meta-analysis of cohort studies among middle-aged and older adults, the MIND diet was associated with better cognitive function and slower cognitive decline in later life(Huang et al., 2023). Furthermore, a study in adults aged $\geq$ 40 years there was an association with slower rate of cognitive decline(Cherian et al., 2019), but evidence for other brain-related outcomes were mixed(Berendsen et al., 2017; Morris et al., 2015). More research is needed to establish this diet in maintaining brain health.

6.4. Eating behaviors and brain health

Daily eating habits are controlled by the circadian clock, meaning eating patterns are distributed rhythmically over 24 h(Mendoza, 2019). Eating most calories and carbohydrates at lunch time and early afternoon while avoiding late evening dinner and keeping a consistent number of daily meals play a pivotal role in healthy glycemic control and insulin sensitivity(Bo et al., 2017; Takahashi et al., 2018). Traditionally, there is a bi-directional relationship between the circadian rhythms of the host and the gut microbiota(Leone et al., 2015). Supporting a healthy gut microbiota is a source of dietary and non-dietary biological products beneficial in regulating gut-to-brain communication and cognitive health. Meal timing and diet quality are critical to maintaining circadian rhythms that are important for metabolic, gut, and cognitive health.

6.5. Effects of caloric restriction on brain age and function

6.5.1. Caloric restriction and intermittent fasting

Caloric restriction (CR) can be accomplished by continuous CR (CCR) or intermittent fasting (IF) or intermittent caloric restriction(Sundfor et al., 2018). CCR without malnutrition is loosely defined as the intentional reduction of energy intake by ~20–50% or ~500–700 kcal per day(Jensen et al., 2014; Kennedy et al., 2007). Despite being the cornerstone of diet-based weight management strategies and longevity research, CCR is often difficult to sustain and justifies the development of creative CR strategies (i.e., IF). IF programs are similarly effective weight loss and health promoting strategies (Johnstone, 2015; Schubel et al., 2018; Tinsley and La Bounty, 2015; Varady, 2011).

There are many types of IF regimens, most commonly including time-restricted feeding (consuming daily kcal within a 6–10 h timeframe), alternate day fasting (complete abstention from energy intake on alternate or every second day with *ad libitum* feeding in between), and modified alternate-day fasting (akin to alternate day fasting but with a small ~25% or 500–600 kcal per day intake allotment on fasting days) (Patikorn et al., 2021; Regmi and Heilbronn, 2020).

The link between CR and brain health or protection from neurodegeneration is an emerging line of research(Trisal and Singh, 2024), and a substantial body of evidence in humans does not yet exist. From a practical standpoint, personal preference should be the primary driver for selecting one CR approach over the other. It is probable that future study will lead to a more nuanced understanding of the relationship between CR, including IF regimens, and preservation of brain health in aging populations across states of metabolic disease.

6.5.2. Effects of caloric restriction on brain age and function

In the metabolically impaired state, even a short duration of IF may induce favorable effects on cognitive performance(Kapogiannis et al., 2024) and neurodegenerative disease pathology(Babygirija et al., 2024). Kapogiannis et al. report an 8-week 5:2 alternate day fasting regimen significantly improved measures of cognitive performance, such as executive function and memory in insulin resistant adults. Importantly, intermittent fasting (IF) was not reliably superior to an assumed continuous caloric restriction (CCR) induced by following a standard “healthy living” diet(Kapogiannis et al., 2024). In contrast, IF with caloric restriction (CR) enhances neuroprotection in mice beyond CCR alone in the setting of Alzheimer’s disease (Babygirija et al., 2024; Schafer et al., 2015a). Ancillary analyses of the CALERIE trial(Rickman et al., 2011) which assessed 2-year response to CCR (12% deficit) versus *ad libitum* intake, however, found that CCR slowed measures of biological aging but did not translate to long-term improvement in cognitive performance(Dorling et al., 2021; Ravussin et al., 2015; Waziry et al., 2023). Effect sizes were modest and mediated by weight loss across both studies. These seminal findings (Kapogiannis et al., 2024; Waziry

et al., 2023) nonetheless help illustrate the concept that, provided a net negative energy balance is induced and sustained, one approach is not clearly superior to another for promotion of metabolic or brain health (Longo and Mattson, 2014; Schubel et al., 2018).

