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REVIEW ARTICLE

Interactions Between Gut Microbiota and Brain: Possible Effects on Sport Performance

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Abstract

Purpose This review examines the bidirectional interactions between gut microbiota and the brain, with a specific focus on their implications for sport performance. The main research question addresses how gut-brain communication responds to physical activity and actively contributes to athletic performance in elite athletes subjected to high physiological demands.

Methods A comprehensive review was conducted analysing the characteristics and development of gut microbiota, the methods used to investigate microbiota-brain interactions and the bidirectional communication pathways. The analysis distinguished the two directions of interaction brain-induced effects on microbiota and microbiota-induced effects on brain activity, with specific integration into sports contexts.

Results The review identified that gut-brain communication constitutes a dynamic system that responds to physical activity through multiple pathways. Elite athletes, subjected to high-intensity training regimens, specialized nutritional approaches and specific performance goals, exhibit distinctive microbiota conditions. Brain-derived neurotrophic factor (BDNF), serotonin and butyrate emerged as key mediators that contribute to adaptive gut microbiota conditions and facilitate microbiota-brain interactions.

Conclusion The microbiota-gut-brain axis represents a fundamental system actively contributing to sport performance. The interdisciplinary evidence from neuroscientists, microbiologists, nutritionists and sports scientists demonstrates that understanding these interactions opens new frontiers for optimizing athletic performance through targeted modulation of this bidirectional communication system.

Keywords Microbiota · Gut-Brain axis · Cognitive Function · Sport Performance · Athletes

The Characterization of Gut Microbiota

The gut microbiota is a complex and diverse system composed of a number of *Prokaryota*, viruses and *Eukaryota*. Eukaryotic parasites are not strictly considered part of healthy microbiota, but they are the disturbing component interacting with it [10]. Despite these considerations, the vast majority of microbiota studies focused on bacteria [69]. Every different human being is characterized by a gut microbiota, with a specific balance of different microorganisms and in particular of anaerobic bacteria including *Bacteroides* and *Firmicutes*. Gut microbiota characterization has been linked to healthy or pathological human conditions and for this reason many attempts have been made to classify all the microbial species found in this organ [51, 101].

Up to the discovery of DNA sequencing technologies the only way to characterize microbes was through cultivation protocols. This slow procedure has been replaced by molecular tools based on genomic characterization. In the last 20 years an important technological revolution has affected DNA sequencing. High-throughput approaches have overcome the manual Sanger protocol opening the Next Generation Sequencing (NGS) era. The availability of new sequencers, together with the evolution of new bioinformatic tools, has reshaped several branches of biology and medical science. In microbiology, the characterization of biodiversity in environmental and clinical samples has

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become fast and automated. The adoption of metagenomic or metabarcoding (mainly focused on 16S rDNA sequencing) protocols allowed the characterization of α and β-diversity at different taxonomical levels [83].

The metagenomics approach is defined as "whole-genome shotgun sequencing", it is based on the sequencing of the sample's DNA at random points and on its subsequent reconstruction. Briefly, this protocol starts from the fragmentation of a genome in order to generate fragments of a few hundred base pairs. Fragmentation occurs at random points in the various copies of the genome present in the sample and this allows the generation of partially overlapping fragments. Their sequencing is then followed by a bioinformatic analysis where the overlapping parts are recognized and the individual sequences are integrated together to obtain a single large sequence, and ideally the entire genome. This approach allows in theory to identify all the taxonomic groups of the life forms of a sample, having available a comparison database containing even just a few sequences of a given species [7]. Until now, the metagenomic analysis of a sample was more expensive than other NGS techniques [86].

The metabarcoding approach has been widely used to characterize bacterial biodiversity. In this case, the sample is enriched using a PCR aimed at specific genomic markers that are highly discriminating for the species of a given taxonomic group. The result of the PCR is then subjected to sequencing. The barcode amplification step allows us to exclude DNA contaminants, greatly reducing background noise. The barcode most used for bacteria is the 16S ribosomal RNA gene (16S rRNA) and in particular the variable regions which allow a high taxonomic discrimination. The identification of the species is based on a comparison of the sequences obtained with annotated and specific nucleotide databases for the various taxonomic groups. For the identification of microbial eukaryotes other barcodes are available, like the internal transcribed spacer for fungi, or the nuclear 18S and 28S ribosomal rRNA genes [98]. Specific databases like UNITE and the SILVA are available for taxa identification. While a metagenomic approach can be useful for the detection of low abundant microorganisms, the metabarcoding based on 16S rDNA seems a robust methodology for comparative studies [86].

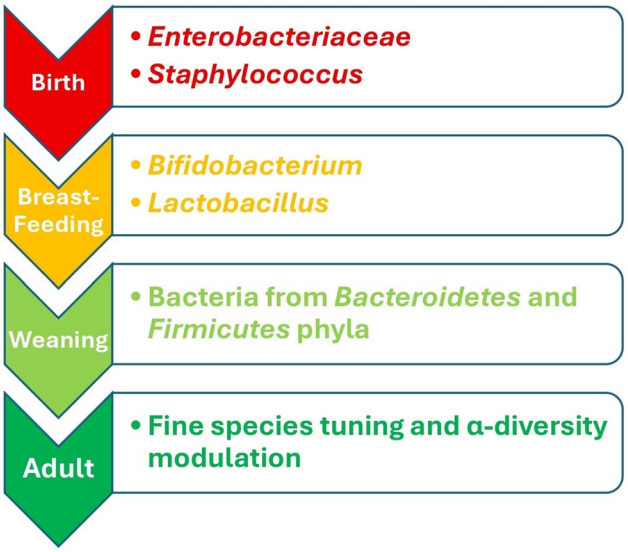
Recently, imaging techniques have been considered for spatial characterization of gut microbiota [16]. Ideally, the analysis of spatial distribution of the microbiota, or the quantification of bacterial load in specific gut regions, can be useful for the understanding of dysbiosis conditions. The approaches have been tested in animal models and generally are based on fluorescence in situ hybridization protocols or their evolution for 3D imaging [74]. Considering that these techniques can be applied only on biopsy material, their role in clinical diagnosis is still limited. A promising live imaging approach for gut microbiota has been described in animal models, combining positron emission tomography-computed tomography (PET-CT) and oral administration of 2-deoxy-2-[18F]fluoro-D-sorbitol, a compound preferentially absorbed by Gram-negative bacteria, especially Enterobacteriaceae. This approach is clearly useful for monitoring microbiota density alterations in animal models, but it is not clear if acceptable for routine clinical tests [113].

The Development of Gut Microbiota

The microbial colonization of human gut starts quickly after birth, and it is the result of interactions with the environment and in particular the maternal body (Table 1). In this context, the intestinal microbiota of newborns can be affected by the type of delivery (caesarean section or vaginal) and breastfeeding. The mother shares immediately part of her microbiota, and the analysis of meconium shows the presence of bacteria from the mother's reproductive organ [49]. In addition, *Enterobacteriaceae* and *Staphylococcus spp.* can initially populate the newborn gut, but they are rapidly replaced by *Bifidobacterium* and some lactic acid bacteria like *Lactobacillus spp.* [97]. The role of breastfeeding is crucial in this transition and *Bifidobacterium* can be found in human maternal milk [64]. *Bifidobacterium* is important for Human Milk oligosaccharide (HMO)-degradation and indolelactic acid production, a metabolite involved in intestinal homeostasis and immune response regulation [59]. These bifidobacterial species are probably the result of a host-microbe coevolution, that led to the selection of bacteria genetically adapted to the degradation of human milk glycans [72]. The presence of *Bifidobacterium* in breast milk has been associated with the reduction of food allergy in infancy, probably influencing the colonization of intestinal microbiota and by producing protective metabolites [103]. HMO are considered important prebiotics, presenting a protective and stabilizing effect on the pediatric gut. Formula-fed infants show more microbes associated with inflammation, and their gut microbiota moves rapidly to an adult-type composition [53].

