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Review

Microbiota–gut–brain axis: the mediator of exercise and brain health

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Abstract

The brain controls the nerve system, allowing complex emotional and cognitive activities. The microbiota–gut–brain axis is a bidirectional neural, hormonal, and immune signaling pathway that could link the gastrointestinal tract to the brain. Over the past few decades, gut microbiota has been demonstrated to be an essential component of the gastrointestinal tract that plays a crucial role in regulating most functions of various body organs. The effects of the microbiota on the brain occur through the production of neurotransmitters, hormones, and metabolites, regulation of host-produced metabolites, or through the synthesis of metabolites by the microbiota themselves. This affects the host's behavior, mood, attention state, and the brain's food reward system. Meanwhile, there is an intimate association between the gut microbiota and exercise. Exercise can change gut microbiota numerically and qualitatively, which may be partially responsible for the widespread benefits of regular physical activity on human health. Functional magnetic resonance imaging (fMRI) is a non-invasive method to show areas of brain activity enabling the delineation of specific brain regions involved in neurocognitive disorders. Through combining exercise tasks and fMRI techniques, researchers can observe the effects of exercise on higher brain functions. However, exercise's effects on brain health via gut microbiota have been little studied. This article reviews and highlights the connections between these three interactions, which will help us to further understand the positive effects of exercise on brain health and provide new strategies and approaches for the prevention and treatment of brain diseases.

Keywords: brain health; microbiota; exercise; fMRI; anxiety disorders; depression; cognition; food reward

Introduction

Brain health has a significant impact on every facet of our daily functioning, including sensory perception, motor control, orientation and cognitive function, emotion regulation, and execution of appropriate behaviour under social cognition (Wang *et al.*, 2020). In addition to emotional and cognitive processes, food reward is intimately connected to brain health. It is encoded by specific neural pathways in the brain and can be influenced by metabolic signaling; visual, olfactory, and gustatory stimuli derived from perception of food; and cognitive mechanisms such as attention, learning, and memory (Berthoud *et al.*, 2017). When the brain's reward system is overactivated, the human body will consume foods abundant with fat, carbohydrates, and energy, which may lead to overweight and obesity over time (Brondel *et al.*, 2022). A scientific assessment of brain health is necessary to define and promote optimum brain health. A number of questionnaires have been devised to examine the health of the brain by having frequent caregivers or close family members self-report or observe everyday activities or skills. But given the multifaceted nature of brain health, it is still difficult to provide a thorough assessment or measurement of brain health using a single indicator. Fortunately, functional magnetic resonance imaging (fMRI) has been used to assess the functional connectivity and integrity of the brain network (Modi *et al.*, 2017).

Microorganisms colonize extensively on the skin, respiratory tract, urogenital tract, eyes, and gastrointestinal (GI) tract, with most residing in the gut. The gut harbors various microorganisms, including bacteria, archaea, fungi, and viruses. Among all these, bacteria are the most abundant, diverse, and extensively studied microorganisms in the human body (Cryan *et al.*, 2019; Fülling *et al.*, 2019; Morais *et al.*, 2021).

Physiological and homeostatic functions are under regulation of a bidirectional gut–brain axis (Osadchiy *et al.*, 2019). In the past decade, the rapid development of microbiome science has been accompanied by a shift in our understanding of the traditional gut–brain axis, toward a more systemically biological perspective known as the microbiota–gut–brain (MGB) axis (Mayer *et al.*, 2022). The MGB axis is constituted with a two-way signal pathway connecting the GI tract and the central nervous system (CNS). The MGB axis executes inter-organ functions through three signaling pathways, including the neural, endocrine, and immune pathways (Kasarello *et al.*, 2023).

The intestinal microbiota has been extensively recognized and studied for its potential to affect host organism diversity and quantity, however, it is important to acknowledge that the host also reciprocally influences the dynamics and functioning of the microbiota (Clarke *et al.*, 2013; Erny *et al.*, 2015; Lyte, 2014; Sharon *et al.*, 2019). Currently, aerobic exercise has been demonstrated

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to affect the GI system by enhancing microbiome and functional metabolism in both humans and mice (Dalton *et al.*, 2019). Meanwhile, exercise has demonstrated promising potential in ameliorating symptoms of anxiety and depression, improving cognitive function, and modulating appetite and food reward mechanisms. Such effects are mediated by alteration in bacteria distribution and subsequent metabolite production (Beaulieu *et al.*, 2020; Cornier *et al.*, 2012). Consequently, there has been a notable increase in scholarly attention to the intricate correlation between exercise and the MGB axis. Meanwhile, the emergence of brain imaging technology, specifically fMRI, enables visualization of the key brain regions associated with the regulation of anxiety disorders, depression, cognition, and food reward in response to exercise (Mayer, 2011). This review endeavors to provide a succinct summary of the complex interaction among metabolites derived from gut microbiota, physical exercise, and cognitive well-being.

Gut microbiota-derived metabolites and brain health

Metabolites, the small molecules formed during microbial metabolism, serve as the key mediators regulating the interaction between gut microbiota and the brain. In perfect alignment with this intriguing interplay, the World Health Organization dedicates attention to the crucial subject of brain health, which encompasses multifaceted dimensions such as social-emotional, cognitive, and sensory functions. Extensive gut microbiota-derived metabolites have been unraveled as mediators that predispose individuals to various brain diseases. Hence, attaining a more comprehensive understanding of the role and dynamics of metabolites originating from gut microbiota would provide promising potential for the discovery of mechanistic predictive biomarkers for brain diseases and the development of possible screening and therapeutic options. The gut microbial metabolites can be further categorized into the following three groups, based on the ingredient and synthetic pathways: (i) metabolites produced by bacteria from dietary components, (ii) metabolites produced by the host and influenced by gut bacteria, and (iii) metabolites synthesized *de novo* by gut bacteria.

Metabolites produced by bacteria from dietary components

Short-chain fatty acids

Short-chain fatty acids (SCFAs) primarily arise from the microbial fermentation of plant-synthesized polysaccharides including celluloses, fibers, starches, and sugars. Among the SCFAs, acetic, propionic, and butyric acid are the predominant forms (Guilloteau *et al.*, 2010).

The production of butyrate is predominantly attributed to the *Firmicutes F. prausnitzii* and *Eubacterium rectale* (Flint *et al.*, 2012). Among SCFAs, butyrate is the SCFAs that is most readily taken up by the brain (Oldendorf, 1973). Owing to its potential as a neuropharmacological agent, butyrate has been extensively examined and studied, particularly at supraphysiological doses, to explore the epigenetic mechanisms regulating CNS neuronal transcription and behaviours (Stilling *et al.*, 2016). Previous studies have revealed that butyrate can improve memory in mouse models presenting with Alzheimer's disease (AD) (Govindarajan *et al.*, 2011). Additionally, numerous studies have documented that the blockage of histone deacetylases (HDACs) could enhance memory encoding and demonstrate a favorable effect over the biological expression of synaptic plasticity genes (Bieszczad *et al.*, 2015; Shang and Bieszczad, 2022). Recently, a study using obese mouse models reported that cognitive decline can be induced by quinolinic acid. Following the administration of butyrate treatment to the animals, it was discovered that butyrate treatment could inhibit the HDACs 2 activity, leading to enhanced histone H3 acetylation, thus favouring binding to the brain-derived neurotrophic factor (BDNF) promoters PII and PIV. This mechanism helps prevent the quinolinic acid-induced reduction in BDNF, thus reversing the synaptic and cognitive impairments (Ge *et al.*, 2023). Additionally, studies by Duncan and Elli and their colleagues documented a reduced concentrations of butyrate and butyrate-producing bacteria in the feces of those with obesity, suggesting that butyrate may contribute to the prevention of obesity-related cognitive decline (Duncan *et al.*, 2007; Elli *et al.*, 2010). Meanwhile, given there has been limited evidence, further studies may be required to elucidate the correlation between butyrate-mediated activation of brown adipose tissue and appetite control (Li *et al.*, 2018).