CR appears to be an evolutionarily conserved mechanism for preservation of cognitive and health function during reduced energy abundance(Leclerc et al., 2020; Lu et al., 2023; Matai et al., 2019; Mattison et al., 2017; Rao, 2003; Ravussin et al., 2015). In general, CR is believed to induce an adaptive response that protects brain volume and function at the expense of peripheral energy stores(Weindruch and Sohal, 1997). Although CR and longevity have been studied for nearly 100 years in rodents, others (Colman et al., 2009; McCay et al., 1989) have provided the first compelling experimental literature in nonhuman primates to support the link between CR without malnutrition and mitigation of age-associated pathologies, including brain atrophy and gray matter volume. Many studies(Lopez-Lluch et al., 2006; Schafer et al., 2015b) indicate CR-induced improvements in hippocampal mitochondrial bioenergetics, leading to enhanced synaptic plasticity. CR may also increase cerebral blood flow and stimulate ketone body utilization (Lin et al., 2015).

Many proposed mechanistic theories help explain the observed effects of sustained CR on brain aging and therefore neurodegenerative disease resistance(Mao et al., 2021; Mattson and Arumugam, 2018). Beyond modulating substrate availability, there is evident influence of peripheral metabolic health, nutrient flux, and molecular signaling on the brain(Zhou et al., 2025). For instance, release of ketones tends to stimulate neuronal resilience, activity, and plasticity across brain regions secondary to increased BDNF abundance(Kishi et al., 2015; Mattson and Arumugam, 2018).

BDNF is considered a chief modulator of the brain's response to fasting(Harvey and Rios, 2024; Lee et al., 2002; Longo and Mattson, 2014). It also serves as a link between central and peripheral metabolic health as a regulator of energy intake, energy expenditure, synaptic plasticity, neurogenesis, and neuronal resilience. More specifically, BDNF supports neuroregeneration by stimulating synthesis and survival of new neurons, as well as promoting growth, repair, and maintenance of exiting dendrites and synapses(Longo and Mattson, 2014). CR-induced hippocampal activation results in increased BDNF production and a relative state of neuroprotection (Arumugam et al., 2010).

Additional overlapping and nutrient sensing signaling pathways within the brain and body which respond to CR and are implicated in brain aging include those downstream of glutamate, insulin, and glucagon-like peptide 1 (GLP−1)(Longo and Mattson, 2014). CR-induced insulin sensitivity and increased GLP−1 or production of glutamate may synergistically lead to a cascade of events that regulate master transcriptional regulators of neuroinflammation (NF-kB) and mitochondrial biogenesis (PGC−1a), as well as kinases that promote protein synthesis and cell turnover (Akt and mTOR)(Longo and Mattson, 2014).

CR may also support DNA restoration by activation of repair proteins (e.g., APE1) and ameliorate neuroinflammation by way of decreased proinflammatory cytokines (e.g., TNF-a, IL-1b, and IL-6) release and improved antioxidant defense capacity(Arumugam et al., 2010; Mattson, 2012; Rao, 2003; Shin et al., 2018; Zhao and Zhao, 2013). In addition to supporting higher neurotropic factor levels, CR can also upregulate protein chaperones to ameliorate neuroinflammation (Arumugam et al., 2010; Longo and Mattson, 2014; Mattson, 2012). CR seems to produce a systemic hormetic response within the endoplasmic reticulum (ER), further supporting proteostasis via enhancement of the ER unfolded protein response(Matai et al., 2019). Continued research may prove this a groundbreaking discovery considering protein misfolding (e.g., alpha-synuclein) within the brain is a hallmark feature of most neurodegenerative diseases(Chaudhuri and Paul, 2006).

Exhibiting influence on proteostasis and transcription factors with regulatory control of mitochondrial function, neuronal bioenergetics, and neuroinflammation builds a persuasive case for CR protection against age-associated neurodegeneration. Collectively, these mechanisms point towards restoration of signaling pathways central to brain aging and neurodegeneration, translating to improved cognition in mouse models of Alzheimer's disease, Parkinson's disease, and Huntington's disease in response to CR(Bruce-Keller et al., 1999; Duan et al., 2003; Griffioen et al., 2012; Halagappa et al., 2007; Liu et al., 2019; Shin et al., 2018; Zhou et al., 2019).

Regardless of obesity status, whether the cognitive and metabolically protective effects of CR occur independent of weight loss in humans is up for debate (Prehn et al., 2017; Silver et al., 2023). Nonetheless, genes involved in the CR response may serve as meaningful targets for the development of neurodegenerative disease interventions or therapies designed to slow the normative brain aging cascade.