After weaning, *Bifidobacterium* is replaced by other bacterial genera belonging to the phyla *Bacteroidetes* and *Firmicutes*, like *Bacteroides, Prevotella, Ruminococcus, Clostridium*, and *Veillonella*. The transition from milk feeding to solid food is a crucial moment for gut microbiota, not only for its composition but also for immunological

Table 1 Gut microbiota formation starts immediately after birth, but it is reshaped during the first days due to breastfeeding. After weaning, *Bacteroidetes* and *Firmicutes* are the main phyla present in the gut. Throughout life, a modulation of the α-diversity occurs in response to lifestyles and social/environment interactions.



reactions. Experiments on germ-free mice showed an increase in pro-inflammatory cytokines induced by microbiota during weaning. This immunological step seems fundamental to protect mice from inflammatory pathologies later in life [1]. Experiments on rabbits underlined the importance of weaning for the maturation of gut, suckling cessation triggers the activation of genes involved in epithelial differentiation and immunoglobulin [6]. The gut microbiota of healthy human adults shows a predominance of *Firmicutes* (40%) and *Bacteroidetes* (30%), with low percentages of *Actinobacteria* and *Proteobacteria* [29]. At the genus level, many differences can be reported between distinct individuals. While higher *α*-diversity is largely associated with a healthy condition, what aspects indicate a healthy state remains controversial and it is not possible to describe a definitive optimal composition for human gut microbiota [109]. Its fine composition can be affected by several factors like diet, physical activity, illness, therapies and social interactions. In particular, close social relationships, for example in cohabitation, have a strong effect on microbiota composition [96]. Highly abundant genera are shared in close relationships, and increased microbial similarity can be found in close marital relationships [33]. Close interactions, like those occurring during romantic relationships, are associated with increased gut microbiota diversity and health benefits, while relationship dissolution is associated with a stress condition, and it is possible to speculate negative effects also on microbiota *α*-diversity (Table 1) [23].

Microbiota-Brain Interactions

In recent years, the interactions between the brain activity and gut microbiota are gaining increasing attention, mainly due to their now substantiated implications in health. The communication between the gut and the central nervous system, namely the microbiota-gut-brain axis, is bidirectional and very complex, with various anatomical substrates, substances and microbial metabolites playing key roles. The neural, hormonal and immune system are involved in such a communication system [88].

From a neuroanatomical point of view, the bidirectional neuroelectric communication between the gut and the brain is based on the sympathetic and parasympathetic sections of the autonomic nervous system [34]. These two sections, along with the vagus nerve, inform the central nervous system on gut conditions and send back neural commands to respond to peripheral requirements supporting various physiological processes and homeostasis of brain and gut functions. Proper activity of this system is crucial for optimal functioning of the gut, which in turn constitutes a fundamental basis of physical and psychological well-being of the whole organism. The importance of the vagus nerve for the interaction between gut flora and the brain is substantiated by diverse direct evidences, such as the observation that vagotomy abolishes the beneficial effects of probiotic diets and reduces neurogenesis in the hippocampus, the demonstration that a reduction of the vagal tone can cause dysbiosis, and the observation that mice gut commensal bacteria might use the vagus nerve for translocation to the host brain [11].

A further structural component of the brain-gut communication is the hypothalamic-pituitary-adrenal axis (HPA), which has its main role in hormonal control and in the regulation of physical and psychological stress response [87]. Exposure to stress induces neurons in the hypothalamic paraventricular nucleus to secrete the corticotropin-releasing hormone into the hypothalamic-pituitary portal circulation. This hormone stimulates the production and release of adrenocorticotropin from the anterior pituitary gland which, in turn, stimulates the release of glucocorticoids from the adrenal cortex. Glucocorticoids can modulate metabolism, as well as both the immune function and the activity in the brain, coordinating the adaptive physiological response to stress. At the same time, several brain networks modulate the activity of the HPA axis. In particular, corticotrophin-releasing neurons in the paraventricular nucleus are inhibited by the hippocampus and the prefrontal cortex, and excited by the amygdala and the brainstem. In addition, glucocorticoids exert a negative feedback control of the HPA axis by regulating the paraventricular and hippocampal neurons. High glucocorticoid exposure has been shown to have

negative effects on the hippocampus, such as reduced dendritic branching, loss of dendritic spines, and reduced neurogenesis. The conversion of cortisol to cortisone, increased by physical activity, can protect from the negative effects of prolonged elevated cortisol levels, preventing various psychopathological conditions [23]. Recent evidence suggests that an abnormal activation of the HPA axis during the early life can have negative outcomes on the formation of the gut microbiota altering its microbial composition in the direction of a reduced diversity and abundance of beneficial bacteria, increasing intestinal permeability possibly allowing harmful substances to enter the bloodstream, increasing the possibility of inflammatory processes in the gut which can contribute to gastrointestinal disorders, and affecting negatively general metabolism favoring the onset of chronic diseases such as diabetes or obesity [14]. Abnormal stress-related HPA axis activation has also been linked to increased gut permeability [27]. The described effects can be exerted by gut microbial environment through both the nervous and the immune system. As an example of the complex interplay between these structures, the vagus nerve can trigger a cytokine-mediated immune response which provokes inflammation at gut levels. In response, afferent feedback from the gut via the vagus nerve can act on diencephalic regions of the brain and on the hippocampus, resulting in an activation of the HPA.

The mutual influence brain-gut-brain is further exerted through neurochemical changes involving several substances such as endorphins, anandamide, as well as neurotransmitters like serotonin and dopamine. The effects of these molecules range from motor activity to cognition, from sleep quality to mood [20].

The neurotransmitter serotonin is a key player in this context. Most (95%) of this substance is synthesized in the gut by intestinal enterochromaffin cells under induction signals coming from *Turicibacter sanguinis* and Clostridia bacteria. Serotonin contributes to intestinal motility and acts as a neurotransmitter under the co-regulation of different gut microbes such as *Bacteroides, Lactobacilli, Bifidobacteria,* and *Clostridia*. Gut mechanisms and microbiota have also an important role in the reuptake of serotonin and in the expression of its intestinal receptors [99]. Serotonin is also involved in motor behavior as a regulator of central fatigue [71] and is one of the most important regulators of mood, which is well-known to have a strict link with gastrointestinal health. Higher levels of serotonin induce improved mood, while lower levels are associated with anxiety and depression. Exercise increases the availability of the precursor of serotonin, tryptophan, which can cross the blood–brain barrier, increasing serotonin levels in the brain. Serotonin has a role in various brain functions such as thermoregulation, mood control, emotional behavior, food intake, and sleep–wake cycles. Excessive serotonin levels can lead to neurological issues, including mental and autonomic disorders [8].

A further key neurotransmitter is dopamine, which is synthesized through the phenylalanine-tyrosine-dopa-dopamine pathway both in the brain and in the gut, where it has several roles. In the nervous system it is implicated in reward and pleasure, learning, motivation, motor control, and pain modulation [47]. It is well known that failures of dopamine in the motor control function, which is based on the neural pathway from the substantia nigra to the striatum, are the primary cause of Parkinson's disease, but also other psychological dysfunctions depend at least in part from dopamine, such as addiction, autism, and schizophrenia. It is important to note that catecholamines, such as dopamine and norepinephrine, are usually unable to cross the blood-brain barrier, which can instead be achieved by some of their precursors such as L-3,4-dihydroxyphenylalanine (L-DOPA) for dopamine. In the gut, dopamine is involved in the regulation of intestinal motility, in the protection of the mucosa and in other physiological functions by binding to its own or to adrenergic receptors. The effects of dopamine in the two compartments (gut and nervous system) interact between them as demonstrated, e.g., by the fact that the microbiota can affect brain reward functions such as food intake, drinking, and addiction behavior by influencing the function of central dopamine receptors.

Furthermore, the two main neurotransmitters in the brain, namely glutamate and γ-aminobutyric acid (GABA), are related to the microbiota [70]. Glutamate, which is also a precursor of GABA synthesis, is the main excitatory neurotransmitter in the brain where its concentrations can be altered by gut dysfunctions. Vice versa, glutamate concentrations in the brain can affect the prevalence of various bacteria families in the microbiota. In the gut, through its ionotropic and metabotropic receptors, glutamate participates in motor and secretory reflex responses and in the perception of visceral pain. GABA, which acts instead as the main inhibitory neurotransmitter in the brain, can exert a similar function also in the gut, where it is also synthesized and where it controls motility and secretion processes playing also a key role in the microbiota-gut-brain axis. Through its two main receptors, GABAa and GABAb, GABA also controls the release of other neurotransmitters from enteric neurons.

Through these signaling mechanisms, gut microbiota can also influence immune responses and neuroinflammation in the brain, while the brain can modulate immune functions in the gut. This communication system is nowadays clear to have a basic role in shaping feeding behavior, energy homeostasis, overall health, and well-being. Dysregulation of gut microbiota has been linked to various

neurodegenerative disorders such as Parkinson's disease, Alzheimer's dementia, multiple sclerosis and Huntington's disease. These diseases have been associated with altered gut function, potentially resulting in increased gut permeability and inflammation. This can create an abnormal environment in the gut, which also affects communication with the brain [94].