Propionic acid is primarily produced by *Bacteroides* spp. (Flint *et al.*, 2012). Importantly, propionic acid has the potential to influence food reward. It signals through SCFAs receptors, specifically FFA3, which are expressed on the portal nerves. The action of propionate enhances the activity in the dorsal vagal complex, a region that receives inputs from both the vagus nerve and the hypothalamus. The hypothalamus is a crucial brain region contributing to the regulation of appetite and metabolism (De Vadder *et al.*, 2014). Clinical studies demonstrated the ingestion of either control inulin, or an alternative biological compound called inulin-propionate ester, a unique dietary molecule favoring the synthesis of propionate within the GI tract, will diminish striatum-regulated anticipatory reward responses toward foods with high calorie levels (Byrne *et al.*, 2016). Therefore, it is suggested that propionic acid may play a contribute to personal food choice, while further studies may be warranted to elucidate the possible mechanisms. Overall, SCFAs demonstrate its ability to regulate processes related to mood, cognition, and food reward via the gut–brain pathways.

Metabolites produced by the host and influenced by gut bacteria

Serotonin

Serotonin, a common neurotransmitter widely distributed in the CNS and GI tract, has demonstrated an intimate association with gut microbiota. In both the CNS and peripheral system, Tryptophan (Trp) is a biological molecule serving as the precursor for central and peripheral serotonin production (Richard *et al.*, 2009). Central serotonin in the brain is synthesized via the Trp hydroxylase 2 enzyme, whereas enterochromaffin cells produce >90% of the total serotonin through the Trp hydroxylase 1 enzyme. Despite the fact that serotonin synthesized peripherally would not be able to cross the blood–brain barrier (BBB) (Agus *et al.*, 2018), peripheral serotonin and related metabolites in the GIT have indirect influence over the CNS by acting on the enteric nervous system (De Caro *et al.*, 2019; Pascale *et al.*, 2020). Moreover, the intestinal microbiota secretes enzymes that modulate the metabolic pathways of tryptophan, altering the level of downstream metabolites including serotonin, kynurenine, or indole derivatives, thus exerting influence on serotonin levels in the brain (Agus *et al.*, 2018). Central serotonin is extensively synthesized in the hippocampus (HPC), entorhinal cortex, and other brain structures, as a significant neuromodulator for cognitive function (Pourhamzeh *et al.*, 2022). Microbiota can directly influence the synthesis and metabolism of neuroactive molecules, as well as displaying autocrine functions

(Socała *et al.*, 2021). For example, *Candida*, *Escherichia*, *Enterococcus*, and *Streptococcus* belong to serotonin producers (Dinan *et al.*, 2015). Evidence for direct regulation comes from germ-free (GF) animals. GF mice, in particular, consistently exhibit challenges in visual and working memory deficits mediated by the HPC (Ogbonnaya *et al.*, 2015). Serotonergic signaling is integral to pathogenesis of an extensive spectrum of psychiatric presentations, notably GAD and major depressive disorder. Medications remains to be the mainstay of the treatment through increase in CNS serotonin level via several mechanisms: selective inhibition of CNS serotonin reuptake, non-selective inhibition of both serotonin and norepinephrine reuptake, and inhibition of monoamine oxidase function (Roth *et al.*, 2021). Meanwhile, the serotonergic system functions tonically inhibit food intake and demonstrate a positive correlation toward the regulation of carbohydrate preference. Previous studies focusing on the rat population have demonstrated that administration of metergoline, a ligand acting as antagonist over the 5-HT receptor, will increase food intake and a higher preference for carbohydrates (Stallone and Nicolaidis, 1989). A recent article has also highlighted the role of GI microbiome on modification and alteration of behaviours associated with host dietary choices, with a hypothesis that Trp level might explain the underlying pathophysiology. Therefore, we might unravel a potential association between the gut microbiota and host foraging behavior (Trevelline and Kohl, 2022). However, more comprehensive studies may be warranted to elucidate the specific mechanisms regarding how serotonin modulates personal food choices.

Interestingly, in addition to its role in serotonin synthesis, Trp also contributes to the synthesis of kynurenine (Cervenka *et al.*, 2017). Mice that received fecal microbial transplants from depressed patients exhibited increased anxiety levels, higher circulating levels of kynurenine and elevated kynurenine/Trp ratios (Evrensel *et al.*, 2020; Kelly *et al.*, 2016). Furthermore, in GF mice, Clarke *et al.* reported an elevated Trp level, with an increased incidence of anxiety-like behavior. These findings may imply that pathophysiology of anxiety and depression could be multi-factorial (Clarke *et al.*, 2013).

BDNF

BDNF, one of the most widely expressed and comprehensively studied neurotrophins, is found in multiple regions of the brain, including the cortex and HPC. BDNF exerts a significant impact on the development, survival, and maintenance of neurons in the CNS (Numakawa *et al.*, 2018). Tropomyosin-related kinase B (TrkB) and p75 neurotrophin receptor (p75NTR) are the two receptors of BDNF (Podyma *et al.*, 2021). Owing to its direct involvement in neural functions, the role of BDNF in brain health has sparked considerable scholarly interest and investigation. BDNF signaling pathways has been extensively studied for its contribution toward the pathogenesis of mood disorders. It was reported that individuals with depression exhibit a decreased levels of BDNF messenger RNA (mRNA) and protein, particularly in the HPC, using cytology and post-mortem biopsy (Castrén and Monteggia, 2021; Ray *et al.*, 2014). Furthermore, reduced BDNF expression in older adults has been associated with impaired memory, neurodegeneration, and other cognitive impairments commonly seen in AD (Camuso and Canterini, 2023). Of note, BDNF, TrkB, and p75NTR are recognized for their contribution to whole-body energy homeostasis. TrkB signaling predominantly exhibits anorexigenic effects, counteracting weight gain, while p75NTR induces weight gain in response to lipid-rich diet and increases food consumption following the fasting state (Podyma *et al.*, 2020, 2021).

Several reports have highlighted the possible involvement of the gut microbiota in regulating BDNF expression (Lee *et al.*, 2018; Ranuh *et al.*, 2019). Aged rats exhibit a reduction of hippocampal BDNF level of ∼50% compared with younger rats. Li *et al.* performed a fecal microbiota transplantation (FMT) test that transferred gut microbiota from the elderly mice to their younger counterparts. Subsequently, they observed a reduction in the hippocampal BDNF levels, suggesting a possible correlation between gut microbiota and BDNF regulation (Li *et al.*, 2020). Coincidently, fecal transplantation increases microbiota diversity among young rats, including sub-species of *Prevotella*, *Bacteroides*, and *Parabacteroides* (Li *et al.*, 2020). Meanwhile, the administration of oral antimicrobials to specific pathogen-free mice caused a transient alteration in microbiota composition, resulting in an elevated level of *Lactobacilli* and *Actinobacteria* species, alongside with lower quantity of *γ-proteobacteria* and *Bacteroidetes*. Furthermore, hippocampal BDNF expression and exploratory behavior are favored by this therapy (Bercik *et al.*, 2011). These findings imply that the composition of the GI microbiome plays a crucial role in modulating HPC BDNF levels.

Cytokines

Cytokines are signaling molecules secreted by immune cells. Inflammation in the GI tract can be initiated after local infection, imbalance in the microbiota quantity and diversity, or exposure to various food antigens. Such triggers would lead to the production of pro-inflammatory cytokines, such as Interferon-γ, Interleukin-1β (IL-1β), IL-6, and tumor necrosis factor-α, which can cause damage toward the tight junctions within the intestinal epithelium, leading to reduced BBB integrity (Parker *et al.*, 2020). Numerous neurological conditions can arise in conjunction with comorbid GI inflammatory diseases and secondary alteration in serum level of pro-inflammatory biomarkers (Benakis *et al.*, 2020). The decline in cognitive function associated with aging is linked to a chronic, low-grade inflammatory state in both the enteric system and CNS. This leads to an increase in the level of microglia cells, T-lymphocytes, and border-associated macrophages in the brain, along with alterations in the gut microbiome composition (Golomb *et al.*, 2020; Mrdjen *et al.*, 2018). Therefore, we should postulate a close association between intestinal inflammation and neurological impairments pertaining to behavior and brain function. Further investigations with the special focus on the bidirectional communication between the gut and the brain could enlighten new strategies and opportunities for the prevention and treatment of relevant neurological disorders.