7. Inter-organ crosstalk support for metabolic and brain health

7.1. Importance of inter-organ crosstalk for brain

Crosstalk refers to endogenous, bi-directional inter-organ signaling (Afsar et al., 2016) via "organokines." Organokines are traditionally made up of paracrine or endocrine signaling molecules like cytokines from immune cells and adipokines from adipose tissue (Baars et al., 2022; Kirk et al., 2020; Severinsen and Pedersen, 2020). Intact crosstalk is critical for metabolic health promotion and the links between peripheral metabolism and brain health, cognition, and aging. Conversely, dysregulated organokine signaling is implicated in the pathogenesis of major chronic diseases of metabolic origin, such as obesity and T2D and their molecular hallmarks (e.g., lipotoxicity, inflammation)(Baars et al., 2022; de Oliveira Dos Santos et al., 2021). Emerging and related frameworks include the gut-brain axis (Thakur et al., 2024).

Although inter-organ communications are inherently bi-directional, this review focuses on signals originating from peripheral systems that target the brain. Current literature primarily highlights brain communication originating from adipose tissue and skeletal muscle (Fig. 6).

7.2. Adipose-brain crosstalk

Leptin is a key adipokine that crosses the blood-brain barrier (BBB) to act upon hypothalamic receptors (Schulz et al., 2010). It regulates energy balance by inhibiting orexigenic neurons and stimulating anorexigenic neurons (Ahima et al., 2000; Jobst et al., 2004; Myers et al., 2008; Schulz et al., 2010). The anti-aging properties of leptin are mostly limited to *in vitro* studies, including inhibition of neuron death and activation of JAK2-STAT3, Akt, and MEK/ERK signaling(Guo et al., 2008; Russo et al., 2004; Signore et al., 2008). In neurodegeneration models, leptin mitigates amyloid beta (Aβ) burden via β-secretase activation(Fewlass et al., 2004), whereas in humans, circulating leptin levels are inversely associated with Alzheimer's and Huntington's diseases (McGuire and Ishii, 2016; Popovic et al., 2004).

Although adiponectin signaling is maintained in the brain, its BBB transport remains debated (Kos et al., 2007; Yildiz et al., 2004). Adiponectin receptors(Kadowaki et al., 2008) are highly expressed in the hypothalamus and brainstem(Fry et al., 2006; Kubota et al., 2007; Schulz et al., 2010; Wilkinson et al., 2007) to facilitate central adiponectin signaling. However, its biologically active (high molecular weight) isoform is not present in the CNS, and adiponectin can be produced locally within the CNS, at least in mice(Kusminski et al., 2007; Wilkinson et al., 2007).

Adiponectin is consistently linked with insulin sensitization and fatty acid oxidation (Kadowaki et al., 2008; Schulz et al., 2010; Wang and Scherer, 2016), which may indirectly support neuroprotection via neurogenesis and synaptic plasticity promotion (Sun and Liu, 2019). However, circulating adiponectin is positively and counter-intuitively correlated with AD and Aβ burden in humans(Kim et al., 2023).

The present findings may reflect limitations in preclinical models or bidirectional relationships between adipokines and neurodegeneration.

