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UNRAVELING THE CROSSTALK BETWEEN EXERCISE, GUT MICROBIOTA, AND BRAIN FUNCTION

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ABSTRACT

The present review examines the complex and dynamic communication among physical exercise, the gut microbiome and brain activity, all contextualized within the microbiota-gut-brain axis network. Recent research studies indicate that regular physical exercise can significantly alter the structure and physiological activities of the gut microbiome, frequently enhance diversity and elevate the prevalence of beneficial bacteria (such as *Faecalibacterium prausnitzii* and *Akkermansia municiphila*). These microbial changes lead to variations in the levels of microbial metabolic products, like short-chain fatty acids in the circulation. The short-chain fatty acids are the important inducer (triggering) molecules that communicate with the brain (through vagus nerve), endocrine system (hypothalamic-pituitary-adrenal axis), and immune system pathways. The review consolidates the findings how this change in the gut microbiota caused by exercise, affects several aspects of brain function, encompassing cognitive performance, mood control, and significantly lowering the risk of neurodegenerative and psychiatric complications. Comprehending this complex relationship is essential for formulating non-drug therapies, like physical activity and probiotic-prebiotic approaches, to enhance both physical and mental health.

Keywords: Physical exercise, Gut microbiota, Brain activity, microbiota-gut-brain axis, Short-chain-fatty acids, physical and mental health

INTRODUCTION

The human gut contains a wide range and dynamic groups of microorganisms, which constitute gut microbiota. The gut microbiota is very essential for the maintenance of overall health of humans through biochemical, immune and neuroendocrine associated activities **[1]**. Recently, the microbiota-gut-brain axis has been identified as a key frame work that depicts the two-way communication between the central nervous system and digestive system **[2]**. This intricate network includes endocrinal, neural and immune system related signal pathways through which gut microbiota can induce brain activities and behaviour and conversely **[3]**. Among various factors that affect the microbiota-gut-brain axis, physical exercise has earned increasing attention as non-drug approach capable of beneficially impacting gut microbiota populations and their activities **[4]**. Consistent physical activity (exercise) has been found to improve microbial diversity, enhance the number of beneficial bacteria **[5, 6]**. These variations exhibit positive influence on the management of overall body inflammation, energy production and balance of neurochemicals, eventually promoting emotional health and cognitive behaviour **[7]**.

Exercise, gut microbiota, and brain activity involve an intricate molecular interaction. Exercise mediated changes in the gut microbial metabolic products (like short-chain fatty acids), can influence the hypothalamic-pituitary-adrenal axis response, neurotransmitter release and inflammation of neurons **[8]**. In addition, physical activity promotes vagal tone and neurogenesis, and decreases stress-associated actions **[9]**.

Keeping in view the present lifestyle associated issues like obesity, depression, and neuronal decay illnesses, it has become essential to analyse the interrelationship between physical exercise and microbiota-gut-brain axis. The present review emphasizes the impact of physical exercise on gut-microbiota population and their functions, microbiota-gut-brain axis and the communication pathways among them, positive influence of exercise on psychiatric disorders through gut-microbiota and future prospects of the study and recommendations.

