


Systematic analysis of the relationship between intestinal microbiota and neurological disorders: emerging perspective in neurogastroenterology

Análise sistemática da relação entre a microbiota intestinal e os distúrbios neurológicos: perspectiva emergente em neurogastroenterologia

Análisis sistemático de la relación entre la microbiota intestinal y los trastornos neurológicos: perspectiva emergente en neurogastroenterología

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Universidad Estatal de Guayaquil, Ecuadorfanpa_4@hotmail.com**ARTICLE HISTORY****Received:** 17-01-2024**Revised Version:** 23-02-2024**Accepted:** 13-04-2024**Published:** 25-04-2024**Copyright:** © 2024 by the authors**License:** CC BY-NC-ND 4.0**Manuscript type:** Article**ARTICLE INFORMATION****Science-Metrix Classification (Domain):**

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Main topic:

Intestinal microbiota and neurological disorders

Main practical implications:

The article suggests that understanding the interplay between the gut microbiota and neurological diseases can have significant implications for treatment and management strategies. By manipulating the gut microbiota through probiotics, prebiotics, dietary interventions, or other means, it may be possible to modulate neuroinflammation, neurotransmitter levels, and other factors implicated in these disorders. This could potentially lead to novel therapeutic approaches for managing neurological diseases, particularly those that are currently challenging to treat effectively, such as Parkinson's disease, multiple sclerosis, Alzheimer's disease, autism spectrum disorder, amyotrophic lateral sclerosis, and epilepsy.

Originality/value:

The originality and value of the article lie in its comprehensive review of recent research on the gut-brain axis and its implications for various neurological disorders. By synthesizing findings from a range of studies, the article provides insights into the underlying mechanisms linking the gut microbiota to neurological diseases, as well as potential avenues for therapeutic intervention. care.

ABSTRACT

By the complex gut-brain axis, the gut microbiota (GM) has a critical role in neurological function. The complex link between several neurological illnesses and the gut microbiota (GM) is examined in this comprehensive study. Strong evidence has been found, based on a review of the literature from 2019 to 2024, connecting GM dysbiosis to the etiology and development of conditions such as epilepsy, multiple sclerosis, Alzheimer's disease, autism spectrum disorder, stroke, and amyotrophic lateral sclerosis (ALS). In these cases, GM changes increase disease severity, interfere with immune responses, and worsen neuroinflammation. In particular, dysbiosis affects the prevalence of autoimmune encephalomyelitis in MS and adds to motor impairment and gastrointestinal symptoms in PD. Via pro-inflammatory microorganisms, dysregulated GM in AD exacerbates neurodegeneration. Moreover, the gut-brain axis influences emotion, behavior, and cognition, all of which are impacted by the development of ASD. In epilepsy, GM dysbiosis affects inflammatory responses and seizure frequency; in ALS, it leads to neuroinflammation and motor neuron degeneration. Notwithstanding noteworthy discoveries, the dearth of randomized controlled trials presents obstacles, requiring more mechanistic clarification and investigation of microbiota-targeted treatments for neurological disorders.

Keywords: Microbiota, neurological disorders, neurogastroenterology.**RESUMO**

Por meio do complexo eixo intestino-cérebro, a microbiota intestinal (GM) tem um papel fundamental na função neurológica. A complexa ligação entre várias doenças neurológicas e a microbiota intestinal (GM) é examinada neste estudo abrangente. Foram encontradas fortes evidências, com base em uma revisão da literatura de 2019 a 2024, ligando a disbiose intestinal à etiologia e ao desenvolvimento de doenças como epilepsia, esclerose múltipla, doença de Alzheimer, transtorno do espectro do autismo, acidente vascular cerebral e esclerose lateral amiotrófica (ELA). Nesses casos, as alterações GM aumentam a gravidade da doença, interferem nas respostas imunológicas e pioram a neuroinflamação. Em particular, a disbiose afeta a prevalência da encefalomielite autoimune na EM e aumenta a deficiência motora e os sintomas gastrointestinais na DP. Por meio de microrganismos pró-inflamatórios, o GM desregulado na DA exacerba a neurodegeneração. Além disso, o eixo intestino-cérebro influencia a emoção, o comportamento e a cognição, todos afetados pelo desenvolvimento do TEA. Na epilepsia, a disbiose intestinal afeta as respostas inflamatórias e a frequência das convulsões; na ELA, leva à neuroinflamação e à degeneração dos neurônios motores. Apesar das descobertas notáveis, a escassez de estudos controlados e randomizados apresenta obstáculos, exigindo mais esclarecimento mecanicista e investigação de tratamentos direcionados à microbiota para distúrbios neurológicos.