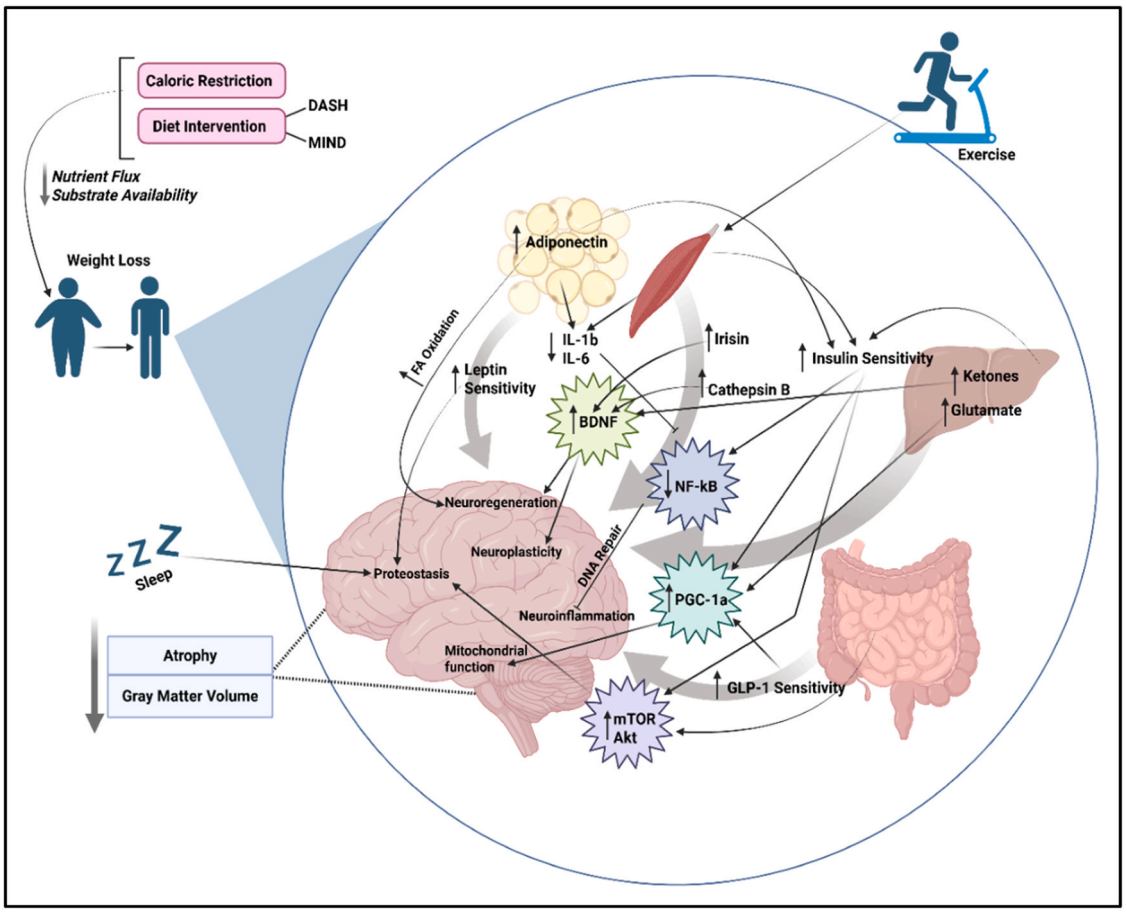

Fig. 6. Inter-organ crosstalk for metabolic and brain health (between the brain and periphery) due to diet choice, sleep patterns, and physical activity. Nutrition-related factors stimulate inter-organ tissue crosstalk to promote brain health and neurodegenerative disease resistance, such as reduced gray matter volume and reduced brain atrophy. Calorie restriction and diet intervention (e.g., MIND) alter nutrient flux and substrate availability, typically followed by downstream weight loss, which modulates production of adipokines in adipose tissue, thereby improving inflammation via NF-KB and whole-body insulin sensitivity. Weight loss also improves sensitivity to leptin produced by adipose tissue and GLP−1 produced by the small intestine. Increased secretion of adiponectin further drives insulin sensitivity, as well as stimulates fatty acid oxidation, which may promote neuroregeneration. Synergistic effects of glutamate production and improved GLP−1/insulin sensitivity stimulate a cascade of events that regulate master transcriptional regulators of neuroinflammation (NF-kB), mitochondrial biogenesis (PGC−1a), and cell turnover (Akt, mTOR). Exercise-induced myokine (irisin, cathepsin B) production also promotes BDNF stimulation, in addition to liver ketone production resulting from diet-induced depletion of glycogen stores. Abbreviations: Akt (protein kinase B), BDNF (brain-derived neurotrophic factor), DASH (dietary approaches to stop hypertension), FA (fatty acid), GLP−1 (glucagon-like peptide 1), IL-1b (interleukin 1 beta), IL-6 (interleukin 6), MIND (mediterranean-DASH intervention for neurodegenerative delay), mTOR (mammalian target of rapamycin), NF-kB (nuclear factor kappa B), PGC−1a (peroxisome proliferator-activated receptor gamma coactivator 1-alpha).

Thus, future work should consider mass and function of adipose tissue and tissue-specific adipokine sensitivity.

7.3. Muscle-brain crosstalk

Myokines are neuroprotective molecules released in response to physical activity (Severinsen and Pedersen, 2020). During exercise, interleukin−6 (IL-6) is acutely released from working myocytes (Pedersen, 2019). Interestingly, its transcription within skeletal muscle is independent on NF-κB activation that characterizes the traditional pro-inflammatory response within macrophages(Pedersen and Febbraio, 2008). While evidence for myocyte-derived IL-6 crossing the BBB is limited(Devasahayam et al., 2021), IL-6 is produced in small amounts within the human brain in response to prolonged exercise (Nybo et al., 2002).