MAJOR ACTIVITIES OF GUT-MICROBIOTA IN CONNECTION WITH THE HUMAN HEALTH

The gut microorganisms, just do not exist as simple inhabitants, they associate with the host (human) mutually, exhibiting various vital functions like maintenance of overall health of the host and protecting it from infections, apart from basic digestion **[10]**. A stable gut microbiome is an indication of host homeostasis. The gut microbiome plays an important role in regulating gut homeostasis, continuous peristaltic movements and enhancing the gastrointestinal barrier **[11]**. One of the basic and key functions of the gut-microbiome is metabolism of nutrients and energy generation. Complex carbohydrates and dietary fibers are resistant to human digestive enzymes. Such complex dietary components like non-starchy carbohydrates and cellulose are fermented by gut microbes and vital metabolic products, more particularly, short chain fatty acids are released (Butyric, Propionic and acetic acids). Butyric acid serves as the key energy source for the intestinal epithelial cells, thus conferring the strength to the integrity of gut-barrier **[12]**. Similarly, pripionic acid, another fermented product serves as a starting compound for the preparation of glucose in the liver and acetic acid moves into blood circulation and involved in the metabolism of cholesterol. Further, the intestinal microbiota is essential for the biosynthesis of essential vitamins, specifically Vitamin K and various vitamins of B complex, which are required for blood clotting and cell metabolism **[13]**. One of the most important and widely studied aspects of the immune system's activity is obviously the link between gut-microbiota and the immune system. The microbiota is an effective controller of mucosal and systemic immunity, which continuously interacts with gut-associated lymphoid tissue, which includes largest number of immune cells. Microbes synthesize various metabolites and regulate the balance between pro-inflammatory and anti-inflammatory responses by mediating the proper development and maturation of immune cells. A healthy and diversified microbiota regulates immune tolerance and prevents improper reactions with self-antigens or common natural factors **[14]**. The microbiota imparts colonization resistance which acts as barrier to control infections **[15] (Figure 1)**.

