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Gut Microbiota and Its Connection to Neurological Disorders- summary of current knowledge

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ABSTRACT:

Introduction and Purpose: The gut microbiota plays a crucial role not only in absorption, metabolic, and immune processes but also increasingly in shaping behavior and is strongly linked to the gut-brain axis. Different sections of the digestive system, due to varying environmental conditions and physiological functions, have a unique microbiota composition, both quantitatively and qualitatively, including bacteria, fungi, and archaea. This study aims to review current scientific research on the impact of the gut microbiome on the gut-brain axis and to explore how this influence may affect neurological disorders.

Brief Description of the State of Knowledge: Dysbiosis in the digestive system leads to changes in the composition of the gut microbiome, which can significantly impact the development and progression of various mental health conditions, as indicated by numerous clinical studies examining the gut-brain axis correlation. The main challenge is the insufficient understanding of which microorganisms within the human microbiota have positive or negative effects on mental health. Therefore, further research is needed to better elucidate these mechanisms.

Summary: Neurological disorders are a common challenge in clinical practice. Evaluating gut microbiota and metabolic states may provide valuable diagnostic and therapeutic insights, potentially improving patients' quality of life.

Materials and Evidence: A literature review was conducted using the PubMed database.

Keywords: gut microbiome; microbiota; neurological disorders; microbiota-gut-brain axis

INTRODUCTION

The microbiome refers to the collective genomes of microorganisms that inhabit a specific environment. In the human gastrointestinal tract, approximately 100 trillion microorganisms, primarily bacteria, reside. The human genome comprises around 23,000 genes, whereas the

microbiome consists of over three million genes that produce thousands of metabolites. These metabolites perform numerous functions that support the host organism, playing a crucial role in its health, phenotypic expression, and overall well-being [1,2]. The gut microbiota fulfills several key functions, with one of the most critical being the optimal utilization of available ecological niches through diverse metabolic activity. This diversity enables the effective inhibition of pathogen colonization in various regions of the gastrointestinal tract. Additionally, the increased concentration of acidic fermentation products produced by the diverse bacteria, fungi, and archaea that colonize the gut leads to a localized reduction in pH, creating an environment less conducive to pathogen proliferation [1,3]. Among numerous environmental factors, the gut microbiota is currently recognized as a critical element influencing energy metabolism and susceptibility to various infectious diseases [4]. Akkermansia muciniphila is considered one of the most effective and significant bacteria in maintaining gut health, energy homeostasis, and lipid metabolism. This bacterium has garnered particular attention for its potential role in modulating metabolic disorders [5].

Preclinical studies in murine models have demonstrated that supplementation with live Akkermansia muciniphila can reduce body weight gain by up to 50% and significantly decrease both visceral and subcutaneous fat. Subsequent research has confirmed the efficacy of this supplementation. Additionally, recent data indicate that A. muciniphilasupplementation improves glucose tolerance, enhances gut barrier function, and modulates adipokine balance. These findings suggest that A. muciniphila may play a pivotal role in the future therapeutic management of non-alcoholic fatty liver disease (NAFLD). Consequently, it is important to further investigate this bacterium and explore its potential connections with the gut-brain axis [4,6].

Recent studies increasingly highlight a significant association between the gut microbiome and a range of diseases beyond gastrointestinal disorders. Understanding the interactions between the host and the gut microbiota is becoming essential for advancing knowledge about the pathogenesis of numerous conditions and for developing effective prevention and treatment strategies [7].

Factors affecting the microbiome

The composition of the gut microbiota begins to develop during the prenatal period. The gut microbiota plays a crucial role in the maturation of the immune system, stimulating innate immunity in the early years of life, which leads to the development of gut-associated lymphoid tissue (GALT) and adaptive immunity. Gut microbiota stability is typically achieved between 6 and 36 months of age. The neonate's body, which is entirely sterile at birth, is immediately exposed to a variety of microbial communities, including the maternal gut, vaginal, and skin microbiota [18,19,21].

Maternal lifestyle significantly influences the infant's gut microbiota. Factors such as maternal diet, obesity, smoking, antibiotic use during pregnancy, mode of delivery, and breastfeeding are considered key determinants of the initial gut colonization in the neonate. Increasing evidence indicates that the composition and development of the microbiota during early life have a substantial impact on long-term health risk factors in adulthood [18,21]

However, in later life, the microbiome can be influenced by various factors. Key determinants of gut microbiome structure in the general population include pancreatic exocrine function, genetics, diet, age, sex, and obesity. The gut microbiome can also be altered by various substances, including medications, which affect its enzymatic structure, bioavailability, bioactivity, and toxicity. Understanding these phenomena is essential for the effective and safe application of medical therapies[18,19,21].

Age is also a significant factor influencing changes in the gut microbiome. Age-related dysbiosis can modulate immune responses, leading to exaggerated reactions that are often associated with a range of gastrointestinal and systemic diseases. Therefore, it is crucial to raise awareness about the importance of maintaining a healthy microbiota [12].