Other key myokines include cathepsin B and irisin. Irisin, derived from cleaving of the PGC1-α-dependent FNDC5 membrane protein, likely mediates the effect of exercise on brain BDNF upregulation in a similar manner as cathepsin B(Bostrom et al., 2012; Jedrychowski et al., 2015; Lourenco et al., 2019; Wrann et al., 2013) to upregulate BDNF-dependent neurogenesis upon crossing the BBB(Moon et al., 2016; Pedersen, 2019). Brain myokine signaling remains incompletely understood, especially in humans(Moon et al., 2016; Suzuki, 2016), and the mechanism by which exercise activates these neuroprotective pathways is currently elusive.

Peripheral–brain crosstalk highlights the central role of metabolic health in brain aging. Organokines represent promising targets for lifestyle and pharmacologic interventions to preserve cognitive function and reduce neurodegeneration risk.

8. Gut microbiome and brain aging/neurodegeneration

The gut microbiome communicates with the CNS through intricate and integrated pathways, collectively referred to as the microbiome-gut-brain axis (MGBA) (Cryan et al., 2019)(Fig. 7). One major pathway is through neural signaling, facilitated by the activation of enteric nervous system (ENS) afferent neurons and signal transduction along the vagus nerve, which establishes a two-way connection (Bravo et al., 2011; McVey Neufeld et al., 2019; Menezes and Shah, 2024). Derived from diet, gut microbe species metabolize food and secrete diverse

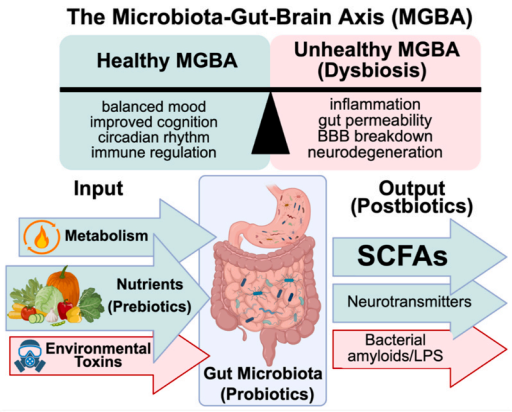

Fig. 7. The microbiota–gut–brain axis (MGBA) and the optimal homeostatic balance of inputs and outputs. A balanced (eubiotic) MGBA connects the gut microbiota with the central nervous system via neural, immune, and metabolic routes, promoting neuroprotection and cognitive resilience. A healthy MGBA (blue) requires a prebiotic (input). Probiotic bacteria associated with the MGBA provide postbiotics such as short-chain fatty acids (SCFAs) and neurotransmitters that optimize health. By contrast, an unhealthy MGBA (red) leads to dysbiosis, driven by a deficiency in prebiotics and abundance of environmental toxins, which induce lipopolysaccharides (LPS) and amyloid release, BBB disruption, and neurodegeneration.

compounds, often referred to as "postbiotics". Depending on microbiota composition, these postbiotics include transcription factors, epigenetic regulators, neurotransmitters, and neurotrophic factors, which collectively modulate gut epithelium and neural function (Erny et al., 2015; Molinero et al., 2023; Yano et al., 2015).

Bacterial metabolites, such as SCFAs, secondary bile acids, and tryptophan derivatives (e.g., serotonin, kynurenic acid, and quinolinic acid), interact with cells in the gut, and may affect the CNS directly after translocation across the gut barrier and BBB (Agus et al., 2018; Braniste et al., 2014; Erny et al., 2015; Molinero et al., 2023). Cytokine production is also regulated by the microbiota, affecting the hypothalamus-pituitary-adrenal (HPA) axis and the brain (Sudo et al., 2004). Furthermore, gut microbial metabolic effects can influence nutrient absorption and fat metabolism, potentially leading to epigenetic changes (Agus et al., 2018; Erny et al., 2015; Molinero et al., 2023).