Metabolites synthesized *de novo* by gut bacteria

Lipopolysaccharides

Gram-negative bacteria's primary cell wall component, lipopolysaccharides (LPS), is regarded as a bacterial endotoxin when it enters the circulation. By attaching itself to the extracellular toll-like receptor 4 on a variety of cell types, LPS causes a strong inflammatory reaction, increases microglial activity, and causes neuronal cell death. Such a process will ultimately lead to cognitive impairment and cytokine-mediated sickness behavior, which may include impaired exercising capacity, reduced appetite, food intolerance, and withdrawal from social activities (Mailing *et al.*, 2019; Zhao *et al.*, 2020). *Lactobacillus rhamnosus* can reduce circulating LPS levels by altering gut permeability (Long *et al.*, 2021).

Recently, new evidence reported that the flora-derived peptidoglycan fragment muramyl dipeptide can cross the BBB and act

on Nod2 receptors on GABAergic neurons in hypothalamic areas, hence regulating appetite and body temperature in mice (Gabanyi *et al.*, 2022).

Exercise influences brain health

An increasing number of research articles have suggested that exercise plays a crucial role in enhancing brain health. Regular exercise has demonstrated remarkable benefits toward mental health, memory enhancement, improvement in cognitive function, and modulation of food reward responses. Nowadays, fMRI serves as a valuable tool that provides high-spatial resolution, allowing spatially accurate measurement of functional and structural CNS changes post-exertion (Won *et al.*, 2021). Therefore, this review will also focus on the use of fMRI to investigate the effects of exercise on various aspects of brain function.

The impact of exercise on anxiety disorders, and depression

An extensive number of studies have consistently reported a beneficial correlation between exercise and emotional well-being, including reductions in anxiety levels and depression symptoms (Andersson *et al.*, 2022; Goodwin, 2003; Pearce *et al.*, 2022; Singh *et al.*, 2023; Ströhle, 2009).

Exercise and anxiety disorders

General anxiety disorders (GAD) are characterized by psychological symptoms, including anxiety, fear, nervousness, and generalized worry, alongside with the presence of physical symptoms, such as palpitations, dyspnoea, dizziness, and muscle tension (Leichsenring *et al.*, 2023). The diagnosis of anxiety disorders is established by evaluating the severity, frequency, and duration of the symptoms, and whether such anxiety is linked with substantial psychosocial stigma and/or impairment in occupational, social, and other crucial areas of daily functioning (Leichsenring *et al.*, 2023). Many studies have established a correlation between anxiety disorders and the gut microbiome (MacKay *et al.*, 2024). Patients with GAD exhibited decreased microbial quantity and diversity, along with distinct metagenomic composition, suggesting microbiota dysbiosis in GAD patients (Jiang *et al.*, 2018). According to fMRI results, frontal lobe lesions causing a loss of functional connectivity between cortical areas such the insula, amygdala, anterior cingulate cortex, medial temporal, and prefrontal cortex (PFC) are characteristics of anxiety disorders (Fonzo, Etkin, 2017; Kenwood *et al.*, 2022; Steinhäuser *et al.*, 2023). Machine learning studies using fMRI as a feature have demonstrated the capacity to differentiate patients with anxiety disorders and healthy individuals within the controlled group. This would suggest a promising potential for enhancing diagnostic accuracy and tailored targeted treatments at an earlier stage (Rezaei *et al.*, 2023).

The traditional treatment for GAD involves medication and cognitive behavioral psychotherapy. However, in the last decades, physical exercise, specifically aerobic exercise, has been extensively prescribed as a distinctive domain under the non-pharmacological therapy for anxiety disorders (de Souza Moura *et al.*, 2015; Ramos-Sanchez *et al.*, 2021). In a randomized controlled trial (LeBouthillier and Asmundson, 2017), 48 individuals diagnosed with anxiety-related disorder were randomly assigned to a 4-week exercising program with fortnightly participation. Participants were randomly distributed several groups: aerobic exercise, resistance training, or no exercise. Statistics revealed effectiveness in both aerobic and resistance training for the improvement of anxiety disorder. Aerobic exercise specifically improves overall psychological distress and anxiety, while resistance training relieves disorder-specific symptoms, anxiety sensitivity, distress tolerance, and intolerance of uncertainty. Surprisingly, some research found that even a single episode of exercise can help alleviate anxiety (Broman-Fulks *et al.*, 2015; Connor *et al.*, 2023), Although anxiety has shown effectiveness in alleviation of anxiety-related symptoms, there remains disagreement regarding its effectiveness as compared with the conventional medication and psychological therapies. Meanwhile, there has been no consensus determining the ideal exercise intensity for the most effective response. Subsequent studies should involve participants with moderate to high anxiety levels and incorporate fMRI to visually assess whether exercise enhances activation of brain regions related to anxiety disorders, notably including the PFC as well as anterior cingulate cortex (Connor *et al.*, 2023).

Exercise and depression

Depression is characterized by depressed mood and anhedonia. It is a pervasive mental illness linked to high rates of morbidity and death (Zhao *et al.*, 2020). The etiology of depression remains unclear. Potential causes would include genetics, neurotransmitter changes, diet, and psychosocial factors (Rajendram *et al.*, 2021). Activation of cytokine-mediated kynurenine pathway results in an increase breakdown of Trp, ultimately leading to decreased serotonin levels, which is a widely acknowledged feature of depression (Polityńska *et al.*, 2022). Meanwhile, depression is closely linked to structural and functional changes in the brain. In terms of structural changes, reductions in volume have been observed in the HPC and the dorsolateral PFC (DLPFC) (Campbell and Macqueen, 2004; Geerlings and Gerritsen, 2017). In terms of functional changes, there has been evidence indicating a decreased activity in the DLPFC, the HPC, the orbitofrontal cortex (OFC), and DLPFC-OFC connectivity. Notably, the increase in HPC activity is directly correlated with the improvement in mood symptoms (Han *et al.*, 2023). Additionally, recent studies employing single-nucleus RNA sequencing have uncovered disturbances in deep layer excitatory neurons, astrocytes, and oligodendrocyte precursor cells in the PFC of males experiencing depression. Conversely, females with depression exhibit diminished activation of microglia and heightened synaptic connectivity (Maitra *et al.*, 2023).

Evidence from systematic reviews suggests that exercise has a moderate effect size for treating depression and has comparable effects to evidence-based therapeutics including medications and CBT (Mutrie *et al.*, 2018).

In an 11-year longitudinal study involving 33 908 adults, regular exercise demonstrated efficacy in mitigating depression. Remarkably, participation in 1 hour of exercise per week was associated with a 12% reduction in the incidence of depression (Harvey *et al.*, 2018). Exercise has been shown in animal research to enhance the development and functionality of the HPC in individuals with depression. Following a 6-week treadmill exercise program (20 minutes per day), rats exhibiting depressive-like symptoms demonstrated a notable reversal in hippocampal volume decline. Additionally, an overall increase in the astrocytes and an elevated density of newly emerged astrocytes within the HPC were observed (Li *et al.*, 2021). Similar results have been replicated in clinical research. Various studies have revealed that appropriate aerobic exercise exerts a favourable effect on preserving hippocampal volume integrity, fostering HPC regeneration, activating PFC function, and eventually improving the brain neuroprocessing efficiency while postponing cognitive decline in patients with depression (Alderman *et al.*, 2016; Olson *et al.*, 2017; Zhao *et al.*,

2020). Additionally, an 8-week organized, supervised exercise intervention's effects on hippocampal function and total brain activity in hypoactive persons with or without depression are examined in a small fMRI pilot research that uses the subsequent memory paradigm. According to this research, exercise causes a general deactivation of the HPC and other memory-related brain areas in people with depression. Therefore, this indicates a potential correlation between exercise and enhanced cortical inhibition or increased neural network efficiency in brain regions that are known to inhibit memory encoding during the process of memory encoding (Gourgouvelis *et al.*, 2017).