Effects of Brain Activity and Behavior on Gut Microbiota

The percentage of older people is always increasing and finding ways of promoting physical and cognitive health is always more important. Among the behaviors/lifestyles that can be easily put into action, physical activity is considered an effective approach to counteract not only physical but also cognitive decline, having a powerful role in reducing chronic inflammation. The connection between the gut microbiota, the immune system, and neuroinflammation highlights the role of the gut–brain axis in maintaining brain health and preventing neurodegenerative diseases. However, the underlying mechanisms that drive the benefits of behavior on the gut are not fully understood [56, 77]. In the framework of the effects of exercise, cognitive activity and lifestyle on the gut microbiota it should be taken into account that exercise and cognitive activity interact closely, and several mechanisms of this interaction have been unveiled in the last years [39]. The most known effect is that aerobic exercise has beneficial impact on brain structure and function preventing age-related brain volume loss and promoting increased brain volume in key areas underlying cognition, in particular in the hippocampus, the structure which underlies memory processes. Exercise improves also symptoms of both mood and psychological disorders. Cognitive improvements due to exercise have been observed in healthy subjects, stroke patients and in psychopathological conditions such as depression and schizophrenia [26]. These beneficial effects can extend also to the digestive system in particular by promoting a diversification of gut microbes. Although the research on the effects of behavior on gut microbiota is recent, several beneficial effects of physical activity have been observed on gut health. Exercise can promote gastrointestinal motility decreasing the transit time of food in the gut therefore reducing the exposure of pathogens to the gastrointestinal mucus layer. This seems in turn to have beneficial implications in brain metabolism though improved mitochondrial function. Furthermore, the central nervous system regulates other important aspects of gut function like mucus secretion, barrier integrity, and visceral sensitivity [65].

Physical activity increases population sizes of *Firmicutes* and *Actinobacteria* as well as butyrate synthesis, promoting favorable effects on psychopathological issues such as mood, motor control, anxiety and depression. Furthermore, physical activity reduces both diarrheal disorders and intestinal stool time inducing a decrease in infections and inflammation processes and an increase of antioxidant enzymes, which can improve cognitive activity and sleep. Finally, physical activity promotes the synthesis of short chain fatty acids (SCFAs) along with a decrease of *Bacteroides* and an increase of *Faecalibacterium* and *Lachnospira*, effects related to beneficial outcomes on neurogenesis and brain plasticity. Physical activity is also associated with increased connectivity in inhibitory appetite control brain regions and with microbiota and metabolite signatures protective towards mental disease and metabolic disorders [94].

It is nowadays clear that understanding the brain-muscle-gut interplay is of fundamental importance to develop strategies to promote brain health, fight age-associated cognitive decline, and improve muscle health and longevity [15]. Physical activity has beneficial outcomes conveyed by an interaction between muscles, brain and gut. In fact, even skeletal muscles play a role in this context, with receptors for SCFAs and bile acids (BAs) found on muscle fibers. Furthermore, during exercise, myokines secreted by skeletal muscle stimulate the secretion of intestinal hormones, which can influence food intake and energy balance. The concept of the brain–gut–muscle axis is becoming increasingly recognized as important for regulating energy homeostasis and overall health. Preliminary results suggest that among gut bacteria, the *Firmicutes* and *Actinobacteria* could be the most responsive phyla to exercise-induced changes. Among these, *Lactobacilli* and *Bifidobacteria*, although with strong modifications linked to age, seem to be the ones which facilitate healthy gut conditions. Exercise can influence also the populations of other microbial species such as *Ruminococcus, Butyrivibrio* and *Oscillospira*. On the contrary, faecal *Turicibacter*, *Allobaculum,* and *Clostridium sensu stricto,* as well as propionate in the cecum seem to be decreased by exercise. A further process playing an important role in the links between exercise, brain, and microbiota is the lactate metabolism. Lactate acts as a stress signaling molecule which can be modulated by exercise, as further evidence of the potential role of physical activity in gut metabolism and inflammation, and consequently on brain health. It has been for instance shown that increased lactate levels are neurochemical correlates of schizophrenia and Alzheimer disease [94].

Some of the positive effects of neural activity on gut health seem to be mediated by BDNF, a substance of primary importance in the brain, which plays a critical role in regulating neural plasticity, mood disorders, and cognitive

activity. Lower levels of BDNF in the hippocampus have been associated with pathopsychological conditions (mainly anxiety and depression) but also with worsened gut health [89]. BDNF supports healthy gut microbes, in mice it has been observed that antibiotic treatment against beneficial gut bacteria can delay neural growth in the hippocampus thereby contrasting BDNF effects, and that this process can be reversed by both probiotics' intake and aerobic exercise. It is also known that irisin, a myokine produced during exercise, can promote neuroplasticity and neurogenesis through BDNF signaling [60].

It has been proposed that the better effects of exercise on gut health in particular, and on personal well-being in general, would be obtained exercising and living in a natural environment, where the organism can benefit from a calm and relaxing environment and from the richness of biological (micro)organisms therein available. The facilitation of healthy interactions between the human body and the microbial population in the natural ecology can benefit the populations of the forementioned bacteria. Of note, meditation practices, possibly through its ability to reduce stress, have been proposed to have a positive impact on gut microbial flora. However, research in this field is still at its early stages, and the suggested effects and mechanism need clearer demonstration in the future [63].

In summary, there is considerable evidence that brain function, mainly through physical activity but also through cognitive activity and psychological state can influence the microbiota via multiple mechanisms operating at different levels. The implementation of multimodal strategies that include exercise can thus be highly relevant in the prevention of age-related decline and in the treatment of patients with degenerative diseases. These precautions have the potential to slow disease progression, improving the quality of life and overall well-being of patients.

Beyond the previously established microbiota-brain interactions, recent evidence reveals possible mechanisms through which exercise induced metabolic and morphological changes within the gut are able to modulate central nervous system function and athletic performance. Wu et al. suggest that lactate may play an essential role not only as a metabolic substrate, but also as a neuroactive signaling molecule [110]. This new perspective modifies the traditional narrative that considered it a simple metabolic waste product. Supporting this, in murine models during high-intensity exercise, it has been observed that lactate could function as neuronal fuel improving brain function and neurodegeneration through the Hydroxycarboxylic Acid Receptor 1 (HCAR1) which would be able to enhance Vascular Endothelial Growth Factor A (VEGFA) [76]. This metabolic preference appears elevated when energy demand is greater, furthermore during exercise lactate increases BDNF expression, favors learning and memory through Sirtuin 1 (SIRT1) dependent pathways, establishing a possible link between peripheral metabolism and central nervous system plasticity [38]. Moreover, supporting this hypothesis, Schiffer et al. demonstrated in human subjects that sodium-lactate infusion appears to increase blood BDNF concentration [91]. Lactate also appears to possess regulatory effects on mood and maintenance of hippocampal neurogenesis mediated by its influence on HSPA12A-lactate homeostasis pathways [104]. These results, when translated to humans in the future, could indicate that the transient hyperlactatemia accompanying high-intensity exercise might be considered as an exercise pill [76].

In parallel, the gut microbiota contributes to possible brain adaptations mediated by exercise through the production of bioactive metabolites, which may be able to cross the blood-brain barrier [30]. Exercise appears to be able to modify the production of SCFAs including butyrate, propionate and acetate and in murine models, acetate appears to be, in this context, the most important energy substrate, indicating that the intestinal microbiota offers confirmation of the possible idea that it can actively contribute to physical performance [80]. Furthermore, exercise-enhanced SCFAs exert neurobiological effects through multiple mechanisms. Butyrate appears to possess predominantly a role as an energy substrate for colonocytes probably regulating cellular energy metabolism rather than Histone Deacetylase (HDAC) inhibition and furthermore appears to also possess a role in mitochondrial efficiency in the cerebral cortex and synaptic fractions, reducing oxidative stress markers and neuroinflammation [19, 37].

The morphological adaptations of the gastrointestinal tract that support these metabolic and signaling functions show possible plasticity in response to exogenous stimuli such as training and nutrition. Moderate exercise can improve intestinal barrier integrity through zonulin, with increases in Zonula Occludens-1 (ZO-1) and occludin expression [35]. These structural improvements are accompanied in homeostatic situations by a structure in balance with optimal goblet cell and mucin functions, strengthening the primary defensive barrier against pathogenic bacterial translocation [35, 41, 42]. The timing of these morphological adaptations when associated with correct exercise administration follows a physiological pattern where acute exercise initially is able to increase intestinal permeability through an increase in body temperature and temporary Tight Junction (TJ) opening, followed by compensatory strengthening in subsequent weeks that leads to final improvement of intestinal barrier function [58]. Furthermore, it appears that in obese murine models, the molecular mechanisms underlying these morphological changes induced by long-term aerobic exercise involve activation of AMP-activated protein

kinase (AMPK) and Caudal-type homeobox 2 (CDX2) signalling pathways and an increase in ZO-1 and occludin protein expression, favoring intestinal barrier integrity [105].

The emerging evidence, although mostly from murine models, reveals that the gut-muscle-brain axis functions as a possible active regulatory system during exercise, with lactate playing dual roles as metabolic fuel and neuromodulator, with intestinal microbiota metabolites functioning as signaling molecules responsive to exercise and with intestinal morphological adaptations creating a possible structural basis for optimal microbiota-brain communication.