The gut microbiota (GM) composition is heavily influenced by diet. High-fiber diets rich in fruits and vegetables, such as the Med diet, are associated with greater microbial diversity (Beam et al., 2021; Zhang et al., 2010). Conversely, a high-animal-protein diet increases *Bacteroides*, *Alistipes*, and *Bilophila* species but decreases beneficial GM such as *Lactobacillus*, *Roseburia*, and *Eubacterium rectale*, thereby reducing diversity (Beam et al., 2021; David et al., 2014). The GM can also be altered by a high-fat diet that reduces *Bacteroidetes* and increases *Firmicutes* (Beam et al., 2021; Bisanz et al., 2019; Ley et al., 2005; Zhang et al., 2010). Food and drink containing polyphenols, specifically flavonoids in fruits, vegetables and red wine, promote good gut health by increasing *Bifidobacterium*, *Bacteroides*, and *Prevotella*, while reducing lipopolysaccharide (LPS) levels and endotoxemia (Beam et al., 2021; Queipo-Ortuno et al., 2012). In addition, flavonoids promote further SCFA production, thereby lowering gut permeability (Hidalgo et al., 2012). Dietary intervention with flavone-enriched cranberry extract in humans has been associated with decreased systemic inflammation, enhanced insulin sensitivity, and increased abundance of the beneficial *Akkermansia muciniphila* (Anhe et al., 2017; Beam et al., 2021). The potential mechanisms by which GM species promote brain health include provision of serotonin precursor tryptophan to the brain, stimulation of the vagus nerve, and release of neuroprotective gut hormones such as GLP−1 and CCK for strengthening intestinal integrity to prevent LPS leakage and other harmful microbial metabolites into the systemic circulation (Beam et al., 2021; Kaelberer et al., 2018; Tolhurst et al., 2012; Yano et al., 2015).

Prebiotics are substrates that are selectively utilized by host microorganisms, conferring a health benefit (Gibson et al., 2017). Some prebiotics include fructooligosaccharides, galacto-oligosaccharides (GOS), lactulose, and inulin, derived from fruits and vegetables. GM converts these compounds to neuroactive, anti-inflammatory SCFAs (Gibson et al., 2017). A reduction in stress response and anxiety, as well as an improvement in hippocampal synaptic function, has been proposed in preclinical studies using these prebiotics (Gronier et al., 2018; Savignac et al., 2013, 2016). However, clinical data on their direct effects in modulating the MGBA or preventing neurodegenerative disease progression require further study (Merchak et al., 2024).

In addition to being an energy source for gut epithelial cells, SCFAs also inhibit histone deacetylases (HDACs), increasing transcriptional expression and immune response (Hashim and Makpol, 2022; Zou et al., 2021). They promote intestinal health by enhancing the secretion of mucin from goblet cells, decreasing IL-18 expression by activating inflammasomes, promoting sIgA production, suppressing DC T cell activation, promoting the expression of FOXP3, and upregulating anti-inflammatory cytokines IL-10 and TGF-β (Rooks and Garrett, 2016). Together, these effects inhibit LPS translocation and inflammation (Hashim and Makpol, 2022), thereby maintaining intestinal integrity.

The endotoxin hypothesis posits that environmental toxicants disrupt gut homeostasis and cause gut inflammation, which in turn stimulates systemic immune responses. Such chronic immune activation may increase the risk of neurodegeneration due to the disruption of the MGBA (Merchak et al., 2024). We proposed that prebiotic fiber deficiency, underrepresented in a diet high in processed foods, leads to reduced SCFA-producing bacteria (Skawratananond et al., 2025). Loss of SCFAs increases HDAC activity, which ultimately reduces the activity of the all-trans retinoic acid (ATRA)- synthesizing enzyme ALDH1A1, causing local ATRA deficiency in gut epithelial cells. Reduced ATRA-dependent expression of tight junction proteins in the gut increases gut permeability, thereby leading to chronic inflammation, where LPS ultimately penetrates the gut and BBB. In response, production of Aβ, an antimicrobial protein, increases, setting the stage for disrupting homeostasis between amyloidogenic and non-amyloidogenic APP processing.

Generally, physiology and nutrient metabolism supporting the bidirectional MGBA are emerging research areas that could help reduce neuroinflammation. These examples include brain development, and neurotransmitters derived from the gut (Kim and Shim, 2023). Moreover, the MGBA includes activities of nutrient sharing, hormones and their actions, and immunomodulation (Loh et al., 2024). Thus, the MGBA is also an important factor that impacts neurodegenerative disease.