Based on the evidence, it can be inferred that exercise exerts a positive effect in alleviating depression, particularly in cases with mild to moderate presentations, and can be recommended as a complementary approach alongside traditional treatments. Participating in moderate-intensity aerobic exercise sessions, occurring 3–5 times weekly, with durations spanning 4–16 weeks, is recommended for alleviating depressive symptoms (Xie *et al.*, 2021). However, there has been limited evidence examining the correlation between exertional activity, neuroimaging, and depression. The related studies should be strengthened, and there should be a comprehensive evaluation of whether exercise would induce activation of brain regions involved in the pathogenesis of depression.

The impact of exercise on cognition

Tests of visuospatial, memory, attention, language, abstraction, and orientation are relative measures of cognition (Taylor, Workman, 2021). These functions involve several brain regions, including the PFC, amygdala, HPC, parietal cortex, inferior frontal gyrus (IFG), dorsal anterior cingulate gyrus (ACG), and dorsolateral prefrontal gyrus (McGillivray *et al.*, 2021). The functional connectivity among the default mode network (DMN), the fronto-executive network, and the frontoparietal network is intricately linked to cognition (Voss *et al.*, 2010). Poor diet, systemic inflammation, and aging could contribute to cognition impairment, whereas the interventions aimed at modulating the gut microbiome can alter cognition (Leigh and Morris, 2020; Yao *et al.*, 2022).

Between the continuum of typical aging and dementia lies a transitional state referred to as mild cognitive impairment (MCI). The identification and prediction of MCI have notable clinical value in early dementia diagnosis and prediction of prognosis (Yao *et al.*, 2022).

There has been a surprising increase in the significance of exercise as a non-pharmacological therapeutic in the aversion of cognitive decline, enhancement of cognitive function, optimization of daily activities, and clinical improvement in neuropsychiatric symptoms (Huang *et al.*, 2020; Karamacoska *et al.*, 2023; Langoni *et al.*, 2019; Mollinedo Cardalda *et al.*, 2019; Wilke *et al.*, 2019; Xiong *et al.*, 2021). Several observational studies utilizing fMRI technology have indicated that habitual exercise can enhance the functional connectivity of the DMN, as well as improve attention and language networks, in relation to aging-related cognitive decline (Voss *et al.*, 2010; Zlatar *et al.*, 2013). Interestingly, a specific form of exercise, Tai Chi Chuan (TCC), has demonstrated the ability to increase cortical thickness in the posterior cingulate gyrus, a region linked to cognitive function and functional homogeneity (Wei *et al.*, 2014, 2013). These findings suggest that long-tern engagement in 11 hours of TCC practice per week could lead to regional structural changes, implicating that TCC may exhibit similar changes in neural patterns that are observed in aerobic exercise. Several studies investigated how exercise-induced changes affect cognitive function among both healthy individuals and those with MCI using fMRI (Table 1). Most intervention studies conducted on cognitive decline have focused on aerobic exercise. Walking at an average 60% of maximum heart rate for 40 minutes per day over the course of 1 year has been found to enhance functional connectivity between various regions of the frontal, posterior, and temporal cortices within the DMN and a Frontal Executive Network (Voss *et al.*, 2010). Review reports suggest that aerobic exercise, with durations spanning from 3 and 6 months, demonstrates a primary impact on specific temporal, frontal, and parietal regions within the diseased brain (Haeger *et al.*, 2019). Furthermore, the HPC, one of the first structures affected by AD, has been identified as a central region of interest in these studies (Fjell and Walhovd, 2010). In individuals with amnestic MCI, participation in a 16-week regimen of aerobic training, involving 3 sessions weekly, each lasting up to 40 minutes, conducted at a level of intensity ranging from 70 to 80% of cardiac reserve. There has been a notable increase in functional plasticity during associative memory encoding in prefrontal regions, including the left IFG, the left precentral gyrus, and the left middle frontal gyrus (Yogev-Seligmann *et al.*, 2021). Meanwhile, two studies investigated on resistance training and cognitive decline. The first study enrolled 86 women with probable MCI. The diagnosis was made based on clinical history of memory complaints and a reduced score in the Montreal Cognitive Assessment. Participants from the intervention group were assigned to a 6-month training program, whereas participants from the control group were distributed to aerobic training. Both exercising programs were conducted twice per week with equal session duration. The group that underwent resistance training (seven participants) showed remarked increase in both Stroop task and associative memory task compared to control groups. Additionally, resistance training altered the way that the right lingual, occipital-fusiform gyri, and right frontal pole of the brain functioned (Nagamatsu *et al.*, 2012). In the second article, the intervention group were provided with progressive resistance training programs for a total duration of 26 weeks. Each week participants were asked to participate in two 90-minute sessions. It has been reported that resistance training has led to significant improvements in global cognition and an expansion of gray matter in the posterior cingulate. Interestingly, no additional therapeutic benefit was discovered in the combination of resistance and cognitive training (Suo *et al.*, 2016).

Furthermore, multiple studies have examined the influence of the intensity of exertional activities on the perseverance of cognitive function. Although short-term moderate-intensity exercise boosts cognitive functionality, no statistically significant associations were reported between brief high-intensity aerobic exercise and cognitive improvement. Sudo *et al.* reported an impairment in cognitive performance during high-intensity exercise (Sudo *et al.*, 2022), while the majority of studies indicate that high-intensity exercise does not affect cognitive control, or only has a modest but statistically significant improvement on cognitive (Loprinzi *et al.*, 2021; Moreau and Chou, 2019). In a 60-minute acute high-intensity exercise, there was no observed decrease in cognitive functionality following fatigue and tiredness (Davranche *et al.*, 2018). The improvement in cognition due to exercise can be attributed in large part to its upregulation of powerful antioxidant enzymes, resulting in increased antioxidant levels and activation of antioxidant enzyme activity (de Meirelles *et al.*, 2014; Gomez-Cabrera *et al.*, 2008). The intensity of exercise correlates closely with levels of antioxidant enzymes, as strenuous physical activity notably boosts oxidative stress response, consequently elevating the body's antioxidant levels (Gomez-Cabrera *et al.*, 2008;

Table 1: List: of included studies on exercise-related changes affect cognitive function among both healthy individuals and those with MCI using fMRI.

Participant	Ex details			fMRI results after Ex	Reference
	Intensity	Duration	Frequency		
Walkers ($n = 30$) YA controls ($n = 32$) FTB controls ($n = 35$)	Average 60% HRmax	40 min/week	1 year	To walkers: functional connectivity between aspects of the frontal, posterior, and temporal cortices within the DMN, a FE Network, and the FP network↑	(Voss *et al.*, 2010)
Elderly ($n = 120$)	-	-	Habitual Ex	Functional connectivity of the DMN↑	(Voss *et al.*, 2010)
PA ($n = 15$) SO controls ($n = 12$) YA controls ($n = 14$)	-	At least 45 min/week	Habitual Ex	Attention and language networks↑	(Zlatar *et al.*, 2013)
TCC ($n = 22$) health controls ($n = 18$)	-	11 ± 3 hours/week	Habitual Ex	Cortical thickness in the left superior temporal gyrus, medial occipito-temporal sulcus, lingual sulcus, and right insula, precentral gyrus, DLPFC↑	(Wei *et al.*, 2013)
TCC ($n = 18$) health controls ($n = 22$)	-	11.9 ± 5.1 hours/week	Habitual Ex	Functional homogeneity in the PosCG↑	(Wei *et al.*, 2014)
YA ($n = 28$)	NR	7.5 minutes balance training and 35 minutes rest/week	1 day/week for 6 weeks	The FP network connectivity↑	(Taubert *et al.*, 2011)
MCI ($n = 17$) health controls ($n = 18$)	50–60% HRR	Up to 30 min/day	4 days/week for 12 weeks, at least 44 sessions	To all individuals: the activation strength of the 11 brain regions activated in the semantic memory task↓	(Smith *et al.*, 2013)
aMCI: AET ($n = 31$) SAT controls ($n = 39$)	AET: up to 85–90% HRmax SAT: <50% HRmax	Up to 30–40 min/day	4–5 days/week for 12 months	To all individuals: memory and executive function performance↑ To AET: hippocampal atrophy↓	(Tarumi *et al.*, 2019)
aMCI: AET ($n = 13$) BAT controls ($n = 14$)	AET: up to 70–80% HRR BAT: <0% HRR	Up to 40 min/day	3 days/week for 16 weeks	To AET: frontal activity and neural synchronization such as the frontal cortex and TPJ↑	(Yogev-Seligmann *et al.*, 2021)
MCI: PRT + CCT ($n = 27$) PRT + SHAM CCT ($n = 22$) CCT + SHAM PRT ($n = 24$) double SHAM ($n = 27$)	NR	90 min/day	2 days/week for 26 weeks	To PRT: global cognition and gray matter in the posterior cingulate↑ To CCT: functional connectivity between the HPC and superior frontal cortex↑	(Suo *et al.*, 2016)