The gut-brain axis

The gut microbiota is not solely associated with gastroenterological diseases; its influence extends beyond the gastrointestinal tract [12,13]. The Gut-Brain Axis integrates the functions of the brain, gut, and gut microbiota, regulated on multiple levels, with the Hypothalamic-Pituitary-Adrenal (HPA) axis playing a crucial role. The transmission of nerve impulses within this system largely depends on the function of the vagus nerve[13] The brain influences gastrointestinal motility, secretion, and immunity, which are critical for the composition and function of the gut microbiota. Conversely, the gut microbiota plays a key

role in the communication between the gut and the brain, although the mechanisms by which the microbiota affects brain functions remain not fully understood. Research has shown that this communication occurs through neuronal, immunological, and endocrine systems [14,15]. The interactions within this system are nonlinear and bidirectional, involving numerous feedback loops and various communication channels, with the gut microbiota providing significant signals to microglia, astrocytes, and oligodendrocytes [16,17]. The gut microbiota influences the brain through the production of metabolites, such as short-chain fatty acids (SCFAs), which modulate immune responses and the function of the gut barrier. One of the primary functions of SCFAs is to support the integrity of the gut barrier and reduce its permeability, thereby protecting against the translocation of pathogens into the bloodstream and the brain [18] In addition to its influence through the gut-brain axis, the microbiota also exerts other effects on the brain. Increasing evidence suggests that the microbiota-gut-brain axis plays a crucial role in regulating sleep-related behaviors, both directly and indirectly. This axis may be significantly involved in the etiology and pathogenesis of sleep disorders. Sleep deprivation leads to dysfunction of the gut microbiota, and sleep disturbances are associated with changes in its composition [19].

Concurrently, the analysis of clinical trial data on dietary interventions underscores the critical role of gut microbiota in the amelioration of mood disorders. The primary conclusions are as follows:

- Enhancement of dietary quality exerts a positive effect on mood, given that diet is a critical determinant of gut microbiota composition. Sustained dietary patterns, including the specific balance of macro- and micronutrients, meal regularity, and overall dietary behaviors, result in significant and enduring modifications in the gut microbiota. These alterations can subsequently influence the regulation of mood and psychological well-being [20,21].
- Consumption of fructooligosaccharides and galactooligosaccharides (≥ 5 g/day) alleviates symptoms of anxiety and depression and increases the abundance of Bifidobacteria.
- Probiotic supplementation improves psychological and biological markers of depression, anxiety, and stress, particularly in individuals predisposed to these conditions.

- Probiotics may reduce biological stress markers in healthy individuals, depending on the specific strain used.
- A high-quality diet, rich in dietary fiber and omega-3 fatty acids, may mitigate the risk of developing symptoms associated with depression, anxiety, and stress [20]. Evidence suggests that dietary fiber modulates the gut microbiome, leading to the production of diverse metabolites, including carbohydrate derivatives, amino acid metabolites, and modified bile acids. These metabolites have the potential to influence overall health and may play a pivotal role in the prevention and management of cardiovascular diseases, diabetes, inflammatory bowel diseases, and autism. Furthermore, experimental studies in mice have demonstrated that fiber supports gut microbiota diversity and promotes the production of short-chain fatty acids (SCFAs) through fermentation processes [22].

Nevertheless, there is an urgent need for further research to elucidate the precise mechanisms governing the interactions within the microbiota-gut-brain axis. Comprehensive understanding of the full spectrum and detailed nature of these interactions—encompassing the influence of gut microbiota on brain function and the reciprocal effects—is crucial for the advancement of effective therapeutic and diagnostic strategies.

The gut microbiome in neurological disorders

There is a growing body of clinical evidence suggesting that the microbiome may play a key role in susceptibility to neurological disorders such as Alzheimer’s disease, autism spectrum disorders, Parkinson’s disease, and epilepsy [23]. This is noteworthy because understanding the impact of the microbiome on these conditions could open new avenues for diagnosis, prevention, and treatment of these serious neurological disorders.

Alzheimer’s disease

Alzheimer's disease is a chronic neurodegenerative disorder that primarily affects the medial structures of the temporal lobe and the associative structures of the neocortex. It is characterized by the accumulation of β-amyloid peptide (Aβ) in the brain, as well as hyperphosphorylated and fragmented forms of tau protein associated with microtubules [24,25,26].

As a primary cause of dementia, particularly among the elderly, Alzheimer's disease may have its origins in the gut, with subsequent progression of pathology to the brain. This hypothesis is supported by studies showing that Aβ1–42 oligomers introduced into the gastric wall of mice migrate to the brain. Additionally, research involving APP transgenic mice suggests that alterations in gut microbiota composition may facilitate amyloid deposition in the brain, thereby emphasizing the role of gut microbiota in triggering immune responses and pathology associated with Alzheimer's disease [26].