Influences of Gut Microbiota on Brain and Behavior

Still in the aforementioned framework of mutual cooperation, we analyze here the effects of microbiota on brain activity, mental life and physical activity. The microbiota acts like an endocrine organ which releases serotonin, dopamine and other signaling substances which can directly and indirectly affect brain function and behavior [28].

In this framework it should be mentioned that an important role in communication from the gut to the brain is played by the epithelial barriers that constitute the boundaries of these two organs, i.e. the intestinal barrier and the blood-brain barrier [56]. The first is composed of multiple layers, an inner layer of immune cells, a middle layer of intestinal epithelial cells, and an outer mucus layer hosting gut microbiota and defense proteins. These control the passage of antigens and other pathogens, maintaining gut homeostasis. An impaired intestinal barrier increases gastrointestinal permeability, the "leaky gut", allowing harmful organic compounds to reach the bloodstream and affect other body systems. This process could constitute a basis for tissues inflammation. The second epithelial barrier is the blood−brain barrier, composed of endothelial and glial cells, it protects the brain from harmful substances and regulates the passage of molecules and ions from the circulatory system into the brain. SCFAs can modulate the permeability of the blood-brain barrier, acting as a determining factor as to which molecules, either beneficial or harmful, can access brain tissue. If there is a leak in the intestinal barrier, the translocation of bacterial metabolites can trigger an innate immune response, leading to the production of pro-inflammatory cytokines in different organs including the brain. Although microbially derived serotonin and other neurotransmitters synthesized in the gut do not cross the blood−brain barrier, it has been reported that they can increase blood−brain barrier permeability, which could lead to neuroinflammation caused by microglia, which begins to produce proinflammatory molecules specific for the diverse neural disorders. SCFAs are generally considered anti-inflammatory due to their ability to reduce this immune response. Similarly GABA, the major inhibitory neurotransmitter in the central nervous system, is known to dampen cytokine release by proinflammatory immune cells inducing a protective effect against neuroinflammation [30].

It has been reported that the HPA axis can be influenced by the diversity of the gut microbiota. The lack or absence of bacteria can cause a strong HPA activation in response to psychological stress. Diet integration with *Bifidobacterium* reverses this over-activation and can alleviate symptoms of anxiety and distress, observed both in rodents and humans [88].

Gut microbiota can also have neuroprotective effects which seem to be similar to those of physical activity [15]. As mentioned above, physical activity is associated with improved cognitive function and may reduce the risk for various diseases. An emerging area of research suggests that the gut microbiota may have similar neuroprotective effects and even that the microbiota would have a role in the cognitive improvement caused by physical activity, which could be partially mediated by biochemical activity in the gut. Rodent studies support the notion that microbiota changes mediate the effects of diet and exercise on cognition, with potential mechanisms including end-product metabolites and regulation of local and systemic inflammation. When gut bacteria diversity diminishes, there are systemic consequences such as gastrointestinal and psychological illness. Interventions with probiotic supplements that influence microbiota can improve both gut and brain disorders. The first evidence suggests that the gut microbiota may act on cognition indirectly, by playing a role in inflammatory modulation which in turn can have consequences on cognitive activity as well as on neural disease [4].

Also the link between gut microbiota and psychological well-being is gaining increasing interest [27]. A high correlation between physical and emotional stress during exercise and changes in gastrointestinal microbiota composition has been observed, and it seems that even motivation for long-term physical activity in mice is regulated by gut microbes in addition to brain activity. Through the involvement of intestinal sensory neurons expressing cannabinoid receptors, the gut microbiota can influence the phenomenon called "runner's high", a euphoric psychological state which can appear in long runs, associated to the release of endocannabinoids. Anandamide, the endogenous agonist of cannabinoid receptors, is increased during exercise and has a role in various physical and psychological functions. It seems to interact with the amygdala regulating stress as well as with other brain areas relieving sleep disorders and depression. The regulation of stress response after physical exercise depends on the glucocorticoid hormone.

Anandamide is a fatty acid-like molecule which passes the blood–brain barrier and contributes to mood regulation right via the glucocorticoid pathway. Moreover, there is strong evidence that anandamide might have a role in increasing BDNF levels during and after exercise [45].

The amygdala is a key brain region that is critically involved in the processing and expression of anxiety and fear-related signals. A growing number of preclinical and human studies suggest that the microbiota-gut-brain interaction has a role in regulating anxiety and stress-related responses. It has been observed that germ free mice display reduced appropriate behavior in stressful situations, and that the presence of an adequate microbiota is crucial for the proper functioning of the amygdala [45, 89].

An important role in the relations between gut microbiota and physical activity is played by dopamine [47, 48]. In mice, it seems that some types of gut bacteria can simulate enteric nerves activity by generating fatty acid amides which indirectly enhance dopamine levels, facilitating engagement in physical activity. In turn, physical activity further increases the release of dopamine, which plays a role in motor control, memory, synaptic plasticity, and cognition. It also regulates immune functions related to T-cell activation and inflammation. Dopaminergic dysfunctions can lead to various pathological conditions, such as schizophrenia, attention deficit hyperactivity disorder, bipolar depression, addiction, and Parkinson's disease. Depletion of gut bacteria through antibiotic treatment can instead reduce exercise tolerance. Transferring the gut microbiota from high performing mice to germ-free mice increased the functioning capacity of the latter. The principal neural target for the gut microbiota to influence physical activity is the striatum, a key component of basal nuclei, the major subcortical hub controlling motor activity. This region plays also a key role in reward and motivation via its connections with deeper areas such as the ventral tegmental area in the mesencephalon, from where dopaminergic neurons project to the basal nuclei releasing dopamine. This dopamine has a dual role, a peculiarly motor one in their projections to the striatum and one strictly linked to pleasure. Higher levels of dopamine during exercise in this area can thus increase the desire to engage in physical activity linking it to a pleasant experience. It has been observed that regeneration of healthy conditions in the gut microbiota and increased dopamine through injections in the basal nuclei can restore adequate physical activity levels in mice that lack gut bacteria [36].

By stimulating the production of intestinal mediators able to reach the central nervous system (gut-brain axis), the gut microbiota participates also in the modulation of human moods and behaviors [4, 67]. Recent research underlines the importance of appropriate physical activity, nutrition, and a healthy lifestyle to ensure the presence of a functional physiological microbiota working to maintain the health of the whole human organism. This is due to evidence suggesting that gut microbiota imbalances might play a role in mood regulation as well as in psychopathological processes associated with psychiatric and neurological conditions [84]. It has been previously described that the gut plays a crucial role in releasing various hormones, peptides, and microbial metabolites, such as SCFAs, secondary BAs, and products derived from tryptophan and polyphenols. These substances have significant effects on neuronal function and survival. Notably, many of these compounds can cross the blood–brain barrier, including SCFAs, which exploit active membrane transporters on the endothelium to reach the central nervous system [30].

Given the number of body districts involved and the complexity of the mentioned processes, multicomponent lifestyle interventions are nowadays considered the most promising ways to promote brain health and to contrast age-related neural diseases. These include interventions on various lifestyles, such as diet and exercise, behaviors that are known to modulate the gut microbiota [21]. A better understanding of the role of the gut microbiota in physical exercise and cognition may be of further help to optimize these interventions.

Randomized Control Trials and Longitudinal Studies

While the theoretical framework and mechanistic evidence presented support the microbiota-gut-brain axis in sport performance, it is crucial to examine the quality and limitations of available human and preclinical evidence to assess the current state of knowledge and identify research gaps.

Few randomized controlled trials (RCTs) and longitudinal studies (LSs) on humans and rodents facing the relationships between exercise, microbiota, and neural activity can be found in the literature. These studies are of particular interest as RCTs offer high internal validity by minimizing bias through random allocation, enabling robust causal inference, whereas LSs, by tracking individuals over time, allow for the examination of temporal relationships and long-term effects (Table 2). Both designs are essential for generating reliable, evidence-based conclusions in biomedical and behavioural sciences.

Humans

In a randomized placebo-controlled trial, Li et al. examined whether 28-days supplementation with *Bifidobacterium breve* 207-1 could modulate microbiota-gut-brain axis markers and lifestyle behaviours in healthy adults characterized

by stress, overweight, insomnia, and constipation. Participants received either a low-dose, a high-dose, or a placebo [61]. Outcome analyses showed that, compared to placebo, both probiotic groups had an increase in GABA levels and a suppression of HPA-axis hormones, while 5-HT and mood scores remained unchanged. They also showed an improved sleep quality, a slight increase of exercise energy expenditure, and modest weight loss without differences between the two groups. This absence of differences raise questions regarding dose-response effects and the actual need for high-concentration formulations. Gut microbiota composition shifted under treatment, with the low-dose group exhibiting higher acetate and propionate levels and the high-dose group showing a slight drop in α-diversity. These results indicate that *Bifidobacterium breve* 207-1 can act effectively on the microbiota-gut-brain axis, potentially via SCFAs, influencing neurochemical balance and behaviour.