Ex: exercise; YA: young adult group; FTB: flexibility, toning, and balance group; HRmax: maximum heart rate; FE: frontal executive; FP: frontal parietal; PA: physical activity; SO: sedentary old group; PosCG: post-central gyrus; NR: no report; HRR: heart rate reserve, was defined as age-predicted maximal heart rate (220 − age) minus resting heart rate determined after 10 min of supine rest prior to the exercise test; aMCI: amnestic mild cognitive impairment; AET: a control group that participated in an aerobic exercise training program; SAT: a control group that participated in a stretching and toning program; BAT: a control group that participated in a balance and toning program; TPJ: temporo-parietal junction; PRT: progressive resistance training; CCT: computerized cognitive training; ↑: increase; ↓: decrease.

Nobari *et al.*, 2021). The increase in antioxidant enzyme levels within the body can bolster antioxidant defense mechanisms, decrease oxidative stress, thereby enhancing both physical performance (such as balance, muscle strength, and coordination) and cognitive functions (Madiha *et al.*, 2021).

Exercise training can change the brain's structure and function. According to current publications, two critical open questions warrant further investigations in the future: first, whether the clinical improvement in cognitive function would persist after cessation of the intervention, and if so, what is the maximal duration? Second, could exercise-based intervention inhibit or decelerate the conversion from MCI to dementia state?

The impact of exercise on food reward

Food rewards consist of two distinct components: liking, which relates to the enjoyment and taste of food, as evidenced by brain signals in the insula and the OFC, and wanting, which drives individuals to eat, as observed through brain signals in the cingulate cortex, the thalamus, and the putamen (Berridge, 1996; Born *et al.*, 2011; Schultz *et al.*, 2000). Changes occur in the brain's rewarding functions regarding energy-dense and tasty meals, such as those abundant in lipids and carbohydrates, could be a substantial contributor to the onset of obesity (Brondel *et al.*, 2022). In the brains of obese individuals with disordered eating patterns, the lateral hypothalamus-dorsolateral HPC neural circuitry is

Table 2: Summary: of the study on the effects of exercise on food reward using fMRI.

Participant	BMI (kg/m^2)	Ex details			fMRI results after Ex	Reference
		Intensity	Duration	Frequency		
Healthy individuals ($n = 37$)	24.5 ± 3.7	-	151.1 ± 159.9 min/week	Habitual Ex	To high-calorie foods: the mOFC and left anterior insula↓	(Killgore *et al.*, 2013)
Lean individuals ($n = 22$) Individuals with obesity ($n = 18$)	Lean individuals: 22.6 ± 1.9 Individuals with obesity: 35.2 ± 4.0	-	129.3 ± 97.1 min/day	Habitual Ex	To all individuals: the left postcentral gyrus and middle insula↓	(Luo *et al.*, 2018)
Healthy individuals ($n = 30$)	23.6 ± 0.4	83% HRmax	60 min	Acute Ex	To high-calorie foods: the insula, putamen, Rolandic operculum, and OFC↓	(Evero *et al.*, 2012)
Healthy men ($n = 15$)	24.2 ± 2.4	70% VO_2max	60 min	Acute Ex	To low-calorie foods: the insula, putamen and left pallidum↑and the OFC↓ To high-calorie foods: the DLPFC↑and the OFC, HPC, and left pallidum↓	(Crabtree *et al.*, 2014)
Healthy men ($n = 24$)	23.5 ± 1.6	74% HRmax	AMIE:60 min or HIIT: four minutes of warm-up and five all-out cycling efforts	Acute Ex	MOR binding correlated negatively with the exercise-induced changes in neural anticipatory food reward responses in OFC and cingulate cortices, insula, ventral striatum, amygdala, and thalamus	(Saanijoki *et al.*, 2018)
Healthy men ($n = 23$)	22.9 ± 2.1	70% VO_2max	60 min	Acute Ex	To high-calorie foods: the left precuneous cortex, left frontal pole, and left posterior cingulate gyrus↑	(Thackray *et al.*, 2023)
Individuals with obesity/overweight ($n = 12$)	33.0 ± 4.0	Up to 75% VO_2max	Up to 40–60 min/day	5 days/week for 24 weeks	The bilateral parietal cortices, left insula, and visual cortex↓	(Cornier *et al.*, 2012)

BMI: body mass index; Ex: exercise; mOFC: medial OFC; HRmax: maximum heart rate; VO_2max: maximal oxygen consumption; AMIE: aerobic moderate-intensity exercise; HIIT: high-intensity interval training; ↑: increases neural responses; ↓: reduce the neuronal response

impaired (Barbosa *et al.*, 2023). Limited exertion correlates with increased preference and desire for foods with high energy density, while conversely, habitual moderate-to-vigorous physical activity inhibit such behaviours (Beaulieu *et al.*, 2020).

fMRI studies have shown different hemodynamic responses to visual images representing high- and low-calorie diets at the neuronal level. Such alteration is most notable in brain regions implicated involved reward processing and was further augmented after exercise, suggesting exercising could induce an altered anticipatory reward processing (Table 2) (Killgore *et al.*, 2013; Luo *et al.*, 2018). According to published research, subjects in good health who perform acute aerobic exercise for 60 minutes show decreased neural reactivity to high-calorie foods in the bilateral insula, OFC, and putamen, and increased neuronal reactivity in the left precuneus (Evero *et al.*, 2012; Thackray *et al.*, 2023). High-intensity exercise at 70% of maximum heart rate for 60 minutes decreases neuronal activity to pictures of high-calorie food in OFC and left HPC, as compared with non-foods. It also increases activation in the dorsolateral PFC immediately after exercise, as compared with rest (Crabtree *et al.*, 2014). Furthermore, the endogenous μ-opioid receptor (MOR) system has demonstrated contributory effects toward the rewarding responses for both meals and physical activities. High-intensity interval training of continuous aerobic cycling at 74% maximal heart rate for 60 minutes correlated with alterations in MOR binding and has been adversely associated with the post-activity modifications in neuronal anticipatory food reward in OFC, thalamus, ventral striatum, amygdala, cingulate cortices, insula, and thalamus (Saanijoki *et al.*, 2018). Similarly, long-term exercise has the potential to modify food reward responses on an individual level (Beaulieu *et al.*, 2020; Cornier *et al.*, 2012). After 12 weeks of physical training, obese individuals demonstrated a significant reduction in cravings for fat-enriched foods and a reduced desire for sweet foods (Beaulieu *et al.*, 2020; Thivel *et al.*, 2020). Meanwhile, Cornier *et al.* allocated participants to either a continuous exercise program lasting 24 weeks, with each week having five training sessions of 40–60 minutes, or a control group. Their study revealed that, in the intervention group, there was a remarkable decrease in neuronal activation in the OFC and left HPC when participants received visual stimulus of high calorie foods, as contrasted with inedible stimuli (Cornier *et al.*, 2012).