Palavras-chave: Microbiota, distúrbios neurológicos, neurogastroenterologia.**RESUMEN**

Gracias al complejo eje intestino-cerebro, la microbiota intestinal (MG) desempeña un papel fundamental en la función neurológica. El complejo vínculo entre varias enfermedades neurológicas y la microbiota intestinal (GM) se examina en este estudio exhaustivo. Se han encontrado pruebas sólidas, basadas en una revisión de la literatura de 2019 a 2024, que conectan la disbiosis de la GM con la etiología y el desarrollo de afecciones como la epilepsia, la esclerosis múltiple, la enfermedad de Alzheimer, el trastorno del espectro autista, el accidente cerebrovascular y la esclerosis lateral amiotrófica (ELA). En estos casos, los cambios en la MG aumentan la gravedad de la enfermedad, interfieren en las respuestas inmunitarias y empeoran la neuroinflamación. En particular, la disbiosis afecta a la prevalencia de la encefalomielite autoinmune en la EM y se suma al deterioro motor y los síntomas gastrointestinales en la EP. A través de los microorganismos proinflamatorios, la GM desregulada en la EA exacerba la neurodegeneración. Además, el eje intestino-cerebro influye en la emoción, el comportamiento y la cognición, todo lo cual se ve afectado por el desarrollo del TEA. En la epilepsia, la disbiosis del MM afecta a las respuestas inflamatorias y a la frecuencia de las convulsiones; en la ELA, conduce a la neuroinflamación y a la degeneración de las neuronas motoras. A pesar de los notables descubrimientos, la escasez de ensayos controlados aleatorizados presenta obstáculos, lo que requiere una mayor clarificación mecanicista y la investigación de tratamientos dirigidos a la microbiota para los trastornos neurológicos.

Palabras clave: Microbiota, trastornos neurológicos, neurogastroenterología.

INTRODUCTION

Microorganisms that reside in the gastrointestinal tract (GIT), including bacteria, protists, fungus, and archaea, make up the gut microbiota (GM) (Thursby and Juge 2017). With 100 billion bacteria, around 1000 species, and over three million genes, the GM are 150 times more genetically varied than the human body (Cho and Blaser 2012). Individual GM affects human development, nutritional needs, physiological changes, and genetic variants; these factors have been discovered to be influenced by age, gender, location, food, and genetic variations (Hills et al. 2019). A preventive approach is largely suggested in specialized literature (Navas Llanos & Guzmán Variña, 2023). The GM are classified into two minor phyla, Verrucomicrobia and Fusobacteri, and four main phyla, Bacteroidetes, Firmicutes, Proteobacteria, and Actinobacteria. The gut microbiota has been shown to have a possible impact in brain function during the last 10 years by modulating signaling pathways via microbial metabolites (Grochowska, Laskus, and Radkowski 2019). Innovative research at the nexus of microbiology and neurology has, for the most part, been carried out in the last 10 years. These investigations have shown that animals and the microbial communities that inhabit them have active relationships that promote the growth and function of neurological systems. These intricate interactions—involving immunological, neurological, and chemical communication—are essential to both individual health and our comprehension of neurological illnesses (Felice and O'Mahony 2017). Through its ability to regulate cells in nearby and distant organs, such as the brain, the gut microbiota that lives in the gastrointestinal (GI) tract has a significant impact on the host's overall health. In the gut-brain axis (GBA), bidirectional transmission takes place as a two-way communication channel between the host's neurological system and gut. The immune system, hormones, and brain networks may all transmit this information, supporting the gut flora. According to Collins et al. (2012) bidirectional transmission in the GBA maintains a mutualistic link with the host, governs brain dysfunction mechanistically, and controls the innate and adaptive immune systems (Collins, Surette, and Bercik 2012).

This axis includes several pathways, including the immune system, the hypothalamic-pituitary-adrenal (HPA) axis, the endocrine system, the autonomic and gastrointestinal nerve systems, and the microbiota and its metabolites (Blaser 2017). In order to communicate with host cells, including intestinal epithelial cells (IECs) and immune cells, a healthy gut microbiota produces microbial metabolites and neurotransmitters. Many immune-associated neurological illnesses, such as emotional dysregulation, neurodegeneration, and developmental abnormalities, have been tied to changes in the gut microbiota and microbial metabolite synthesis. The brain is the organ that controls and is accountable for all of a person's conduct. According to Deidda and Biazzo (2021) it is made up of several distinct populations of neuronal and nonneuronal cells linked by very complex structural networks (Deidda and Biazzo 2021).