In a randomized controlled trial, a large sample of adolescents with and without subthreshold mood symptoms was assigned to either a running program (30 min/day, 5 days/week for 12 weeks) or a psychoeducation control (gaming, reading, and singing) [106]. Metagenomic sequencing of faecal samples showed that, before intervention, subjects with subthreshold mood symptoms had lower gut microbial β-diversity. However, after the intervention no differences were observed in overall diversity, taxonomic composition at the phylum, genus, or species levels, functional pathway profiles, and metagenomic linkage groups. A similar randomized trial from the same group investigated young participants with subthreshold depression performing either physical exercise or psychoeducation, both with similar features as in the previous study [107]. Metagenomic sequencing revealed that exercise led to a higher relative abundance of *Coprococcus*, *Blautia*, *Dorea*, and *Tyzzerella* at the genus level, and of *Tyzzerella nexilis* and *Ruminococcus obeum* at the species level compared with the psychoeducation group. Functional profiling via EggNOG (evolutionary genealogy of genes: Non-supervised Orthologous Groups) showed enrichment of defense and signal-transduction pathways that correlated with improvements on the Chinese Patient Depression Questionnaire-9. KEGG (Kyoto Encyclopedia of Genes and Genomes) analysis indicated a depletion of neurodegenerative disease pathways in the exercise group. These findings suggest that the effects of physical activity may appear easier in participants inclined towards depression, but the lack of consistent changes in the overall diversity of the microbiota suggests that the effects are weak and likely mediated by functional rather than structural changes.

To the best of the authors knowledge, only one longitudinal study has been carried out on the topic. Bongiovanni et al. presented a first large-scale evaluation of a probiotic formulation derived from elite athletes and composed of a multistrain *Lactobacillus* consortium on sleep quality, exercise recovery, and gut microbiota in both elite athletes and controls [12]. Utilizing a two-phase design in a professional soccer team, they observed improvements in self-reported sleep quality, energy levels, and bowel regularity following probiotic supplementation. These outcomes were accompanied by reductions in oxidative stress markers and an increased free testosterone/cortisol ratio. Multi-omics analyses revealed distinct alterations in gut microbiome composition and function. These findings highlight the potential of targeted probiotic interventions, particularly those derived from high-performance individuals, to enhance health and performance outcomes in diverse populations and indicate that the interplay between sleep, physical activity, and the gut microbiome offers promising avenues for human health. However, it remains to be clarified whether the observed benefits are a consequence of the specific composition of the consortium or the highly controlled context of the intervention.

These studies offer significant contributions to understanding the microbiota-gut-brain axis. They emphasize the importance of the mutual interaction between physical activity, microbiota and neural function which can impact different psychological aspects of everyday life and take a look at the possible role of probiotics in modulating psychophysical well-being. However, despite growing interest in the topic, randomized controlled trials and longitudinal studies on humans remain scarce and largely insufficient to draw robust causal inferences. At this stage of research, some critical considerations emerge. Methodological variability between studies (different populations, intervention protocols, and analysis techniques) makes direct comparisons difficult and limits the generalizability of the findings. Moreover, the beneficial effects observed on both neuroendocrine biomarkers and microbiota do not always translate into clinical improvements, suggesting that microbiota changes may act on neurobiological circuits which do not influence directly psychological function as measured by the used psychometric tests. These limitations highlight the need for further randomized controlled trials and longitudinal studies with harmonised designs, robust clinical measures, and greater attention to translating results into real-world contexts.

While human studies provide valuable insights into the clinical relevance of microbiota-gut-brain interactions in sports performance, preclinical rodent studies offer complementary mechanistic understanding under controlled conditions.

Table 2 Characteristics of included original studies: Rats, mixed (Humans and Rats) and humans

Study	Type of Study	Scope & Participants	Design & Methodology	Physical Activity/Exercise	Microbiota Changes	Alpha/Beta Diversity	SCFAs Findings	Neurological/ Psychological Effects	Performance Outcomes
Rats									
Ruan et al. 2025 [85]	RCT	Effects of exercise and microbiota on diabetes-induced cognitive impairment. *Male C57BL/6J mice*	16 S rRNA sequencing; fear conditioning. Faecal transplant, other (neuro)biological analyses	Group (G) 1: nondiabetic; G2: diabetes induced (D); G3: D + exercise; G4: D + faecal transplant from G3	G2-4: microbiota alterations partially reversed by exercise	No differences in α-diversity. β-diversity: ↑*Firmicutes*, ↓*Bacteroidetes* in G2-4	N/A	G2-4: ↓Cognition, partially reversed by exercise. Faecal transplant from G3 improved cognition in G4. G3, G4: ↑Hippocampal neurotrophic factors and Synaptic proteins	N/A
Nicolas et al. 2024 [78]	RCT	Exercise effects on neurogenesis impairment induced by gut microbiota disruption. *40 male Sprague-Dawley rats*	Chronic disruption of gut microbiota by antibiotic cocktail. Location recognition, Novelty suppressed feeding and Elevated plus maze tests. Metabolomics analyses	Sedentary, sedentary + antibiotics, voluntary running, and voluntary running + antibiotics	Microbiota experimentally disrupted	N/A	N/A	Sedentary rats with antibiotic: ↓Performance in both tests. Antibiotic groups: ↓ Performance in the elevated plus maze task and hippocampal neurogenesis. Exercise attenuated these negative effects	Gut microbiota disruption did not change body weight and running activity

Table 2 (continued)

Study	Type of Study	Scope & Participants	Design & Methodology	Physical Activity/Exercise	Microbiota Changes	Alpha/Beta Diversity	SCFAs Findings	Neurological/ Psychological Effects	Performance Outcomes
Park et al. 2024 [81]	RCT	Exercise effects on memory and microbiota composition in old rats. *40 BL6 mice*	Step-through and Morris water maze test. Enzyme-linked immunosorbent, Western blot, faecal samples, and metagenomic analyses	Adults: control and exercise group; olders: control and exercise group. Exercise: treadmill 30 min/d, 5d/wk, for 8wks	Old rats: ↓ Beneficial microbiota. Exercise: ↑ Beneficial microbiota in old rats	Old rats: ↓Microbiota diversity. Exercise: ↑Microbiota diversity in old rats	N/A	Old rats: ↓ Decline in short-term memory and spatial learning, ↑ TNF-α and IL-6 concentration, ↓BDNF and TrkB expression. Exercise: ↑Short-term memory, ↓TNF-α and IL-6, ↑BDNF and TrkB expression in old rats	↑Performance in the step-through and Morris water maze tests by younger mice, by active young and active old mice
Vazquez-Medina et al. 2024 [102]	Longitudinal	Exercise effects on microbial tryptophan metabolism. *24 male C57BL/6J mice (12 sedentary, 12 running); 42 days*	16 S rRNA Sequencing and Metabolimics	Voluntary wheel running (average 4 km/h, 6PM-5AM daily)	↑ *Firmicutes* and *Verrucomicrobia*, ↓ *Bacteroidota* ↑ *Romboutsia* and *Akkermansia muciniphila*	↑ α-diversity; = β-diversity	↑ *Akkermansia muciniphila* produces Acetate and Propionate; ↓ Kynurenine pathway metabolites	↑ Blood TRP/LNAA ratio; ↑ Hippocampus and brainstem Serotonin	Running exercise improved gut microbiota diversity and metabolism
Bakonyi et al. 2023 [3]	RCT	Exercise effects on microbiota, *Bifidobacteria*, gastrointestinal parameters, and spatial memory. *14 Sprague-Dawley middle-aged male rats*	Treadmill VO_2 max, spatial memory (Morris maze test), gastrointestinal EMG, 16 S RNA sequencing, electron microscopy, biochemical assays	8 weeks voluntary running vs. sedentary	Intestine Akt, eNOS, and number of caveolae. ↑Relative abundance of *Bifidobacteria* in the microbiome	No effects	↑ Relative abundance of *Bifidobacteria* and *Ruminococcaceae*; suggesting ↑SCFAs	Exercise: ↑ Spatial memory and VO_2 max .	↑ Performance in the parameters of the Morris water maze test in the treadmill group

Table 2 (continued)