Exercise can influence food reward by affecting liking, wanting, and the satisfaction associated with the ingestion of food with higher energy contents. This may have implications for weight management and appetite control. However, it is crucial to acknowledge that the relationship between exercise and food re-

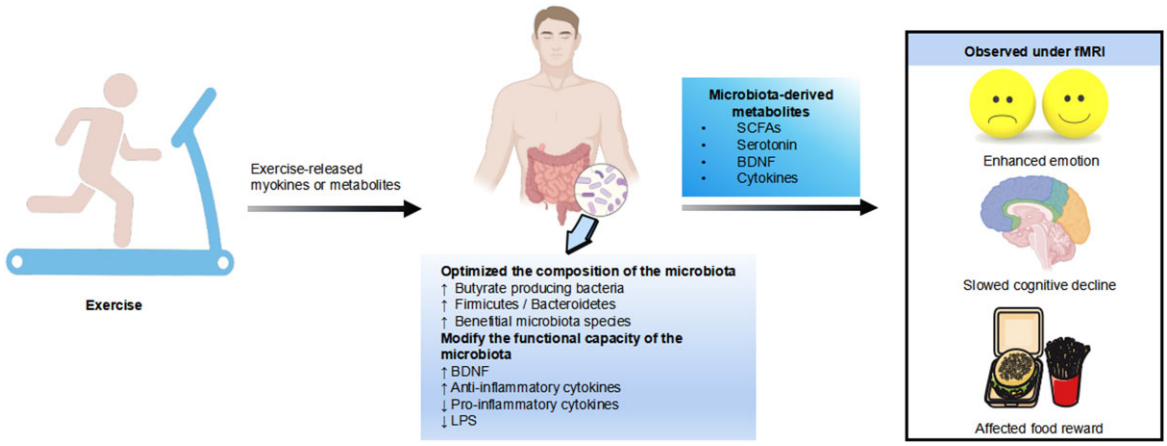

Figure 1: Description of the positive effects of exercise on gut microbiota and brain functions SCFAs: Short-chain fatty acids; BDNF: Brain-derived neurotrophic factor; LPS: Lipopolysaccharide; fMRI: Functional magnetic resonance imaging; ↑: increase;↓: decrease.

ward is multifaceted and could be influenced by multiple contributing factors including physical exercise level and individual characteristics.

Exercise influences gut microbiota

Recently, there has been increasing emphasis on investigating the potential mechanisms linking the gut microbiota with specific brain diseases such as depression and AD (Amin *et al.*, 2023; Kim *et al.*, 2021). It has been hypothesized that an alteration in gut bacterial population may adversely affect the physiological activities of the CNS. As previously mentioned, exercise has a well-established benefit in brain health. Additionally, some articles advised that exercise might demonstrate a promising effect to modify the diversity of intestinal flora, thereby enhancing GBA functionality (Fig. 1).

Exercise can optimize the composition of the microbiota

Exercise can increase the proportion of SCFAs-producing bacteria. A study conducted by Estaki *et al.* reported a rise in total SCFAs production in C57BL/6 mice after engaging in a voluntary wheel running program for 6 weeks (Estaki *et al.*, 2020). Furthermore, sedentary mice fed with a high-fat and high-cholesterol diet received FMT from C57BL/6J mice that underwent exercise had an increased total SCFAs concentration in their feces, as compared to those receiving FMT from sedentary animals (Li *et al.*, 2023). Among the SCFAs, butyrate seems to be notably affected by exertion. In studies conducted on rodents, engaging in 5 weeks of voluntary wheel running has been demonstrated to have a positive influence on certain bacterial taxa, including *Bacteroidales*, *Clostridiaceae*, *Lachnospiraceae*, *Ruminococcaceae*, and the *Clostridiales order* (Evans *et al.*, 2014). These taxa are contributory to the production of butyrate. In humans, exercise appears to be equally effective in boosting SCFAs. A study comparing active women to sedentary counterparts found that women who engaged in at least 3 hours of exercise per week had higher levels of *Faecalibacterium prausnitzii*, *Roseburia hominis*, and *Akkermansia muciniphila* (Bressa *et al.*, 2017). *Faecalibacterium prausnitzii* and *Roseburia hominis* have demonstrated a direct contributory effect toward the synthesis of butyrate, while there has been documented benefits in reducing body mass index and enhanced metabolic functions secondary to elevation in *Akkermansia muciniphila* level (Dao *et al.*, 2016; Louis, Flint, 2009). Metagenomic analyses have revealed that athletes exhibit unique pathways for the biosynthesis of amino acids and breakdown of carbohydrate. Meanwhile, there has been an elevated SCFAs concentration in their feces (Barton *et al.*, 2018). Exercise has the potential to regulate the production of SCFAs. In return, the increase in SCFAs level can directly enhance GI functionality and also have beneficial effects on CNS health (Dalile *et al.*, 2019; Generoso *et al.*, 2021). SCFAs stimulate mitochondrial biogenesis, improve respiratory capacity, and activate antioxidant enzyme activity to improve cognition (Amin *et al.*, 2023).

Several studies, both in animals and humans, provide evidence that exercise increases the ratio of *Firmicutes* to *Bacteroidetes phyla*, which has been reported substantial correlation with maximal oxygen uptake (Durk *et al.*, 2019; Kang *et al.*, 2014; Lambert *et al.*, 2015; Petriz *et al.*, 2014). Initially, a cross-sectional study conducted in 2014 focused on a group of elite rugby athletes. It was reported that they had a higher α diversity and a lower abundance of *Bacteroides* and *Lactobacillus* species than their lean sedentary counterparts (Clarke *et al.*, 2014). Later, in 2018, a controlled longitudinal study was carried out to further assess the influence of exercise on the intestinal flora (Allen *et al.*, 2018). This study enrolled 32 sedentary adults with both lean and obese body habitus. They participated in a supervised endurance exercise program with a total of 6 weeks duration. Allen *et al.* reported that exercise could induce an elevated prevalence of *Faecalibacterium* species and reduced *Bacteroides* species in lean individuals, with contrasting patterns observed in the obese counterparts. A comparable study was undertaken to investigate whether consistent exercise could alter the gut metagenome in previously sedentary, overweight women. Following 6 weeks of light-to-moderate level cycling, Munukka *et al.* observed an increased in the relative abundance of *Akkermansia muciniphila* and a drop in *Proteobacteria* (Munukka *et al.*, 2018).

Physical exercise also appears to have a positive effect on the intestinal flora-induced biosynthesis of Trp, phenylalanine, and tyrosine. This is supported by findings from fecal samples of half-marathon and cross-country trainees. (Tabone *et al.*, 2021; Zhao *et al.*, 2018). Furthermore, a decline in serum Trp levels was noted in individuals assigned with cycling test. Meanwhile, following a single session of endurance exercise, an increased level of kynurenic acid (KYNA) and an overall elevation in KYN/Trp ratio were also

reported (Joisten *et al.*, 2020; Manaf *et al.*, 2018). Therefore, we could hypothesize that the decrease in serum Trp could be secondary to increased CNS uptake, as there has been enhanced serotonin production within the CNS.

Apart from its ability to modify the quantity and diversity of gut microbiota, exercise also demonstrates potential to reduce the prevalence of diarrhoeal disorders secondary to microbiota changes. For instance, a study involving 33 elderly participants in Japan revealed that a 5-week endurance exercise regimen lower the incidence of *Clostridium difficile* infection, a primary culprit behind infectious diarrhea attributed to toxin production in the host intestine (Rupnik *et al.*, 2009; Taniguchi *et al.*, 2018).

Exercise can modify the functional capacity of the gut microbiota

Exercise also seems to positively influence some metabolites regulated by gut bacteria. Exercise increases the expression of BDNF mRNA in several brain areas in animal models (Cotman *et al.*, 2007). The precise processes by which sport induces BDNF expression of genes in the neural network, nevertheless, are yet unclear. According to one theory, exercise may raise BDNF levels by changing the BDNF promoters' epigenetic markers (Guan *et al.*, 2009; Koppel and Timmusk, 2013). We may hypothesize that an endogenous chemical is created after exercise, which can function as a metabolite contributing to BDNF transcription regulation, as exercise may cause metabolic alterations. Exercise causes D-β-hydroxybutyrate, a ketone substance, to accumulate in the HPC, according to some research. According to Sleiman *et al.*, it functions as both a form of energy and an inhibitor of class I HDACs, which causes secondary BDNF expression (Sleiman *et al.*, 2016).

The modulation of inflammatory states through exercise has a notable impact on both gut microbiota and health. After exertional activities, there has been a significant rise in anti-inflammatory cytokines and anti-apoptotic proteins within the lymphocytes residing in the intestine, associated with the decrease in pro-inflammatory cytokines. Therefore, the dual effect may contribute to a reduction in gut inflammation (Donoso *et al.*, 2023). Voluntary wheel running has been demonstrated to exert a regulatory effect over the immune function through decreasing *Turicibacter* quantity and diversity in both faecal samples and the caecum (Evans *et al.*, 2014). Similarly, participants with sedentary lifestyles who actively participate in either sprint interval or moderately vigorous physical activity showed decreases in both systemic and intestinal levels of the pro-inflammatory markers TNF-α and LPS-binding protein (Motiani *et al.*, 2020).