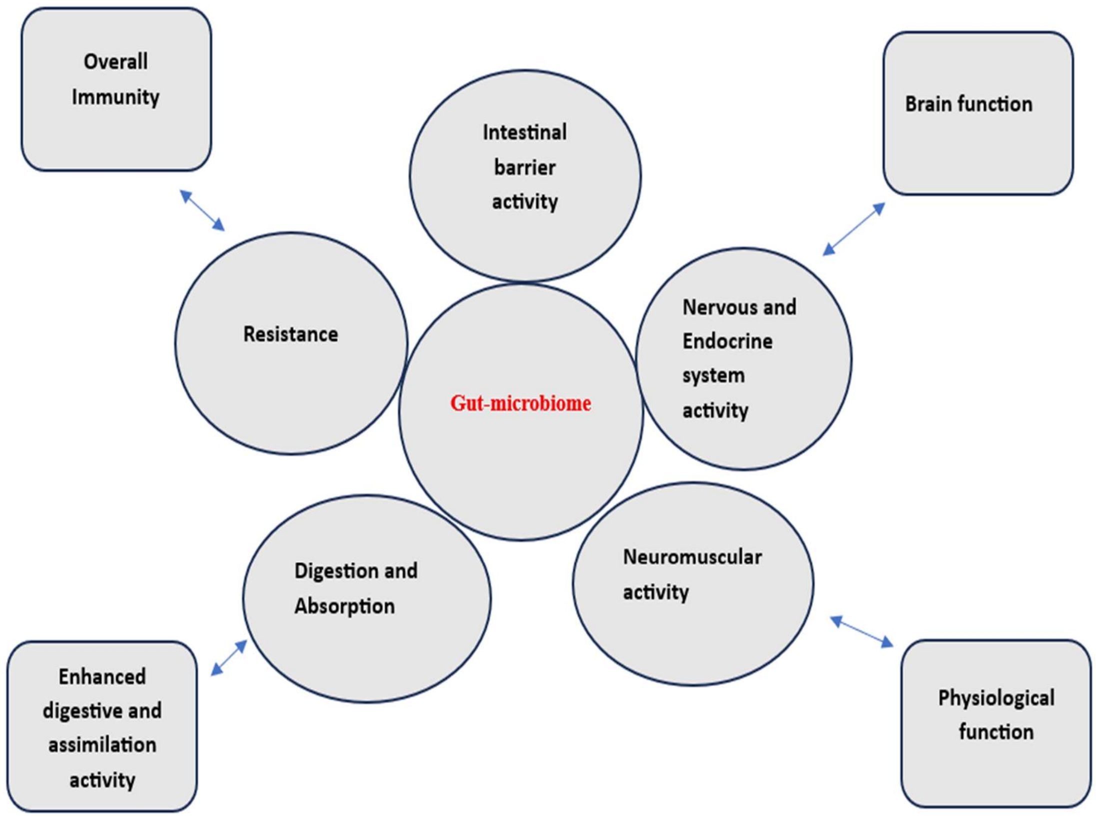

Figure 1: Interrelationship between gut-microbiota and overall human health

INTERACTION BETWEEN GUT-MICROBIOTA AND BRAIN AXIS

Currently, the communication between the brain function and gut microbiome has garnered significant attention due to their presently established influence on human health. The interplay between the gut and brain which is considered as microbiota-gut-brain axis, is bidirectional and intricate, involving different organ structures and microbiological products that play crucial roles. The nervous, endocrine and immune systems are associated with this communication network **[16]**. Microorganisms ferment dietary fiber and release metabolic products, particularly short-chain fatty acids such as butyric acid, propionic acid and acetic acid which can pass through the intestinal wall and modulate human host physiological functions like maintenance of blood-brain barrier and microglial activity **[1, 17]**. Further, the gut-microbiome can influence neural signaling system. For example, some bacteria release neurological transmitters like gamma-aminobutyric acid and regulate the production of serotonin by the host which is found to be 90% in the gut region **[18]**. The vagus nerve acts as a key neural network means for quick and direct transmission of signals from intestine to central nervous system. The research studies on axenic mice have been revealed that early invasion of microorganisms is required for general stress response, especially in modulating the hypothalamic-pituitary-adrenal axis **[19, 20]**. On the other hand, brain can affect the gut microorganisms through the autonomic nervous system and the hypothalamic-pituitary-adrenal axis, influencing conditions such as gut movement, carry period, and release, which in turn affects the composition of microbial communities **[17]**. Dysbiosis (imbalance of microbiome in gut) is majorly responsible for gastrointestinal disorders such as irritable bowel syndrome and various major neurological and psychiatric disorders **[21, 22] (Table 1)**.

Table 1: Communication between gut-microbiota and brain axis

Constituent/Mode/Activity	Function in Gut-Brain interaction	The influenced systems/activities	References
Microbiota-gut-brain axis	Two way and complex interaction between the gut and brain, affecting human health status	Endocrine, immune and nervous systems	[16]
Short-chain fatty acids produced by bacteria (through fermentation)	Regulate human physiological activities such as controlling blood-brain barrier and microglial function	Endocrine system and metabolic activities.	[1, 17]
Neurotransmitters released by bacteria	Effect signalling pathways	Nervous system	[18]
Release of Serotonin	Controlled by gut microorganisms. Around 90% of host's serotonin occurs in the gut.	Nervous and endocrine systems.	[18]
Vagus nerve	Functions as a crucial connecting link for the enhanced and direct passing of signals from gut to brain.	Nervous system	[17]
Dysbiosis (imbalance in microbial communities)	Mainly causes irritable bowel syndrome and responsible for numerous psychiatric disorders and neurological complications	Nervous and immune systems	[21, 22]

INFLUENCE OF EXERCISE ON GUT-MICROBIOTA COMPOSITION

The gut microbiome, which constitutes a wide range of microbial communities inhabiting the gastrointestinal tract, is identified as the key modulator of human host physiological activities, affecting metabolic and immune system functions and psychological well-being. Though the food and genes are the well-known factors that determine the microbial composition, regular physical exercise has now recognized as a crucial and non-therapeutic influencing factor of the succession of microbial communities of the gut ecosystem.

Mika *et. al.,* (2015) based on their studies reported that the gut health is affected by the voluntary aerobic exercise. They conducted a study on rats enclosed in cages connected with running wheels. These rats were able to engage in physical activity during the study. The gut microbiome of rats engaged in physical exercise exhibited enhanced increase of useful bacterial genera such as *Lactobacillus* and *Bifidobacterium* when compared to sedentary group of rats **[23]**. The voluntary exercise has even been proved to enhance the growth of other beneficiary bacterial families like Ruminococcaceae and Lachnospiraceae **[24]**.