The knowledge of the gut microbiota as one of the major regulators of the interactions between the gut and the brain has improved with the introduction of omics approaches (Bhattarai et al. 2021). Research on humans and animals has shown that the gut microbiota may produce hormones, immunological factors, and metabolites that affect brain behavior and cognitive development. It also suggests that altering the gut microbiome may help treat or improve brain disorders (Yano et al. 2015). Through complex neurohumoral networks, signals from the brain may influence the sensorimotor and secretory processes of the stomach. Similarly, signals from the gastrointestinal tract's visceral afferent neurons can influence brain activity. As a risk factor or condition for the development of neuropathological illnesses, the gut-brain axis has lately come to light as a critical player in the control of normal brain functioning under physiologically normal settings (Ma et al. 2019).

The processes underpinning the connections between brain diseases and the gut microbiota, however, remain little validated (Cryan et al. 2019). In order to discover and confirm biological mechanisms of action that have the actual potential to cure human illness, new technologies are being developed to go beyond correlative research. We go over the communication routes and the relationship between the brain and stomach in this overview. In addition, we talk about the role of the microbiome in neurological conditions such mood disorders (depression and anxiety), neuropsychiatric diseases (schizophrenia and ADS), and neurodegenerative illnesses (PD, AD, and MS).

METHODOLOGY

We used an integrated approach in this thorough evaluation to methodically compile and assess pertinent literature from reliable academic sources, such as Scopus, Google Scholar, and PubMed. Because the association between intestinal microbiota and neurological illnesses is complicated, we ensured a comprehensive study by using tried-and-true approaches from comparable review research. Key phrases included in our literature search were "intestinal microbiota," "neurological disorders," "Parkinson's disease," "multiple sclerosis," "Alzheimer's disease," "autism spectrum disorder," "amyotrophic lateral sclerosis," "stroke," and "epilepsy." To hone in on relevant material and refine search queries, boolean operators (AND, OR)

were used.

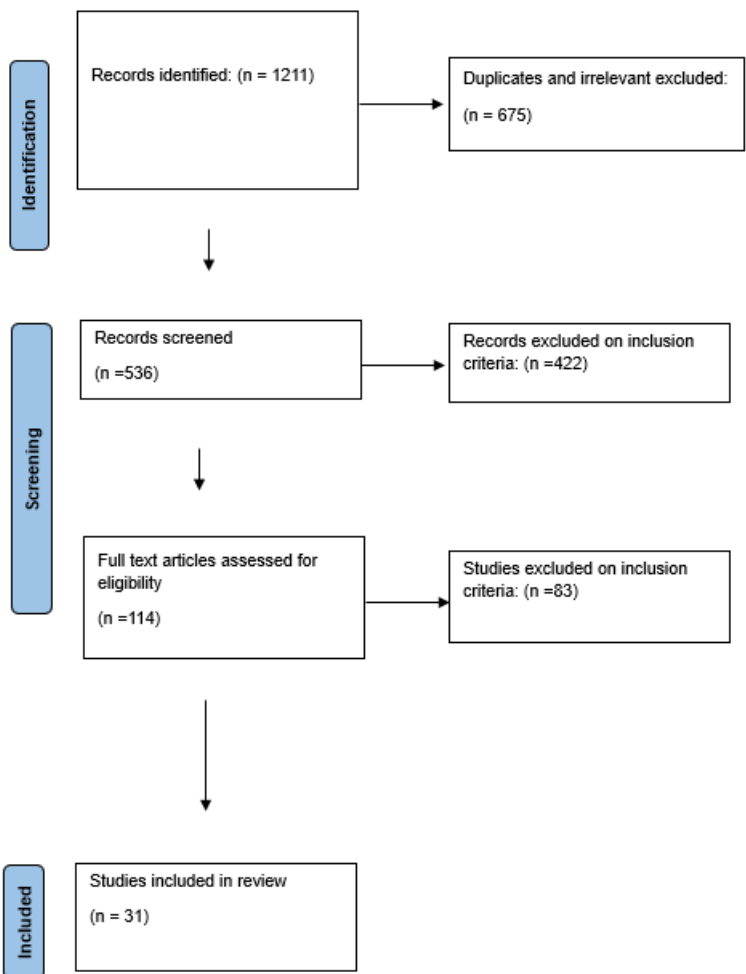
Inclusion and Exclusion Criteria:

Papers published in English during the previous ten years (2019–2024) that addressed the relationship between intestinal microbiota and neurological conditions such as epilepsy, Parkinson's disease, multiple sclerosis, Alzheimer's disease, autism spectrum disorder, and amyotrophic lateral sclerosis were taken into consideration for inclusion. Included were studies using human subjects and those that provided important new understandings of the mechanics, modifications, and therapeutic applications of the gut-brain axis in neurological diseases. On the other hand, research with insufficient methodological rigor or no relevance to the subject matter were not included. After a preliminary screening of the full-text papers based on abstracts and titles, each article was carefully examined to ascertain its applicability and relevancy for the review.

Categorization and Analysis:

To classify and evaluate the information obtained on the connection between gut microbiota and different neurological illnesses, a methodical methodology was used. The review's main goal was to clarify how gut microbiota contributes to the development, course, and possible treatments of neurological diseases. To investigate the effects of changes in the gut microbiota on certain neurological disorders, such as Parkinson's disease, multiple sclerosis, Alzheimer's disease, autism spectrum disorder, amyotrophic lateral sclerosis, stroke, and epilepsy, analytical categories were created. Examining the underlying processes, changes in the makeup of the microbiota, and clinical consequences of these interactions were emphasized. Our goal in structuring the study around these areas was to provide readers a thorough overview of the new developments in neurogastroenterology and how they relate to neurological conditions.

Figure 1. Systematic cycle of literature gathering



Note: own elaboration (2024)

RESULTS AND DISCUSSION

Parkinson's disease:

After Alzheimer's disease (AD), Parkinson's disease (PD) is the second most common neurodegenerative disorder, affecting almost 1% of the aged population and 0.3% of the global population (Ullah et al. 2023). A progressive neurodegenerative disease called Parkinson's disease (PD) is characterized by profound changes in the substantia nigra and striatum's function that impair voluntary movement control. Among these changes are the degeneration of dopaminergic neurons, the build-up of phosphorylated forms of the neuronal protein α -synuclein (α Syn), malfunctioning mitochondria, an excess of reactive oxygen species, and an increase in activation of microglia (Ullah et al. 2023). Key pathogenic processes driving α -synucleinopathies including Parkinson's disease (PD) include misfolding of α -synuclein and inflammation. The buildup of α -synuclein plays a major role in the pathophysiology of Parkinson's disease. The α -synuclein gene is found on chromosome 4q21.3-q22 and consists of five exons. 140 amino acids make up the protein known as synuclein (S. Mehra, Sahay, and Maji 2019). PD symptoms include stiffness in the muscles, tremors, difficulty walking, and a stooped posture. Up to 80% of people with Parkinson's disease may have digestive problems, most often constipation (H. Chen et al. 2015). These problems may occur years before PD diagnosis. There is mounting evidence that gut dysbiosis has a role in the start, development, and course of Parkinson's disease (PD) (Zhu et al. 2022). We observed dysbiosis of the gut microbiota in individuals with prodromal and/or clinically confirmed Parkinson's disease (PD) when comparing them to people under control. Using culture-independent high-throughput sequencing methods, the general structure and composition of the gut microbiota associated with Parkinson's disease (PD) have been investigated; characteristics of the altered microbiota profiles in Parkinson's disease patients have been identified (Zhu et al. 2022). According to many previous research, PD patients showed reduced bacterial diversity but greater α -diversity than healthy individuals (Qian et al. 2018) (Barichella et al. 2019). Furthermore, PD patients and controls differed in β -diversity (between samples), according to one research (Boertien et al. 2019). A correlation has been seen between the bacterial diversity reduction and the clinical features of Parkinson's disease (PD); the α -diversity indices Shannon and Simpson are often used to measure this decline. A new research by Heinzl et al, suggests that the prodromal microbiome may be especially important in explaining several symptoms of Parkinson's disease (PD), such as constipation, subthreshold parkinsonism, smoking, urate levels, physical inactivity, and potential rapid eye movement sleep behavior disorder (RBD) (Heinzl et al. 2021). Contrary to sexual orientation, inactivity, suspected RBD, constipation, and smoking, constipation, occupational solvent exposure, and the three aforementioned characteristics were all associated with β -diversity. Both α and β -diversity were associated with age and anti-urate drugs (Heinzl et al., 2021).