Exercise on the gut microbiota among different populations

Evidence indicates that exercise's type, intensity, frequency, and duration may change the microbiota's variety and composition, potentially providing health benefits (Campaniello *et al.*, 2022; Suryani *et al.*, 2022). Several publications have revealed that medium-intensity endurance exercise leads to most favorable outcomes, but results vary depending on the population and exercise protocol (Lensu, Pekkala, 2021). The relative abundance of SCFA was significantly influenced by the substantial elevation in physical activity among non-athletes. Aerobic training lasting for 60 minutes and physical activity involving more than 60% of maximum heart rate also exerted an influence on β diversity indexes. Compared to non-athletes, athletes exhibited increased diversity in the intestinal microbiota. Nevertheless, this was concomitant a reduced abundance of bacteria responsible for the production of SCFA and lactic acid (Dziewiecka *et al.*, 2022). A study showed that age also has a positive correlation with microbial α-diversity in individuals from Colombia, the USA, and the UK (de la Cuesta-Zuluaga *et al.*, 2019). Elderly individuals who are physically active, for instance, senior orienteering athletes, exhibited a more homogenous microbiota composition, concomitantly associated with a greater presence of *Faecalibacterium prausnitzii* comparing with non-active elderly residents within the community. *Faecalibacterium prausnitzii* has been noted for its beneficial characteristics. Moreover, senior orienteers demonstrated a reduced presence of *Parasutterella excrementihominis* and various unclassified subspecies of *Bilophila*, both of which have been linked with compromised gut functionality (Fart *et al.*, 2020). The composition of the intestinal flora from active elderly individuals resembled that from 18 to 60 years old at both the phylum and family levels (Zhu *et al.*, 2020).

Nevertheless, the existing research primarily targets older adults, obese individuals, and athletes. Therefore, further studies should involve a broader spectrum of the general population and ensure both genders have equal representation. While many studies have reported benefits of exercise on the gut microbiota, there have been inconsistencies and controversies, particularly regarding the influence of exercise on specific microbial populations.

Is the gut microbiota the mediator between exercise and brain health ?

Given the known dysbiosis in many brain health and the effects of exercise on both the gut microbiome and brain health, it is logical to explore how these factors intersect. Studies might look at whether the gut flora of an athlete could have a partial impact on brain health. There has been evidence that the gut microbiota influences brain health, pointing to a possible beneficial feedback loop between the variety of the microbiome and brain function (Madiha *et al.*, 2021). Some animal studies have begun to unpack the intricate relationship among gut microbiota, exercise, and CNS functionality, offering new opportunities into potential mechanisms that elucidate the positive effects of physical activity on brain function (Table 3).

Anxiety disorders and depression

Xie *et al.* administered swimming training to male C57/BL6J mice aged 5 weeks, 5 days a week for a duration of 5 weeks. Their research revealed that swimming exercise reversed depressive behaviors triggered by chronic unpredictable mild stress, with an observed rise in the levels of *Desulfovibrio*, *Streptococcus*, and *p-75-a5* (Xie *et al.*, 2022). Similarly, another research on swimming exercise also indicates that it improves depression-related symptoms through its anti-inflammatory activity and its ability to rebalance gut *Escherichia coli* and *Lactobacilli* (Ding and Du, 2022). In a separate study, Soares *et al.* conducted a 4-week running experiment on male Wistar rats, uncovering potential anxiolytic effects associated with intermittent fasting combined with aerobic training, along with an increase in propionic acid levels (Soares *et al.*, 2021). Watanabe *et al.* investigated the effects of 10 weeks voluntary exercise on the increased expression of BDNF and lowered biosynthesis of two proteins, Zo-1 and Claudin 5, that have been extensively involved in the development of tight junction in the brain. This suggests that exercise may affect the integrity of the BBB, potentially enhancing the exchange of nutrients and metabolites between the blood and the brain. Further-

Table 3: Exercise effects on microbiota and brain health.

Model	Exercise details			Changes in brain health	Gut microbiota outcomes	Reference
	Intensity	Duration	Frequency			
Anxiety and depression						
Male C57/BL6J mice	\ (Swimming)	50 min/day	5 days/week for 5 weeks	Depression-Like behavioral ↓	Abundance of *Desulfovibrio*; *Streptococcus*, and *p-75-a5* ↑	(Xie *et al.*, 2022)
Male C57/BL6J mice	\ (Swimming)	60 min/day	5 days/ week for 4 weeks	Depression-Like behavioral ↓; The expression of cytokines ↓ in the HPC	Abundance of *Lactobacilli* ↑; Abundance of *Escherichia coli* ↓	(Ding, Du, 2022)
Male Wistar rats	15 m/min	30 min/day	5 days/week for 4 weeks	Behavioural parameters of anxiety ↓	*Propionic acid* ↑	(Soares *et al.*, 2021)
Male C57/BL6J mice	\ (Wheel running)	Free and unlimited access	10 weeks	Depression-Like behavioral ↓; The expression of BDNF ↑ and the expression of Zo-1 and Claudin5 ↓ in the HPC	β diversity ↑ ; Abundance of *Bacteroidetes* and *Actinobacteria* ↑; Abundance of *Firmicutes* ↓	(Watanabe *et al.*, 2023)
Cognition						
Male C57BL/6 mice	7 m/min	60 min/day	5 days/week for 16 weeks	Contextual memory ↑; Trend cued memory ↑	Abundance of *Firmicutes* ↑; Abundance of *Bacteriodetes* and *Tenericutes* ↑	(Kang *et al.*, 2014)
Male APP/PS1 transgenic mice	Ten cycles of four minutes at high intensity (20 m/min) and two minutes at low intensity (10 m/min)	60 min/day	4 days/week for 20 weeks	Spatial memory ↑	Abundance of *Eubacteria*, *Roseburia* and *Clostridia* in AD mice↑; Abundance of *Prevotella*, *Bacterioides*, *Bacterioides fra gilis* and *Lactobacillus johnsonii* in AD mice ↓	(Abraham *et al.*,)
Male APP/PS1 mice	\ (Running wheel)	Free and unlimited access	16 weeks	Spatial learning and memory function ↑	Abundance of the *phyla Proteobacteria* and *Tenericutes*, genera *Bacteroides* and *Faecalibacterium* ↑; Abundance of the genera *Allobaculum* ↓	(Wang *et al.*,2021)
Male C57/BL6J mice	At 35–40%, 55–60% or 75–80% of the maximal capacity respectively in young mice and old mice		5 days/week for 4 weeks	Learning and memory function ↑; The expression of C3ar1, C3 and IL-6 ↓ in the HPC	β diversity ↑ ; Abundance of *Bacteroidales* and *Alistipes* ↑ Abundance of *lactobacilliaceae* and *lactobacillus* ↓	(Lai *et al.*, 2021)
Male LCR rats and HCR rats	20 m/min	31.5 min/day	5 days/week for 6 weeks	Postoperative freezing time and the decrement in recall (dwelling time) in LCR rats	α and β diversity ↑; Abundance of *Firmicutes* ↑; Abundance of *Bacteriodetes* ↑	(Feng *et al.*, 2017)

m: Meters; min: Minutes; LCR: Low-capacity runner; HCR: High-capacity runner; IL-6: Interleukin−6; HPC: Hippocampus; APP/PS1: APPSwe/PS1De9; AD: Alzheimer's disease; BDNF(Bdnf): Brain-derived neurotrophic factor; C3ar1: Complement 3a receptor 1; C3: Complement 3; ↑: increases neural responses; ↓: reduce the neuronal response

more, they observed an increase in β diversity (Watanabe *et al.*, 2023).