9. Sleep pattern and the glymphatic system: The emerging role of Aβ clearance during deep sleep

The glymphatic pathway removes brain waste by pumping cerebrospinal fluid (CSF) along arteries into the interstitial space and removing metabolic products via veins(Xie et al., 2013). This process depends on aquaporin−4 (AQP4) channels. AQP4 channels are highly expressed in astrocytic end feet (Fig. 8A) and play a key role in the clearance of brain waste via the glymphatic system(Xie et al., 2013). AQP4 supports CSF-interstitial fluid (ISF) exchange and promotes Aβ removal, underscoring its critical role in brain waste elimination(Xie et al., 2013).

In contrast, AQP4 function and perivascular AQP4 polarization are impaired in neurodegenerative diseases, likely contributing to glymphatic dysfunction (Fig. 8B). Elimination of Aβ and tau is reduced, contributing to increased ISF protein aggregation and accumulation, leading to synaptic dysfunction, neuroinflammation, and cognitive decline.(Xie et al., 2013). Longitudinal ISF sampling revealed that soluble Aβ and tau levels increase in the awake state and decrease during

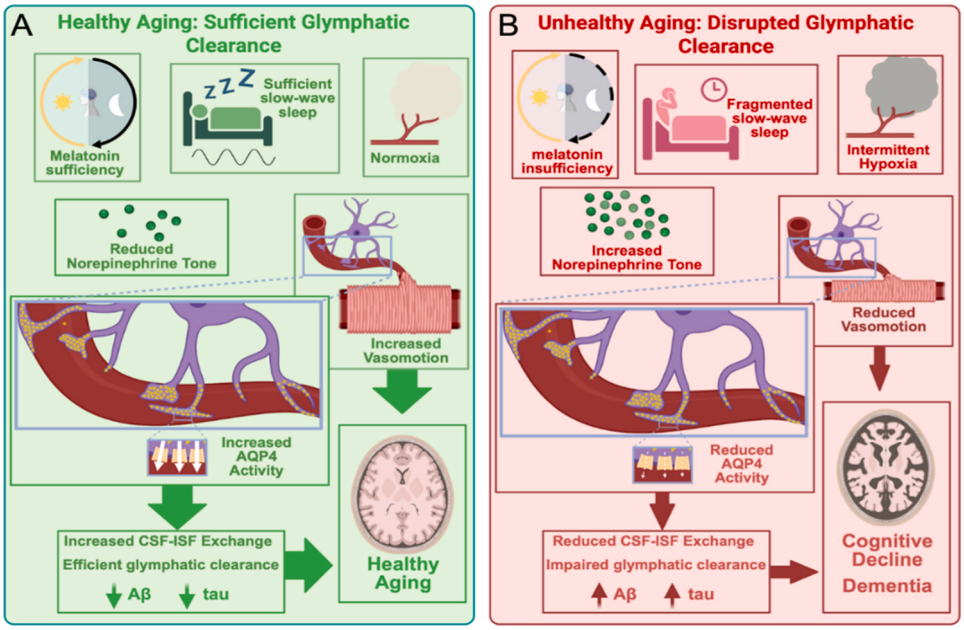

Fig. 8. A, B. Role of the glymphatic system in sustaining healthy aging during sleep. (**A**) Melatonin sufficiency, sufficient deep, slow wave sleep, and normoxia (absence of sleep apnea-related intermittent hypoxia) reduced norepinephrine tone, which enable increased vasomotion. This increased vasomotion enables increased exchange between the cerebrospinal fluid (CSF) and interstitial fluid (ISF), enabling glymphatic clearance of toxic metabolites such as amyloid beta (Aβ) and/or tau, sustaining healthy aging.**(B)** In contrast, melatonin insufficiency and fragmented slow-wave sleep, due to comorbidities such as anxiety depression, and sleep apnea, lead to reduced vasomotion, reduced AQP4 activity, reduced CSF-ISF clearance, leading to accumulation of Aβ and/or tau. This situation accelerates cognitive decline and dementia.

sleep(Xie et al., 2013). In a seminal study, optogenetic activation of astrocytes at slow-wave frequencies counteracted Aβ deposition, restored slow-wave activity, and reversed memory impairment in APP/PS1 mice(Xie et al., 2013). Likewise, non-invasive light flickering at 40 Hz significantly facilitated glymphatic fluid movement in an AQP4-dependent manner by stimulating vasomotion(Xie et al., 2013). In mice, glymphatic function exhibits a pattern of circadian variation. The highest glymphatic influx, like peripheral blood flow, occurs during sleep phases such as naturally occurring sleep in night-active rodents. AQP4 knockout eliminates these circadian rhythms, indicating a crucial role for AQP4 in the daily alteration of glymphatic flow(Hablitz et al., 2020). Also, slow oscillations of norepinephrine during non-REM sleep facilitate vasomotion, further increasing glymphatic clearance (Hauglund et al., 2025). Thus, there is an intricate interplay between neural activity, astrocyte activity, vascular function, and circadian rhythms in sleep-related control of the glymphatic system, providing potential drug targets for the treatment of AD(Gao et al., 2023).