The gut dysbiosis linked to Parkinson's disease (PD) can lead to increased permeability and inflammation in the intestinal plexus. This can result in decreased SCFA-producing bacteria and increased Akkermansia. Moreover, the intestinal neural plexus can be exposed to toxins like lipopolysaccharide (LPS) and pesticides, which can lead to aberrant α -synuclein fibril aggregation and the formation of Lewy bodies (Keshavarzian et al. 2015). People with Parkinson's disease (PD) vary from those without the illness and those with other neurological illnesses in terms of the makeup of their microbiome. Bacteria that produce short-chain fatty acids (SCFAs), primarily butyrate, such as *Faecalibacterium prausnitzii* and taxa from the Lachnospiraceae family, are absent from the intestinal flora of PD patients (Barichella et al. 2019). These bacteria are known to have anti-inflammatory properties.

Multiple Sclerosis:

Another common neurological condition affecting the central nervous system (CNS) that causes autoimmune illness of the myelin sheath is multiple sclerosis (MS). It is characterized by alterations in sensitivity, motor dysfunction, and impaired vision. There is evidence that the microbial makeup of the MS gut is altered. Numerous investigations revealed that MS patients' gut microbiota profiles differed from those of healthy people (J. Chen et al. 2016). Increased regulatory T cells (Treg) counteract proinflammatory T cell activation, which is a result of the gut microbial alterations. The blood-brain barrier permeability (BBB) was enhanced and CNS inflammation was brought on by the increased amounts of circulatory Th1 and Th17 cells. Significantly, transgenic mice bearing the fecal microbiota of MS patients had a greater incidence of autoimmune encephalomyelitis (EAE) than mice receiving microbiota from healthy donors (Suganya and Koo 2020). In a mouse model of EAE, animals treated with a wide spectrum antibiotic avoided both motor impairment and axon damage, but bacterial recolonization weakened both (Mestre et al. 2019). Antibiotics most likely work via involving CD4+CD39+ T cells and CD5+CD1d+ B cells in the mouse central nervous system. Similarly, EAE mice treated with antibiotics showed a delay in the development of clinical symptoms, as well as a drop in IFN- γ and IL-17A and an increase in IL-10 in their blood (Zeraati et al. 2019). Additionally, they discovered that in EAE-induced animals, antibiotic-induced microbiota depletion might raise hippocampus BDNF and improve learning and memory. Furthermore, they observed that in EAE-induced rats, there were reductions in symptoms associated with sadness and elevations in anxiety-like behavior, hippocampus TNF- α , and IL-1 β . These investigations verified the relationship between the gut microbiota and the degree of neurological illness in the progressive MS model.

Alzheimer's Disease (AD):