Wang *et al.*, conducted a 12-week moderate-intensity aerobic exercise intervention on young adolescents with subthreshold depression. They found that the relative abundance of certain gut microbiota, including *Coprococcus*, *Blautia*, *Dorea*, and *Tyzzerella* at the genus level, as well as *Tyzzerella nexilis* and *Ruminococcus obeum* at the species level, increased after the intervention. Additionally, there was an improvement in depression symptoms (Wang *et al.*, 2023), suggesting that exercise may exert clinical benefits on depression through modulation of the composition of intestinal flora. The underlying mechanisms are likely to be complex and multi-factorial, including gut microbiota composition, BBB function, and increased levels of neurotrophic factors such as BDNF. Future clinical studies are needed to confirm these findings and to explore the mechanisms underlying these effects in more detail.

Cognition

Kang *et al.* conveyed a 16-week study focusing on adult mice, indicating improvements in memory along with changes in the variety of gut microbes (Kang *et al.*, 2014). More precisely, the exercise regimen led to an augmentation in the prevalence of *Firmicutes* coupled with a simultaneous decline in the quantity of *Bacteriodetes* and *Tenericutes*. Additionally, using certain measures linked to fear conditioning, the researchers discovered a potential correlation between *Ruminococcaceae* and *Lachnospiraceae*. Although further investigation is warranted, the hypothesis between bacterial richness and context memory may serve as a reasonable microbiota biomarker if further assessment of exercise-induced cognition improvement.

Exercise has been shown to improve AD-related histopathological markers and cognitive abilities in the interim. Exercising may also raise the quantity of bacteria that produce SCAFs and lower the number of germs that contribute to the development of illness. In a study involving APP/PS1 transgenic mice who were given a 20-week treadmill running regimen, researchers observed improvements in spatial memory and an increase in the quantity of *Eubacteria*, *Roseburia*, and *Clostridia* in their bodies. Conversely, there was a decrease in the abundance of *Prevotella*, *Bacteroides*, *Bacteroides fragilis*, and *L. johnsonii* in AD mice. Notably, higher levels of *B. thetaiotaomicron* were associated with poorer performance in the Morris water maze test, which evaluates spatial hippocampal memory, while higher levels of *L. johnsonii* were positively correlated with β-amyloid content and localization (Abraham *et al.*, 2019). Another research found that voluntary wheel running improved gut microbiota and cognitive function in young APP/PS1 mice, suggesting that early initiation of exercise could potentially prevent or delay the onset of cognitive-related disorders (Wang *et al.*, 2021). Low intensity exercise has also been shown to enhance learning and memory in surgical mice while mitigating the neuroinflammatory process secondary to surgical intervention, as well as preserving the diversity of intestinal flora (Lai *et al.*, 2021). These studies provide consolidated evidence that, hypothetically, the gut microbiota may play a role in inflammatory modulation and may contribute positively to cognitive disorders (Feng *et al.*, 2017). In conclusion, there has been strong evidence supporting the crucial role intestinal flora played in inflammatory modulation and cognitive health. Engagement in exertional activities can positively modulate gut microbiota composition and foster the growth of beneficial bacteria. Therefore, this may be considered promising therapeutic approach for future prevention and treatment of cognitive-related disorders.

Food reward

A clinical study has identified a noteworthy association between a sedentary lifestyle and dietary habits characterized by low fiber intake and high consumption of sugars and processed meat. Furthermore, individuals with a sedentary lifestyle exhibited significantly higher levels of visceral and total corporal fat composition. Additionally, the diversity and network complexity of the gut microbiota were notably reduced in sedentary individuals compared to those who were physically active (Castellanos *et al.*, 2019).

Currently, an intricate association between intestinal flora, exercise, and brain health remains an underexplored territory in clinical research. Despite the growing interest in the gut–brain axis and the role of microbiota in overall health, there remains significant information regarding the underlying mechanisms. In the future, a more comprehensive approach combining clinical studies with animal research could lead to deeper insights into this complex interplay. By integrating fMRI with clinical and animal research, researchers can attain a more profound understanding regarding the interplay between the neural networks, the gut–brain interactions, and regulation of cognition and emotion. There are still limited clinical studies examining the intricate relationship among gut microbiota, exercise, and brain health, and future exploration is recommended for clarification of the underlying mechanisms.

Conclusion and future prospective

Research results show that although more variety in the microbiota improves brain function and may be a useful indicator for better health, metabolites from the gut microbiota are associated with negative health outcomes. Therefore, it is critical to get more insight into how exercise affects the microbiota and CNS as well as other consequences related to host health. There is evidence that changes in the gut microbiota's composition occur under physical and mental stress during exercise (Clark and Mach, 2016). Alterations in the composition of GI flora play a pivotal role in the pathogenesis of obesity and cognitive impairment (Gérard, 2016; Motger-Albertí and Fernández-Real, 2023).

The prevalence of AD is expected to more than double by 2050, posing significant challenges to healthcare infrastructure (Angrist *et al.*, 2020). The track record for developing treatments for AD has been marked by decades of failure, and the arrival of expensive, presymptomatic treatments will present specific challenges to the healthcare system. Akbari *et al.* reported in their randomized, double-blinded controlled trial that supplementation of a 12-week course of probiotics containing *Lactobaccilus acidophilus*, *Lactobacillus casei*, *Bifidobacterium bifidum*, and *Lactobacillus fermentum* would have favorable effects on reducing plasma malondialdehyde and serum high-sensitivity C-reactive protein levels, indicating a decrease in inflammatory responses (Akbari *et al.*, 2016). A statistically significant improvement in cognitive function has also been reported, with an average improvement in MMSE score of $+27.90 \pm 8.07\%$ in the intervention group compared to $-5.03 \pm 3.00\%$ in the control group. Despite the promising future for the use of microbiota-derived therapeutics in treatment or prevention of major neurocognitive disorders including AD, further large-scale RCTs with an extended follow-up period should be conducted to further evaluate clinical responses in diverse populations. Meanwhile, as there has been limited evidence regarding the potential risks and complications associated with microtia-derived therapeutics, it could be challenging for patients with cognitive disorders to give informed consent for specific clinical trials. An alternative domain of treatment would include exercise, which

is considered as a more promising, affordable and accessible option for individuals with AD. In comparison to other treatments such as behavioral therapy or microbiota transplantation, exercise may represent a promising, affordable, and easily accessible treatment option for individuals with brain disorders. It is postulated that the secret to this process lies in how exercise affects the gut microbiota's ability to communicate with the brain. The effects are still mostly unclear, thus future study should concentrate on them.

The purpose of this review was to demonstrate the critical function that the MGB axis plays in preserving optimum health by controlling the amount and variety of microbiota as well as the production of secondary metabolites. The potential biomechanisms of interactions displayed in this review may elucidate the possible underlying mechanism and provide further insight into the existing knowledge gap. Potential future research of interest would include further evaluation of possible mechanisms, development of more effective treatment strategies that incorporate exercise programs, and determine the clinical efficacy and accessibility of such interventions. The mechanism and biological basis of MGB axis still remain a vast area for future exploration. The impact of gut microbiota extends beyond GI, metabolic, and immune diseases to include certain mental disorders and the food-reward system associated with obesity. Given that the etiologies of abovementioned disorders have not yet been definitively identified, intestinal microbiota may act as a possible etiology or might have direct and indirect contributions to the current etiologies. Meanwhile, exercise has demonstrated a promising effect as an intervention for cognitive disorders and mental health disorders through targeting the gut microbiota.

Further studies would be also warranted to evaluate the effect of exercise, the intensity under long-term clinical follow-up, as well as the optimal duration, and the frequency of training session. It remains possible that the influence of exertion on intestinal microbiota could have a significant variation over individuals, depending on the frequency and intensity of exercising program: whether it is done as part of a routine to maintain weight and fitness, as part of a weight-loss plan with or without calorie restriction, or as intense physical training done by elite athletes. As such, it is impossible to generalize about how exercise affects the microbiome in general. The contentious topic of exercise intensity, kind, duration, or dosages still exists. Even with the increasing interest in this field, further studies involving exercise with direct microbiota analysis paired with fMRI are still required for future comprehension of the direct effects of exercise and the gut flora and the potential implications for brain health.

Author contributions

Piao Kang (Writing – original draft, Writing – review & editing), and Alan Zi-Xuan Wang (Writing – review & editing)

Conflict of interest

The authors declare no conflict of interest..

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