Study	Type of Study	Scope & Participants	Design & Methodology	Physical Activity/Exercise	Microbiota Changes	Alpha/Beta Diversity	SCFAs Findings	Neurological/ Psychological Effects	Performance Outcomes
Li et al. 2023 [62]	RCT	Exercise effects on cognitive impairment induced by high-fat diet. *40 male C57BL/6J mice*	16 S rRNA sequencing; Morris water maze test	Faecal microbiota transplant from sedentary or voluntary active mice, plus control group	After transplant from active mice: ↑ *Lactobacillus* and *Eubacterium nodatum*, ↓ *Clostrida* UCG-014 and *Akkermansia*	N/A	↑ In the cecum Acetic, Propionic, Isobutyric, Valeric, and Isovaleric acid	↑ Learning and memory abilities (Morris watermaze) and neuroprotective effects in the recipient group of active compared to sedentary mice	↑ Performance in the Morris watermaze parameters by the recipient group from active mice
Watanabe et al. 2023 [108]	RCT	Microbiota-mediated antidepressant effects of exercise. *46 male C57BL/6J mice*	Social, Sucrose preference, Open field, Marble burying, Elevated plus maze, and Forced swimming tests. 16 S rRNA sequencing, SCFAs, faecal bacteria analysis	Sedentary and voluntary running groups treated with or without SDS	Exercise: ↓ Faecal *Turicibacter, Allobaculum, Clostridium*, and propionate in the cecum	No relation of α-diversity with exercise and stress	Exercise: ↓ Lactate, Acetate, Propionate and Butyrate. Social defeat stress: ↑ Propionate and Butyrate	↓ Sucrose drinking in SDS mice, attenuated by exercise. ↑ BDNF, ↓ Zo-1 and Claudin-5 in the brain by exercise	N/A
Dohnalová et al. 2022 [36]	Longitudinal	Microbiome role in exercise motivation and performance. *199 genetically diverse outbred mice; 16 weeks*	16 S rRNA Sequencing, Fiber photometry and Metabolomics	Voluntary wheel running; Treadmill Endurance Testing	↑ *Eubacterium rectale*, ↑ *Coprococcus eutactus* (Performance Enhancing Bacteria)	Microbiome composition predicted performance better than genetics	FAAs such as OEA, stimulate sensory neurons to promote Physical Activity	↑ Ventral striatum dopamine during exercise, CB1 endocannabinoid and TRPV1 receptor activation	Performance reduction with antibiotic treatment; Microbiome predicted performance
Xia et al. 2021 [111]	RCT	Effects of exercise on microbiota and hypertension. *Normo- and hypertensive (HT) male Wistar rats*	Analysis of faecal microbiota, gut pathology, intestinal inflammation and permeability, brain microglia, neuroinflammation. Faecal transplantation	Normo and hypertensive rats, sedentary, trained (12wks moderate exercise) and detrained (8wks moderate exercise followed by 4wks detraining)	Trained and detrained HT rats: Beneficial bacteria ↑ Gut pathology, inflammation and permeability. Faecal transplantation from exercised HT to sedentary HT rats: ↑ Gut-brain axis parameters	Trained and detrained HT rats: ↑ α-diversity, altered clustering in β-diversity	Sedentary HT rats: ↓ Acetate and Butyrate bacteria, Actate-bacterial, training restored these differences. Detrained HT: ↑Butyrate-bacteria	HT rats training: ↓ Systolic blood pressure, activated microglia, neuroinflammation in the hypothalamus. Faecal transplantation from exercised HT to sedentary HT rats: ↓ Systolic blood pressure	N/A

Table 2 (continued)

Study	Type of Study	Scope & Participants	Design & Methodology	Physical Activity/Exercise	Microbiota Changes	Alpha/Beta Diversity	SCFAs Findings	Neurological/ Psychological Effects	Performance Outcomes
Hoffman-Goetz et al. 2010 [50]	Longitudinal	Voluntary exercise effects on intestinal immune responses. *66 female mice C57BL/6; 16 weeks*	Western blot and Flow cytometry	Voluntary in-cage running wheels; Acute treadmill challenge	N/A	N/A	N/A	↑ Plasma corticosterone; ↓ TNF-α, ↑IL-6, ↑IL-10 with training	↑ Running distance and endurance (weeks 4–16)
Mixed (Humans and Rats)									
Scheiman et al. 2019 [90]	Longitudinal	Performance enhancing microbes in elite athletes. *15 Boston Marathon Runners and 87 Elite Athletes (Ultra-Marathon and Rowers) and 32 C57BL/6 mice*	Daily faecal sampling pre/ post marathon. Taxonomy 16 S rRNA Sequencing, Functionality Shotgun Metagenomics and Mouse gavage experiments	Marathon Running, Ultra-Marathon Running and Olympic Rowing	↑ *Veillonella* post-exercise; *Veillonella atypica* isolated	↑ Lactate to SCFAs	Propionate production via Lactate to propionate pathway; Methylmalonyl-CoA pathway enriched	N/A	↑ Exhaustive run time with *Veillonella Atypica* gavage in mouse; ↑ Human pilot trends
Humans									
Bongiovanni et al. 2025 [12]	Longitudinal placebo-controlled (L); open label (OL)	Systemic effects of probiotics. *L: Elite athletes (n = 11). OL: general population (n = 257). Both supplied with probiotic (Lactobacilli). 25 weeks*	L: blood, faecal, testosterone, metagenomics and multi-omics analyses, homemade questionnaire. OL: Homemade questionnaire	N/A	L: specific changes in microbiome composition and function. ↓ Markers of oxidative stress, ↑higher free-testosterone/cortisol ratio	L: no changes in α-diversity	N/A	L: ↑ General health, ↑ sleep quality, ↑ energy level, ↑ bowel movement quality. OL: ↑ Sleep quality, ↓ recovery time, ↓ frequency of fatigue	N/A
Li et al. 2024 [61]	RCT	Systemic effects of *Bifidobacterium breve. 120 healthy adults with mental stress*, *overweight*, *insomnia*, *constipation*	Faecal and blood analyses, PSQI questionnaires. 16 S rRNA sequencing. Gas chromatography–mass spectrometry (GC–MS). LD or HD of *B.breve* or placebo	N/A	↑ GABA, suppression of HPA axis hormones in the probiotic groups, No change in 5-HT	Slight ↓ α–diversity in the HD group	↑ SCFAs in the LD group (acetic and propionic acids)	↓ PSQI, indicating improved sleep quality	Slight ↑ Exercise consumption while dietary intake stabilized. Slight weight loss

Table 2 (continued)

Study	Type of Study	Scope & Participants	Design & Methodology	Physical Activity/Exercise	Microbiota Changes	Alpha/Beta Diversity	SCFAs Findings	Neurological/ Psychological Effects	Performance Outcomes
Fernandez-Sanjurjo et al. 2024 [44]	Longitudinal	Gut microbiota dynamics during cycling Grand Tour. *16 Professional male cyclists; 21 days*	16 S rRNA sequencing, Gas chromatography for SCFAs	Professional Cycling Grand Tour La Vuelta	↑ Performance associated families: *Bifidobacteriaceae, Coriobacteriaceae, Erysipelotrichaceae* and *Sutterellaceae*; ↑ SCFAs producers: *Oscillospiraceae, Veillonellaceae, Bacteroidaceae, Prevotellaceae, Lachnospiraceae* and *Ruminococcaceae*	= α–diversity : Shannon and Simpson	↑ SCFAs performance correlations: Acetic acid ↔ *Coriobacteriaceae*, Isovaleric acid ↔ *Coriobacteriaceae*, Isobutyric acid ↔ *Bifidobacteriaceae*	N/A	Microbiota performance prediction: Accumulated time and Ranking
Wang et al. 2023 [104]	RCT	Effects of aerobic exercise on microbiota. *30 young adolescents divided in exercise and psychoeducation group*	Same as in Wang et al. 2021	Same as in Wang et al. 2021	Exercise group: ↑ *Coprococcus, Blautia, Dorea, Tyzzerella* at genus level; ↑ *Tyzzerella nexilis, Ruminococcus obeum* at species level; ↑ Defense and signal transduction mechanism	No effects	N/A	Exercise group: Improved depressive symptoms	N/A
O'Donovan et al. 2020 [79]	Cross-sectional	Sport-specific microbiota profiles in elite athletes. *37 International Elite Athletes across 16 sports (23 male, 14 female)*	Shotgun Metagenomics Shotgun and Faecal and Urine samples underwent metabolomic profiling	Cycling, Boxing, Judo, Walking, Field Hockey, Fencing, Swimming and Rowing	Moderate endurance/High power: ↑ *Streptococcus suis* ↑ *Clostridium bolteae* ↑ *Anaerostipes hadrus*; High endurance/Low power: ↑ *Bifidobacterium animalis* ↑ *Lactobacillus acidophilus*; High endurance/High power: ↑ *Bacteroides caccae*	Compositional differences by sports classification groups	N/A	N/A	Specific Sport Groups exhibit distinct functional and microbiota profiles
Wang et al. 2021 [106]	RCT	Effects of aerobic exercise on microbiota. *56 with subthreshold mood syndrome and 168 clinically well adolescents.*	Microbiota assessed by metagenomics sequencing. Chinese Patient Depression Questionnaire 9. Exercise vs. psychoeducation	Exercise: running at moderate-intensity for 30 min/d, 5d/wk. Psychoeducation: gaming, reading, singing. Duration: 3 months	No treatment effects in microbiota diversity, phylum, genus, species level abundancies or microbial functions in both groups. No differences in metagenomic linkage groups	Adolescents with subthreshold mood syndrome: ↓β-diversity	N/A	N/A	N/A