Majority of the research studies revealed that there was an enhanced microbial diversity in humans who were engaged in regular physical exercise when compared to sedentary (people who are not engaged in physical activity). Increased microbial diversity, or stable microbial species, is an indication of healthy gut which confers protection against infections and other complications like inflammatory bowel disease and even obesity. In a study performed on athletes (rugby players), revealed that there is an enhanced microbial diversity in the gut of these active individuals when compared to sedentary (control group) **[5]**. These results demonstrate that physical activity, changed intestinal transmit time, and overall physiological alterations enhance the formation of the internal conditions that supports a wider range of microbial communities **[25]**. Furthermore, the physical activity boosts the succession of microbial communities, specifically enhancing the multiplication of beneficial bacteria linked to overall health. In particular, regular physical activity results in the increase of short-chain fatty acids producing bacterial genera like *Butyricicoccus* and *Faecalibacterium* **[6]**. The significant release of short-chain fatty acids is regarded as one of the basic processes through which regular physical activity caters to the overall systemic health advantages **[26]**.

Mika *et. al.* (2015) from their studies demonstrated an interesting aspect that when physical exercise commenced during young childhood period, it alters gut-microflora with an enhanced number of Bacteroidetes and reduction of Firmicutes. Moreover, when compared to adult physical exercise, the exercise during early childhood enhanced the modified bacterial genera and resulted in the enhanced lean body mass. These findings indicate that engaging in physical activity during early age will enhance the rise of beneficial bacteria that can adapt to the host metabolic conditions **[23]**. Furthermore, engaging in physical exercise since early age can support the ideal development of brain activity, thereby enhancing the population of beneficial bacteria associated with health **[27] (Table 2)**.

Table 2: Influence of exercise on the composition of gut-microbiota and its diversity

Research outcomes/significant point	Alteration in microbes	Research on – Subject (Human/Animal)	Findings/Result	References
Voluntary physical activity influences intestinal health	**Increase of *Lactobacillus* and *Bifidobacterium* species**	**Study on rats**	**Increased beneficial bacterial species in comparison with normal rats (sedentary)**	**[23]**
Sportsmen (Athletes) exhibit increased microbial diversity when compared to sedentary groups.	**Diversified groups of microorganisms.**	**On humans**	**Exercise promotes broad range of microbial communities.**	**[5]**
Regular exercise enhances the number of short chain fatty acid releasing bacteria	**Increase of *Butyricicoccus* and *Faecalibacterium***	**On humans**	**Increased production of short chain fatty acids promotes systemic health**	**[6, 26]**
Physical exercise in early life changes gut-microbiota structure	**Increases *Bacteriodetes* and decreases Firmicutes**	**Animals (rats)**	**Increased lean body mass and adaptation of beneficial microbes**	**[23]**
Physical exercise during early age promotes brain functioning and increase of beneficial bacteria	**Enhanced beneficial bacteria number has a positive impact on neuro development.**	**Animals**	**During developmental stages, gut-brain health is enhanced**	**[27]**

IMPACT OF PHYSICAL EXERCISE ON THE MICROBIOTA-GUT-BRAIN AXIS AND THEIR COMMUNICATION PATHWAYS

Various clinical and pre-clinical studies revealed that regular moderate physical activity enhances microbial diversity and alters microflora composition towards the microbial species associated with improved metabolic activities and anti-inflammatory features. These alterations in microbiota structure seem to be affected by not only physical activity (*i.e.,* type of exercise, its intensity and duration) but also on the dietary habits and host life style. **[1, 28]**.

The metabolites released by microorganisms, especially short-chain fatty acids such as acetic acid, propionic acid and butyric acid, are key inducing factors that link changes in microbiota due to exercise with the brain functioning. The short-chain fatty acids strengthen the intestinal barrier, influencing peripheral immune responses, and traverse the blood-brain barrier in limited quantities or communicate through vagal and humoral pathways. They also control the maturation and activities of microglia, which in turn influences neuroinflammation and behaviour. The effects of these microbial metabolites create an arbitrary link from exercise to gut microbiota and the central nervous system **[29]**.