Regarding human studies, levels of soluble Aβ and tau in CSF fluctuate, increasing during wakefulness and decreasing during sleep (McConnell et al., 2025). Loss-of-function AQP4 gene variants are linked to variations in sleep quality, cognitive decline, and brain Aβ deposits, suggesting that AQP4 may serve as a potential biomarker for early-stage neurodegenerative disorders(Shirolapov et al., 2023). Circadian rhythms are crucial for regulating neural activity and cardiovascular function, and they also affect CSF flow and glymphatic clearance in humans(Hablitz et al., 2020). In addition, multisensory γ (40 Hz) stimulation enhances arterial pulsatility and CSF dynamics through modulation of the activity of glial, neuronal, and vascular cells. This mechanism may account for the widespread neurological effects experienced due to γ sensory stimulation(Murdock et al., 2024). Together, these human studies corroborate animal findings by identifying the regulatory systems governing glymphatic flow and its dysfunction in the context of neurodegenerative diseases. This research provides novel directions for therapeutics that include sleep, vascular health, and astrocyte function(Gao et al., 2023).

The role of specific nutrients in the glymphatic system must be characterized to advance our understanding of nutrition, sleep, and the brain(Ota et al., 2025). Recently zinc status appeared to be correlated with brain glymphatic system clearance and zinc levels in healthy adults (Ota et al., 2025). Further, tryptophan and related metabolites influence glymphatic flow by activating aryl hydrocarbon receptor, and gut microbiota appear to influence the glymphatic cognition pathway associated with Schizophrenia (SZ)(Wu et al., 2025). Moreover, gut microbial dysbiosis found in SZ was characterized by a decrease in butyrate-producing bacteria and an increase in pathogenic bacteria(Wu et al., 2025). Therefore, the study of nutrient status between blood and the glymphatic system should be explored to better comprehend the effects of sleep and health status on the brain. In support of the relationship of nutrients levels in blood and the glymphatic system, low levels of zinc and antioxidant nutrients in blood and the glymphatic system are associated with sleep disorders, depressed mood, and cognitive dysfunction. As an example, zinc exhibits antioxidant properties and low zinc levels are found in patients with AD, however; other nutrients such as many B vitamins, and antioxidant nutrients appear to be protective(Ota et al., 2025).

10. Conclusions and future directions

A comprehensive review of evidence for nutrition and diet benefits on the aging brain is given. However, significant gaps remain in understanding mechanisms and applications of nutrition for the adult aging brain. Although emerging actions of nutrition on metabolism and physiology from numerous studies in animal models and fewer in humans indicate that nutrients can benefit cognitive function, plasticity, and energy metabolism. Yet the findings on neuroinflammation, glial and neuronal cells, oxidative stress, mitochondrial function, and the glymphatic system require future investigations on nutrition actions and extent of benefits to aging adults. Importantly, our approach to the topic of nutrition and brain aging eclipsed other reviews on nutrition and the brain. The strengths of our review is the focus on specific nutrients, diets, and flavonoids actions on brain health. We present important relationships of nutrition/exercise/sleep/gut microbiota as synergistic

modulators of metabolic homeostasis that may lessen pathological events in aging brain and neurodegeneration. The challenge to future directions on nutrition/diet and aging brain include personalized nutrition strategies based on genetics, caloric restriction, gut microbiome, metabolic status; and AI methodologies to assess disease and health status in aging adults. The goal is to optimize nutrition and identify valid biomarkers for brain that accurately reflect vulnerability of risk factors in the adult.

Author contributions

Conceptualization: BAW; writing-original draft preparation: BAW, ACS; writing-review and editing: BAW, ACS, SG, MH, ZFH, ME, JJL; All authors have read and agreed to the published version of the manuscript.

Funding

No funding was received for conducting the research and preparation of this article.

Declaration of Generative AI and AI-assisted technologies in the writing process

The authors declare that no Gen AI was used in the creation of this article.

Declaration of Competing Interest

The authors declare that they have no competing interest. The contents of this article are solely the responsibility of the authors.

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