A kind of dementia that usually affects those who are older, Alzheimer's disease (AD) results in memory loss and cognitive impairment because it causes nerve cells to die (Balan et al. 2021). Cortical neurons' dendrites and axons contain tau protein (t-protein), which is linked to the buildup of amyloid beta ($A\beta$) in the neurons and the dephosphorylation of microtubules (Jin et al. 2023). AD is distinguished by these biomarkers. AD patients' brains are affected by mitochondrial dysfunction, which results in aberrant mitophagy and impacts mitochondrial quality control via oxidative damage and mitochondrial malfunction (Nabi et al. 2022). Additionally, mitochondrial dysfunction is a marker of AD. Pro-inflammatory cytokines are elevated in unstimulated and non-centrifuged blood and GM species profile is altered by microbial infections such as spirochaetes, fungal infections, and Chlamydia pneumonia (Fülöp et al. 2018). Dysregulation of the microbiota can result in systemic inflammation and worsened neurodegeneration in patients with brain amyloidosis and cognitive impairment when pro-inflammatory bacteria like *Escherichia coli* and *Shigella* coexist with anti-inflammatory bacteria like *Escherichia coli* (Bairamian et al. 2022). In rats, fumonisins (FBs), mycotoxins produced by the fungus *Fusarium verticillioides*, have been shown to alter the chemical makeup of the myenteric and submucosal neurons in terms of the neurochemical profile of enteric neurons, but not the structure of the intestine. Along with their involvement in a diet that contains foods that restrict the formation of myenteric neurons, fumonisins also hinder neural development, including that of the B1 and B2 types (Kras et al. 2022). Microglia and astrocytes around amyloid plaques become less in number when antibiotic treatments are combined. Less insoluble amyloid plaques are seen in the hippocampus of persistent transgenic animals (Meyer et al. 2022). Toxic proteases, such as gingipains, have been linked to tau and ubiquitin pathology in AD patients' brains, according to a research. The brains of mice infected with *P. gingivalis* by oral infection become colonized, and they produce more amyloid- β ($A\beta_{1-42}$), the material seen in amyloid plaques. For the purpose of treating *P. gingivalis* brain colonization and neurodegeneration, gingipain inhibition is crucial. Additionally, it suppresses the formation of $A\beta_{1-42}$, lowers neuroinflammation, and protects hippocampal neurons during a *P. gingivalis* brain infection, all of which lower the bacterial burden (Dominy et al. 2019). A total of 108 elderly persons participated in a clinical research study carried out in the United States; of them, 51 had no dementia, 24 had AD, and 33 had other disorders. In order to determine the expression of the P-glycoprotein protein, a crucial regulator of intestinal homeostasis, they used metagenomic analysis using stool samples and an invitro assay for intestinal epithelial cells, testing the results every five months. They found a taxonomic group in which Lachnospirillum species are less prevalent and Bacteroides species, Alistipes species, Odoribacter species, and Barnesiella species are more common. There are fewer members of the Butyrivibrio genus and other butyrate-producing bacteria, and their prevalence in the AD microbiome is therefore lower. This work also implies that AD microbiota may dysregulate the P-glycoprotein pathway, which would have a deleterious effect on intestinal epithelial homeostasis (Haran et al. 2019). The greater production of GM inflammasome proteins acts as a crucial trigger for the subsequent activation of inflammatory and cytotoxic mediators. GM modification may be an essential therapy for neurological diseases associated with the genetic propensity to AD since the gastrointestinal inflammasome NLRP3 protein may enhance neuro-inflammation (Shen et al. 2020). Research has shown that probiotic use and dietary changes, including ketogenic diets, may help stop the advancement of Alzheimer's disease (Naomi et al. 2022). The pathogenesis and therapy of AD may be affected by genetically modified organisms (GM) as these data suggest.

Autism Spectrum Disorder (ASD):

Repetitive behavior patterns and difficulty with social interaction and communication are hallmarks of autism spectrum disorder (ASD), a neuro-developmental condition. As to the findings of the Autism and Developmental Disabilities Monitoring (ADDM) network of the CDC, ASD affects about one kid in every 44. In addition to maternal auto-antibodies against -7proteins in the developing brain, other variables that contribute to ASD include malnutrition, infections, and developmental abnormalities in infancy (Ramirez-Celis et al. 2021). Recent findings suggest that the neuropsychiatric condition autism may be impacted by interactions between GM and the brain. Additionally, gastrointestinal issues affect around 40% of individuals with ASD (Saurman, Margolis, and Luna 2020). Soon after birth, the microbiota settles in the infant's gut and expands to link with the brain. Every inflammation or obstruction that arises during development causes abnormal behavior, mood and memory swings, and cognitive impairment. Pro-inflammatory conditions and vancomycin susceptibility have been linked to GM organisms that cause ASD (A. Mehra et al. 2023). Studies have shown the ability to influence animal social behavior by the use of probiotics, which are live microbial cultures that are advantageous to the host, and/or prebiotics, which are non-digestible carbohydrates like fibers that are advantageous to the host and/or microbiota (Tiwari et al. 2023). Applying these results to people may result in innovative microbiota-based therapeutics for the treatment of ASD, which makes them fascinating.

Amyotrophic Lateral Sclerosis:

Another deadly neurodegenerative illness that causes progressive loss of upper and lower motor neurons in the brain, brainstem, and spinal cord is called amyotrophic lateral sclerosis (ALS). ALS is marked by muscular weakness. In the brain and spinal cord, ALS also results in neuroinflammation and cell death. ALS was linked to problems such as autophagy