The vagus nerve and enteric nervous system serve as crucial neural communication pathways for signaling between gut and brain. Physical activity can alter gut sensory signaling and the function of the enteric nervous system through luminal metabolic products, hormones of endocrine system and local inflammation, which subsequently change the vagal afferent input to the areas of brain involved in the control of mood and stress responses. Pre-clinical studies revealed that the behavioural advantages of certain microflora manipulations are relied on vagus nerve, indicating that vagus nerve is a vital channel for certain physical exercise effects on the brain that are facilitated by microbiota **[30]**.

Physical exercise also integrates with nervous, endocrine and immune systems that form the communication between microbiota and brain. Exercise regulates the hypothalamic-pituitary-adrenal axis, body cytokine concentrations, and movement of peripheral immune cells. These modifications affect the permeability of intestine, immunity of mucosa, and diversity of microbial populations. Furthermore, the modified microorganisms and their metabolic products subsequently modulate systemic inflammation and hypothalamic-pituitary-adrenal axis response, establishing a reciprocal interaction that links exercise, stress and microbial signaling **[1, 31]**.

Neurotrophic and neurotransmitter pathways are considered as additional terminal points. Physical exercise enhances brain-derived neurotrophic factor and improves synaptic plasticity. The gut microbes can affect brain-derived neurotrophic release through immune and metabolic signaling. Hence, physical activity can promote neuroplasticity and cognitive ability both directly (muscle to brain) and indirectly (from muscle to gut to microbial products to brain) **[1, 32] (Table 3)**.

Table 3: Interrelationship among exercise, gut-microbiota and brain function

Aspect/constituent	Significant impact of physical activity	Alterations pertaining to microflora	Influence on brain function	References
Diversity of gut-microbiome	Consistent moderate physical activity enhances microbial diversity; the impact differs based on the type of physical activity, dietary habits, duration of exercise and overall, of lifestyle.	Transition to microbial species linked to enhanced metabolism and anti-inflammatory properties	Enhanced metabolic balance and lowered systemic inflammation indirectly promote brain health	[11, 28]
Short-chain fatty acids	Physical activity increases the release of short-chain fatty acids by influencing gut microbiota	Elevated levels of short-chain fatty acids; enhanced intestinal barrier; modulated peripheral immunity	Short-chain fatty acids traverse the blood brain barrier in less amount or communicate through vagal and humoral pathways; they modulate microglia development and decrease	[29]

			inflammation of nerves.	
Signaling of vagus and enteric nerve systems	**Physical exercise influences gut sensory signaling and the functionality of the enteric nerve through metabolites, hormonal changes, and the status of inflammation.**	**Modified vagus nerve afferent induction indicates microbiological composition of the gut**	**Effects areas of the brain that are linked to brain and stress; certain microbial driven behavioral outcomes rely on vagus nerve.**	**[30]**
Nervous, endocrine and immune systems regulation	**Physical activity controls cytokine concentrations, peripheral immune cells movement, functioning of hypothalamic-pituitary-adrenal axis**	**Alters gut permeability, immunity of mucosa, and diversity of microbiota; The metabolic products of microbes regulate overall body inflammation.**	**Optimized hypothalamic-pituitary-adrenalin reactions; decreased stress associated signaling; improved brain-gut communication loop**	**[1, 31]**

EFFECT OF PHYSICAL EXERCISE ON THE PSYCHIATRIC DISORDERS THROUGH POSITIVE INFLUENCE ON THE GUT-MICROBIOTA

Physical activity is becoming more widely acknowledged as a non-drug therapy that promotes mood, alleviates anxiety, and improves cognitive abilities across neurological complications. Numerous clinical and translational research studies demonstrate that one approach for these advantages is engaging in physical activity alters the microbiota structure, diversity and metabolic products of gut microbial populations, which subsequently modify immune-endocrine-neural communication that play crucial role in controlling anxiety and mood **[33]**.