Table 2 (continued)

Study	Type of Study	Scope & Participants	Design & Methodology	Physical Activity/Exercise	Microbiota Changes	Alpha/Beta Diversity	SCFAs Findings	Neurological/ Psychological Effects	Performance Outcomes
Moreno-Pérez et al. 2018 [75]	RCT	Protein supplementation effects on gut microbiota. *24 Cross-Country male Runners (12 intervention and 12 control); 10 weeks*	16 S rRNA Sequencing, qPCR, Gas chromatography-mass spectrometry	Cross-Country Runners Intervention group with Protein supplementation (20gr daily of whey isolate + beef hydrolysate) and Cross-Country Runners Control Group with Carbohydrates supplementation (Maltodextrin)	Intervention group increased ↑ *Bacteroidetes* and *Bacteroides*; ↓ *Lachnospiraceae, Roseburia, Blautia, Coprococcus, Bifidobacterium longum* and Synergistetes phylum	= Shannon and Simpson indices within/ between groups	= SCFAs (Acetate, Propionate, Butyrate and Branched-chain)	N/A	N/A
Clarke et al. 2014 [25]	Cross-sectional	Exercise and diet impact on microbial diversity. *40 elite Professional Rugby male Players and 46 High/Low BMI Controls*	16 S rRNA Sequencing and Plasma biomarkers	Professional Rugby Union	↑ *Akkermansia* genus; ↑ Abundance of 40 different bacterial taxa; ↓ *Bacteroides*	α–diversity : ↑ Athletes 22 distinct phyla vs. ↓ 11 (Low BMI) and 9 (High BMI) Controls	N/A	N/A	↑ Metabolic functional capacity; ↓Inflammatory markers; Protein intake correlated with Microbial Diversity

RCT Randomized controlled trial, *16 S rRNA* 16 S ribosomal RNA gene, ↑*Increased*, ↓ Decreased, *N/A* Not applicable, *TNF-α* Tumor necrosis factor alpha, *IL-6* Interleukin-6, *BDNF* Brain-derived neurotrophic factor, *TrkB* Tropomyosin receptor kinase B, = Unchanged, *RP* = Tryptophan, *LNAA* Large neutral amino acids, *SCFAs* Short-chain fatty acids, *EMG* Electromyography, VO_{2max} Maximal oxygen consumption, *SDS* Social defeat stress, *ZO-1* Zonula occludens-1, *FAAs* Fatty acid amides, *OEA* N-oleoylethanolamide, *CB1* Cannabinoid receptor type 1, *TRPV1* Transient receptor potential vanilloid 1, *IL-10* Interleukin-10, *5-HT* 5-Hydroxytryptamine, *PSQI* Pittsburgh sleep quality index, *LD/HD* Low dose/high dose, *GABA* Gamma-aminobutyric acid, *HPA* Hypothalamic-pituitary-adrenal axis, ↔ Correlation, *qPCR* quantitative Polymerase Chain Reaction, *BMI* Body mass index

Rodents

Several recent studies in rodents highlighted the potentially positive effects of the interactions between physical activity, microbiota and brain function which can restructure the gut brain axis with adaptive outcomes. Cognitive benefits were observed in a recent study by Ruan et al.: they reported that aerobic exercise can mitigate cognitive impairment in diabetic mice by reshaping the gut microbiota, enhancing synaptic plasticity, reducing neuroinflammation, and improving neuronal glucose metabolism [85]. A further study showed that even transplanted faecal microbiota from exercised mice can counteract cognitive deficits related to a high fat and cholesterol diet, by improving insulin signalling, mitochondrial function, neuroplasticity and SCFAs profiles [62]. Specific memory enhancing effects were observed recently by Park et al., demonstrating that treadmill exercise, in particular in aged rats, can reverse memory decline and neuroinflammation, increase BDNF and TrkB expression, and enrich beneficial gut bacteria, as well as by Bakonyi et al. who found that, in rats, voluntary running can improve spatial memory along with an increase of both intestinal endothelial nitric oxide synthase and protein kinase B levels, and of *Bifidobacteria* [3, 81]. Analyses devoted more directly to neurobiological effects showed that exercise can lower blood pressure in hypertensive rats by improving microbial diversity, gut barrier integrity, and reducing neuroinflammation and that voluntary exercise can mitigate the negative impact of antibiotic-induced dysbiosis on rat hippocampal neurogenesis [78, 111]. Finally, also from a point of view of psychopathology the triad physical activity-microbiota-brain can play a central role: Watanabe et al. found that voluntary exercise in mice alleviates depressive-like behaviours by altering gut microbiota composition and reducing propionate levels, thereby enhancing blood-brain barrier permeability and BDNF expression [108].

This preclinical evidence suggests that physical activity, whether voluntary or induced, can positively modulate the microbiota-gut-brain axis, with beneficial effects on memory, neuroplasticity, neuronal metabolism, and emotional behaviour. The studies covered a wide range of normal and pathological conditions, suggesting a systemic impact of physical activity. Moreover, the use of advanced techniques such as faecal transplants and the analysis of various metabolites should support reliable results. However, although the outcomes are promising, translation to humans remains uncertain as neurobiological responses in animal models do not always reflect those in humans. Moreover, experimental heterogeneity, including differences in exercise protocols, diets, microbiota analysis techniques and behavioural measures, make comparative synthesis difficult. This is possibly a cause of the fact that several hypotheses have been proposed including the role of inflammation, metabolic and neurotrophic pathways, the function of different substances, but that the underlying mechanisms are not yet fully understood. Finally, as in humans, there is a severe shortage of longitudinal studies as most are acute or short-term investigations, limiting the knowledge of lasting effects and adaptive trajectories.

Specific Characteristics of Competitive Athletes

Elite athletes are subjected to high physiological demands due to high-intensity training regimens, specialized nutritional approaches, and performance goals customized to individual and sport-specific characteristics (Table 2) [18, 66, 112]. These factors create distinctive conditions for the gut microbiota, although exercise also impacts the microbiota of non-athletes [5, 73, 82]. Moderate exercise at intensities below 60% of maximum oxygen consumption (VO_{2max}) is able to promote an increase in microbial diversity with possible increases in the *Firmicutes* phylum [32]. Furthermore, it stimulates the production of SCFAs, especially butyrate, acetate and propionate which are energy substrates for colonocytes and positively influence brain function [30]. Regular exercise increases neuroplasticity by enhancing BDNF levels, which are essential for neurogenesis and synaptic plasticity. Preclinical studies have shown that BDNF levels are restored after supplementation with *Bifidobacterium* [24]. Furthermore, as concerns serotonin regulation, its synthesis and metabolism increase both in the brainstem and in the hippocampus in response to exercise, contributing among others to the reduction of depressive and anxious symptoms [32]. In addition, a recent study published by Dohnalová et al. provided possible preclinical evidence for the role of the gut microbiota in regulating exercise motivation via the gut-brain pathway, which influences dopaminergic signaling [36]. In the same study authors identified a mechanism by which gut microbiota-dependent production of endocannabinoid metabolites stimulates the activity of sensory neurons expressing Transient Receptor Potential Vanilloid 1 (TRPV1), thereby increasing dopamine levels in the ventral striatum during exercise. Furthermore, they demonstrated that stimulation of this pathway improves running performance, while microbiota depletion, inhibition of peripheral endocannabinoid receptors, ablation of spinal afferent neurons, or dopamine blockade significantly reduce exercise capacity. Of particular note is the finding that microbiota-produced fatty acid amides (FAAs), such as N-oleoylethanolamide (OEA), activate Cannabinoid Receptor Type 1 (CB1) receptors expressed on TRPV1 neurons, thereby sending an afferent signal to the brain that promotes

the down-regulation of monoamine oxidase expression in striated muscle; this down-regulation would contribute to higher dopamine levels and would increase exercise capacity [36].

In contrast, high-intensity exercise above 60% VO_{2max} presents nowadays a more complex picture. Professional athletes show greater microbial diversity than sedentary individuals, with possibly higher proportions of the phylum *Firmicutes* and a greater presence of *Akkermansia muciniphila*, but not all sports present the same microbiota adaptations [25]. Indeed, the composition of the gut microbiota shows specific adaptations based on the specific sport type, where endurance athletes present higher levels of *Prevotella* associated with carbohydrate metabolism, and power athletes show higher populations of *Bacteroides* related to protein metabolism [79]. Furthermore, Scheiman et al. identified *Veillonella atypica* as more abundant post-race in professional marathon runners, demonstrating that its ability to convert lactate to propionate could contribute to endurance performance through a gut-muscle metabolic cycle [90]. Balanced exercise improves the function of the intestinal barrier while intense and prolonged exercise can induce splanchnic hypoperfusion, increase intestinal permeability, increase the risks of intestinal dysbiosis and can promote endotoxemia [24, 40]. This is particularly relevant considering that for example, a high percentage of endurance athletes report gastrointestinal symptoms during competitions and are subject to possible upper respiratory tract infections [54].