dysregulation, RNA metabolism alterations, mitochondrial malfunction, glutamate excitotoxicity, and activation of microglia and astrocytes. The biology and etiology of ALS, however, are not fully understood. According to recent research, changing gut bacterial composition and dysbiosis may have a role in the genesis and development of ALS (McCombe et al. 2019). The makeup of the microbiome in individuals with ALS was recently described by prospective longitudinal research (Di Gioia et al. 2020). Patients with ALS were shown to have an imbalance between neurotoxic/proinflammatory groups (Cyanobacteria) and beneficial microbial groups (Bacteroidetes). It was discovered that ALS patients have greater genera of Enterobacteriaceae, Akkermansia, Eubacterium, Prevotellaceae, and Ruminococcaceae. On the other hand, the control group had higher abundances of the genera Subdogranulum, Ruminococcus, and Parasutterella, as well as those from the Veillonellaceae and Lachnospiraceae families. Furthermore, microbial biodiversity was shown to vary between ALS patients and controls. The control group had considerably greater levels of the Chao1 index (alpha-diversity), which is linked to the abundance of sequences for each operational taxonomic unit (OUT), than the ALS group (Di Gioia et al. 2020). Significant alterations in the microbial composition of ALS patients were revealed by the analysis of their fecal microbiota; Bacteroidetes was found to be more prevalent than the control group at the phylum level, and Kineothrix, Parabacteroides, Odoribacter, Sporobacter, Eisenbergiella, Mannheimia, Anaerotruncus, and unclassified Porphyromonadaceae at the gene level (Zeng et al. 2020). In contrast, the ALS group showed a substantial decrease in Firmicutes at the phylum level and in Megamonas at the gene level when compared to the control group. Moreover, it was discovered that the ALS group's metabolic pathways for amino acids, nucleotides, and carbohydrates were less developed than those of the control group. The bacterial and archaeal makeup of the gut microbiota and metabolism in ALS patients were also compared in a research (Zhai et al. 2019). A notable difference was seen in the bacterial mix of persons with ALS and those in good health. In contrast to healthy persons, ALS patients had reduced gene levels of helpful bacteria like Faecalibacterium and Bacteroides, but their phylum level Firmicutes/Bacteroidetes ratios were often greater in these patients. Furthermore, it was shown that ALS patients had greater levels of endotoxin, NO₂-N/NO₃-N, and gamma-aminobutyric acid than did healthy controls. Sod1 transgenic (Sod1-Tg) mice that were prone to ALS exhibited dysbiosis and changed metabolite composition. Under GF circumstances, antibiotic therapy exacerbates the severity of the illness (Blacher et al. 2019). In Tg mice, ALS symptoms are made worse by Ruminococcus torques and Parabacteroides distasonis, but commensal supplementation of Akkermansia muciniphila alleviates ALS symptoms. According to their research, ALS may have a gut microbiota etiology.

Epilepsy:

Approximately 65 million individuals worldwide suffer from epilepsy, a persistent neurological illness. Even with anti-epileptic drug (AED) therapy, only 70% of epileptics are able to completely control their seizures. Consequently, refractory seizures that impair with everyday activities affect around one-third of epilepsy patients (Arulsamy et al. 2020). Because of its greater incidence of morbidity and death, it has a large socio-economic impact and highlights the need for more efficient, prospective therapies that are also curative. Since intestinal bacterial species have been shown to be associated with epilepsy, genetically modified organisms may be able to cure epilepsy (Dahlin and Prast-Nielsen 2019). The immune system may be connected to a balanced gut microbiota because the microbial communities that are present in healthy gut microflora have been shown to have effects on pro- and anti-inflammatory situations. Research has shown that epilepsy develops and progresses as a result of chronic inflammation. Additionally, GM has the ability to control immunological and inflammatory responses (Zhang et al. 2022). Differences in GM profiling employing several therapeutic techniques for uncontrolled epilepsy compared with a healthy population suggest that manipulation of GM diversity may be a potential therapy strategy. It has been shown that Firmicute bacteria may regulate neurotransmitter levels, and higher concentrations of Bifidobacterium and Lactobacillus are linked to fewer annual seizures (Tiwari et al. 2023). Drug-resistant patients have a much greater α -diversity in GM than drug-responsive patients who are comparable to healthy controls. Elevated levels of α -diversity are linked to several uncommon intestinal bacterial species, with notable variations seen at the genus level, suggesting that bacteria might be crucial in treating epilepsy. The intestinal GM alter zonisamide metabolism by acting as an anti-epileptic drug. In dietary treatment, it has been shown that the ketogenic diet (KD) alters the content and structure of GM and decreases the frequency of seizures in epilepsy patients (Dahlin and Prast-Nielsen 2019). In the GF mouse model of epilepsy, a KD mediates the anti-seizure effects in the temporal lobe. Transplanting KD microbiota species, including *Akkermansia muciniphila*, *Parabacteroides distasonis*, and *Parabacteroides merdae*, has been shown to enhance the seizure threshold. There is not as much evidence for the function of GM in epilepsy as there is for other disorders. Consequently, studies should concentrate on how the microbiome influences the physiology and behavior of epilepsy diseases.