Autism spectrum disorder (ASD)

Autism is defined as a spectrum of heterogeneous neurodevelopmental disorders characterized by qualitative impairments in social communication, social interaction, and social imagination, along with a restricted range of interests and often repetitive, stereotyped behaviors and mannerisms. Sensory sensitivities or insensitivities to environmental stimuli are also prevalent [27,29]. Recent research has elucidated that interactions between the gut microbiota and the brain are pivotal in neuropsychiatric conditions. Approximately 40% of individuals with autism spectrum disorder (ASD) present with gastrointestinal disturbances, including alterations in gut motility, abdominal pain, diarrhea, reflux, and vomiting [27]. Furthermore, children with autism demonstrate a markedly altered gut microbiota composition, and their gastrointestinal symptoms may result from inflammatory processes associated with increased intestinal mucosal permeability to neurotoxic bacterial peptides [2]. The correlation between gastrointestinal symptoms and the severity of autism underscores the critical importance of the gut-brain axis in understanding and potentially addressing ASD [27,28,29].

Parkinson’s disease

Parkinson's disease is a neurodegenerative disorder characterized by hallmark motor symptoms associated with the presence of Lewy bodies and the progressive loss of dopaminergic neurons in the substantia nigra [30,31]. Given the early involvement of the gastrointestinal tract in the disease's pathogenesis and the high probability of physiological interactions between the gut microbiota and the host, it is proposed that the gut microbiome may play a role in the development of Parkinson's disease. Gastrointestinal dysfunction, particularly constipation, is observed in up to 80% of patients with Parkinson's disease and

may manifest years prior to the onset of motor symptoms. Idiopathic constipation is a prominent comorbidity in Parkinson's disease and is correlated with neurodegenerative changes within the enteric nervous system (ENS) [2,23,30,31]

Epilepsy

Epilepsy is a chronic neurological disorder characterized by the predisposition to recurrent, spontaneous seizures, which arise from excessive and aberrant neuronal activity within the brain. These seizures are a result of disrupted equilibrium between excitatory and inhibitory neuronal networks, leading to disturbances in electrical signal transmission. Additionally, glial cells play a critical role in this process by regulating neuronal function through the maintenance of ionic homeostasis and neurotransmitter metabolism, including glutamate and gamma-aminobutyric acid (GABA) [32,33].

Emerging evidence suggests that probiotics may have a beneficial effect on seizure control in patients with drug-resistant epilepsy. Probiotics could potentially serve as an adjunctive therapeutic option. Given their safety profile, probiotics may contribute to improved seizure management and enhanced quality of life for individuals with refractory epilepsy [34,35]. In clinical studies, probiotics have been associated with a reduction in seizure frequency of 50% or more in 28.9% of patients. Analysis of six cases of drug-resistant epilepsy revealed that five patients achieved complete seizure remission, while one patient experienced a reduction in seizure frequency exceeding 90% following probiotic therapy. However, this effect was observed to diminish after two weeks, which may indicate a transient impact on the gut microbiota. Furthermore, there is evidence suggesting that the gut microbiota may influence immune and inflammatory responses, which is relevant in the context of epilepsy therapy. Modulating the gut microbiota appears to be a promising therapeutic strategy, particularly for drug-resistant epilepsy. Probiotics, being a safe intervention, have the potential to improve patients' quality of life. However, to determine which microorganisms are beneficial and which may be harmful, further clinical research is required [32,33,34,35].

Summary: Alterations in socio-emotional behaviors and gastrointestinal symptoms, which are associated with various pathways within the immune, neuroendocrine, and metabolic systems, may indicate the presence of neurological disorders. Healthcare professionals should

pay close attention to patients exhibiting such symptoms, as early identification is critical for enhancing patient comfort and overall health.

Disclosure:

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Author's contribution

Conceptualization: Oliwia Sysło, Weronika Goliat; methodology: Konrad Haraziński, Maximilian Jung; software: Aleksander Jaworski; check: Barbara Sławińska; formal analysis: Magdalena Jung; investigation: Piotr Gutowski; resources: Konrad Haraziński; data curation: Maciej Rzepka; writing – rough prepatation: Magdalena Nalepa, Aleksander Jaworski; writing – review and editing: Maximilian Jung, Oliwia Sysło, Weronika Goliat; visualization: Piotr Gutowski; supervision: Barbara Sławińska; project administration: Oliwia Sysło; receiving funding: Not applicable

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Our work did not involve direct human subject research or obtaining their consent for participation in the study

Data Availability Statement

As a review paper, our work does not present new data or analyses. Therefore, there are no specific databases or data availability to report. The information and findings presented in this review are based on previously published studies, which can be accessed through their resective sourses as cited in the reference section.

Conflicts of Interest Statement

The authors declare that there are no significant conflicts of interest associated with this research work.

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