Physical exercise basically improves the growth of specific beneficial bacterial groups that synthesize short-chain fatty acids (*viz.,* butyric acid, propionic acid and acetic acid). The short-chain fatty acids exhibit numerous effects with respect to brain health. They improve the activity of intestinal barrier (which decreases the systemic interaction with endotoxins), control both peripheral and central immune activities by decreasing pro-inflammatory cytokines and effect the development and functions of microglia, **[24, 34]**. These core relationships demonstrate how metabolic products produced by exercise induced microbial activity can bring about neurological changes that alleviate psychiatric symptoms.

Clinical data of humans is still in its emerging stage. A three-month structured aerobic group physical exercise program with teenagers revealed that depression symptoms in them were improved and there was a significant change in gut microbiota at the genus and species level when compared to controls in a randomized controlled study **[35]**. This study is significant as it assessed both clinical mood outcomes and simultaneous microbiota alterations, which subsequently lead to reduction of clinical symptoms of selected clinical group.

FUTURE PERSPECTIVES AND EMERGING TRENDS

Recent developments in microbiome studies have unveiled novel approaches for comprehending how exercise coordinates intricate molecular and microbial transformations that affect both cognitive activity and gut health. Future research is anticipated to investigate the unique microbiome profiles that react to different intensities of physical activity and its types in order to determine individualized exercise recommendations **[36]**. With the emergence of sophisticated technologies such as metagenomic, metabolomic and transcriptomic tools, researchers can presently unravel the mechanisms by which gut associated metabolic products, like short-chain fatty acids and neurotransmitter precursors, interact with central nervous system through gut-brain axis **[1]**.

Integrative approaches that merge exercise programs with dietary modifications or probiotic additions are increasingly drawing attention due to their combined effect on the structure and activities of gut microbiome **[37]**. These combination treatments may improve resilience to psychiatric disorders such as anxiety, cognitive defects and depression and neuroprotective effects **[8]**. Furthermore, in order to establish more robust casual interrelationship between physical activity stimulated microbial changes and brain functioning, future clinical trial studies are expected to use longitudinal research methodologies that track microbial and neurological alterations, rather than employing cross-sectional studies **[6]**.

Combining artificial intelligence and machine learning models with microbiome studies will probably change the forecasting of response of humans to exercise depending on their microbiome structure **[38]**. These models could enable to develop microbiome associated therapies, where individual workout plans can be suggested to improve brain activity, reduce neuroinflammation, and keep emotional balance. Furthermore, combining multi-omics data will confer the researchers the approaches to formulate a complete strategy on how microbial populations, metabolic products and neurological networks combinedly evolve in concurrence with improved physical activity **[39]**.

CONCLUSION

Physical exercise, gut microbiome and brain activity are intricately intertwined, and this is fast growing area of bioscience research. Recent clinical and pre-clinical research studies demonstrated that sustained physical activity is a powerful regulator of gut microbial structure and activity, increasing the number of advantageous bacterial species. These microbial population alterations are intimately linked with enhanced synthesis of short-chain fatty acids, increased intestinal barrier integrity, and decreased inflammation conditions that are responsible for better brain activity and mental wellbeing. Through neurological signaling pathways including the vagus nerve, immunological regulation, and neurotrophins, physical activity stimulated microbial metabolic products are crucial in integrating the gut-brain axis. Additionally, research studies demonstrate that the punctuality and strength of the physical exercise affect the intensity of gut-brain functions. In spite of tremendous development, future studies must concentrate on tracing out the personalized exercise therapies based on individual microbiome composition and identifying the molecules linked to exercise triggered microbial alterations. The use of exercise as a non-drug approach to modulate the gut microbiome presents a significant therapeutic method for improving brain functioning and overall well-being. The interconnectedness between physical exercise, gut microbiota and brain activity highlights comprehensive nature of human physiology.

CONFLICT OF INTEREST

The authors declare no conflicts of interests.

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