An integrative discussion:

Within the field of neurogastroenterology, the link between intestinal microbiota and neurological diseases is an exciting and quickly developing field of study. A rising amount of research over the last ten years indicates that the gut microbiota is important in controlling communication pathways that affect brain function. With a focus on several neurological disorders such as Parkinson's disease (PD), multiple sclerosis (MS), Alzheimer's disease (AD), autism spectrum disorder (ASD), amyotrophic lateral sclerosis (ALS), and epilepsy, this review offers a thorough summary of the current

understanding of this complex relationship.

For instance, changes in the gut microbiota have been linked to the pathophysiology of Parkinson's disease, and research indicates that microbial metabolites may be responsible for triggering neuroinflammation and α -synuclein aggregation (Ullah et al., 2023). Similar to this, dysbiosis of the gut microbiota has been reported in multiple sclerosis, and modifications in the makeup of microorganisms have been connected to modifications in immune response and permeability of the blood-brain barrier (J. Chen et al., 2016). These results highlight the potential therapeutic benefits of managing neurological illnesses by focusing on the gut flora.

Key pathogenic pathways in Alzheimer's disease have been identified as mitochondrial failure and neuroinflammation; new research indicates that the gut microbiota may play a role in controlling these processes (Balan et al., 2021). Furthermore, studies have indicated a connection between microbial dysbiosis and aberrant behavior patterns, pointing to interactions between the gut microbiota and the growing brain as possible contributors to the pathogenesis of autism spectrum disorder (Saurman, Margolis, and Luna, 2020).

Similar changes in gut microbial composition have been linked to the development of amyotrophic lateral sclerosis, where dysbiosis is linked to neuroinflammation and motor neuron degeneration (McCombe et al., 2019). Lastly, disruption of the gut microbiota in epilepsy has been connected to chronic inflammation and a predisposition to seizures, emphasizing the possible therapeutic benefit of focusing on microbial diversity in the treatment of epilepsy (Zhang et al., 2022).

CONCLUSIONS

This study concludes by highlighting the complex interaction that exists between several neurological illnesses and the gut microbiota, and by illuminating probable processes that underlie the development and progression of these disorders. Changes in the gut microbiota may affect neurological function and vice versa, forming a bidirectional communication system known as the gut-brain axis. The microbial metabolites generated in the gut can affect brain health and play a role in the development of neurological conditions like Parkinson's disease, multiple sclerosis, Alzheimer's disease, autism spectrum disorder, amyotrophic lateral sclerosis, and epilepsy by modulating signaling pathways and immune responses. The significance of the gut microbiota as a possible target for therapeutic treatments in the management of neurological illnesses is highlighted by these results, which open up new directions for investigation and therapy development.

There are a number of restrictions to take into account, even with the increasing amount of data pointing to the gut microbiota's involvement in neurological illnesses. First off, a lot of the research done thus far has been correlational in nature, which makes it difficult to prove causation. Furthermore, the gut microbiota is very dynamic and impacted by a wide range of variables, including as medication usage, nutrition, and lifestyle choices, which may make it more difficult to interpret research results. Moreover, findings cannot be broadly applied to broader populations since the majority of research has been limited to small-scale human studies or animal models. In order to overcome these constraints and get a deeper understanding of the intricate relationships between gut microbiota and brain function, future research endeavors have to use bigger sample numbers, consistent methodology, and longitudinal investigations.

There are a number of exciting directions this topic may take future study. Technological developments like metagenomic sequencing and metabolomics have the potential to provide a deeper understanding of the gut microbiota and clarify its function in neurological illnesses. Furthermore, innovative treatment options may be explored via the use of therapies that target the gut microbiota, such as fecal microbiota transplantation, probiotics, and prebiotics. Furthermore, to further our knowledge of the gut-brain axis and apply research results to clinical practice, multidisciplinary cooperation involving microbiologists, neuroscientists, and clinicians will be crucial. By conquering these obstacles and using the gut microbiota's potential, we could eventually help patients with neurological conditions and open the door to individualized therapy and preventative strategies.

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A. theoretical and conceptual foundations and problematization:	25%	25%	20%	5%	20%	5%
B. data research and statistical analysis:	25%	5%	20%	15%	20%	15%
C. elaboration of figures and tables:	25%	25%	5%	20%	20%	5%
D. drafting, reviewing and writing of the text:	20%	25%	25%	10%	10%	10%
E. selection of bibliographical references	25%	20%	20%	25%	5%	5%
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