Several sport-specific studies evidence a key modulatory role of exercise on microbiota [73]. Positive effects have been reported in rugby players showing high microbiota variability with large proportions of beneficial bacteria such as *Firmicutes*, the presence of *Akkermansia muciniphila* and of species involved in the metabolism of amino acids and carbohydrate and SCFAs production in comparison to sedentary high body mass index controls [25]. A further study found differences in the microbiota between athletes from different sports indicating that the specific requested performances play a fundamental role in shaping the gut microflora [79]. Studies on rodents have demonstrated that exercise can lead to increased antioxidant enzyme levels, anti-inflammatory cytokines, and proteins that prevent cell death decreasing pathogenic cytokines and proteins [50]. Aerobic exercise is also able to influence the regulation of serotonin in rats, both its synthesis and metabolism increase in the brainstem and in the hippocampus in response to exercise, in parallel with a decrease in depressive and anxiety symptoms [32]. As mentioned above, serotonin constitutes a strong link between brain activity, exercise and the gut, where it is mostly present. The antidepressant effect induced by sport and exercise are at least partially caused by a suppression of serotonin uptake by the gut microbiota along with an increase of blood-brain barrier permeability [102].

At the molecular level, it has been observed that in both athletes and non-athletes SCFAs produced by the microbiota, especially butyrate, can play a key role in health. Its interaction with the brain could induce in some cases gastrointestinal, metabolic, neurological and psychiatric disorders although this issue is still under investigation [22, 44, 55, 92]. SCFAs can also modulate gene expression in the brain through epigenetic mechanisms, influencing neural plasticity and the response to stress. Preclinical and clinical studies have shown that the microbiota also influences the permeability of the blood-brain barrier, with potential implications for neuroinflammation, cognitive function, stress, and resilience [2, 13, 68]. The interaction between physical exercise, the microbiota and brain function has direct implications for cognitive and sports performance [56, 100]. A homeostatic microbiota can be considered as an endocrine organ, which is associated with a better regulation of the HPA axis, potentially improving the stress response during competition and throughout normal life [9, 46]. To optimize the microbiota-gut-brain axis in athletes, strategies such as nutritional periodization, supplementing adequate amounts of dietary fibres during recovery periods, which consider that suboptimal diets for specific athlete categories can reduce microbial diversity and SCFAs production are of essential importance [31, 52, 75, 93]. Targeted probiotic supplementation with specific bacterial strains such as *Bifidobacterium* and *Lactobacillus* has shown positive effects on stress management, mood, immune function, and gut function [54]. Sleep quality, immune function and psychological resilience are all critical factors for athletic performance, and management of hunger and satiety are also influenced by the composition of the gut microbiota [43, 95]. Evidence suggests that athletes with a richer microbiota may experience fewer upper respiratory infections and show greater resistance to stress [9]. Furthermore, travel and competition schedules are additional challenges for athletes' gut and mental health. Jet lag, dietary changes, and competition stress can alter the gut microbiota, potentially contributing to gut dysbiosis [57].

These studies highlight that gut-brain communication is not a passive process, but a dynamic system that responds to physical activity and actively contributes to physical performance. In-depth understanding of the exercise-microbiota-brain interaction might open new frontiers in sports medicine and neuroscience, with the potential to revolutionize the approach to training and athletic performance through modulation of this virtuous triangle (Fig. 1).

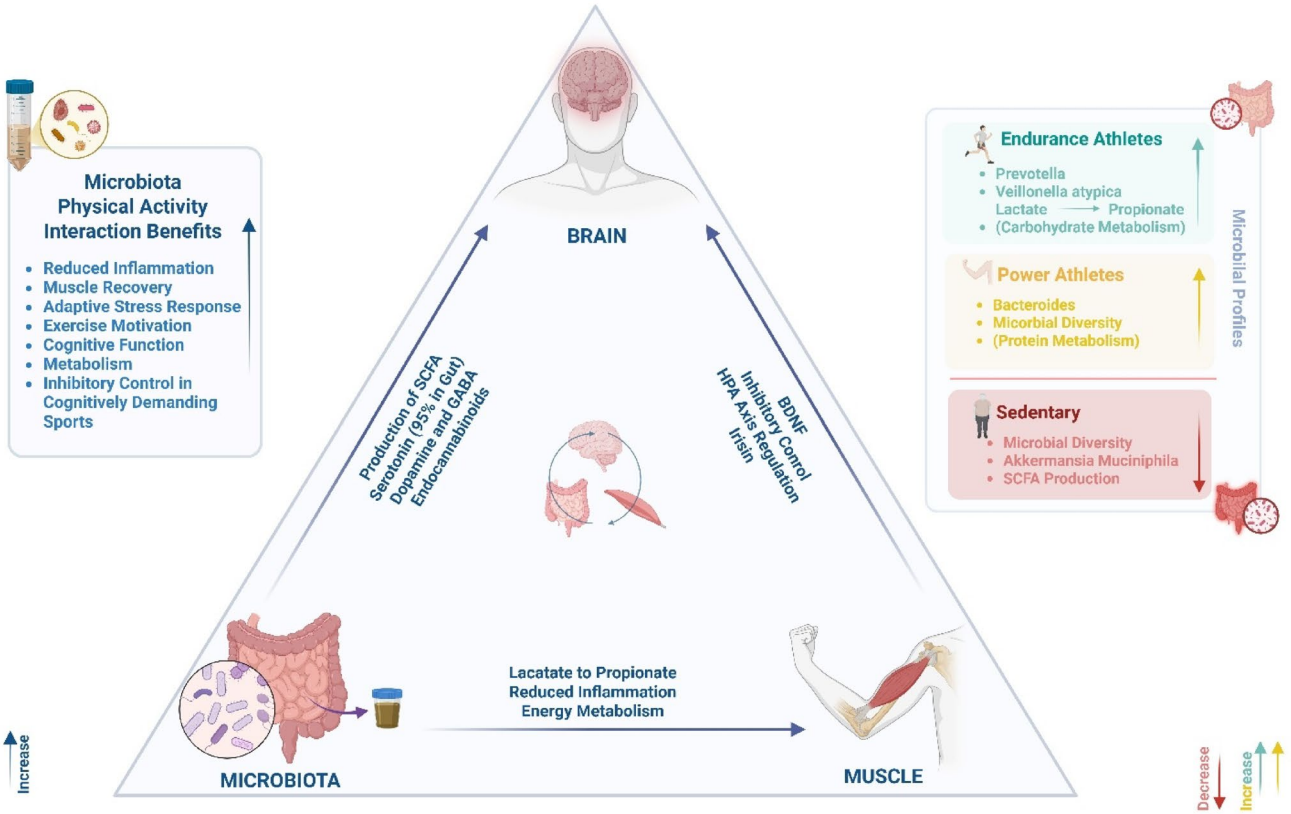


Fig. 1 Gut microbiota-brain axis and sports performance. Schematic representation of bidirectional communication between brain, gut microbiota and skeletal muscle with key signalling pathways indicated. Sport-specific microbial signatures show endurance athletes with *Prevotella/Veillonella* enrichment and carbohydrate metabolism, power athletes with *Bacteroides* predominance and protein metabolism and sedentary individuals with reduced diversity. The axis confers benefits including reduced inflammation, enhanced recovery, and improved cognitive function in athletes. (SCFA = Short Chain Fatty Acid; GABA = γ-Aminobutyric Acid; BDNF = Brain-Derived Neurotrophic Factor; HPA = Hypothalamic-Pituitary-Adrenal axis)

Conclusion

Based on the reviewed evidence, the microbiota-gut-brain axis represents a fundamental system that actively contributes to sport performance. Elite athletes, subjected to high-intensity training regimens, specialized nutritional approaches and specific performance goals, exhibit distinctive microbiota conditions [17]. BDNF, serotonin and butyrate emerged as key mediators contributing to adaptive conditions for gut microbiota and its interactions with brain activity. The interdisciplinary evidence from neuroscientists, microbiologists, nutritionists and sports scientists demonstrates that understanding these interactions opens new frontiers for optimizing athletic performance through targeted modulation of this bidirectional communication system.

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Declarations

Conflict of interest The authors declare no conflict of interest.

Ethical Approval Not applicable.

Consent to Participate Not applicable.

Consent to Publish Not applicable.

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