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Review

The Impact of Microbiota on Neurological Disorders: Mechanisms and Therapeutic Implications

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Abstract

Interactions in the gut-brain crosstalk have led to the development of an entirely new concept: the "microbiota-gut-brain axis". Microbiota has gained considerable attention in relation to disorders of a more neurological nature, such as neurodevelopmental and neuropsychiatric illnesses like autism spectrum disorder, anxiety, and mood disorders. This review aims to summarize the recent trends and insights into the role and consequences of gut microbiota in brain health and pediatric neurological disorders. Dysbiosis may be associated with an increased risk of neurological diseases that lead to different disruptions and conditions, including mental health issues. During microbiota dysbiosis, neuropsychological stress hormones that usually affect oxytocin and GABA neurons are significantly reduced. Current

studies report that anxiety, major depression, and cognitive dysfunction are closely associated with dysbiosis. In the last few years, a handful of clinical studies have emerged, illustrating the potential for a bidirectional relationship of gut-brain interactions in humans. Perhaps some of the most crucial clinical investigations demonstrating overlapping relationships with the human gut-brain axis come from human trials focusing on modulating the microbiota significantly and noting significant cognitive correlates. A new field is emerging such as gene-editing technology that could represent a potential tool to improve gut microbial characteristics. This approach could be particularly relevant for neurodevelopmental and neurodegenerative disorders and brain-gut axis diseases linked with loss of microbial species and/or high pathobiont load.

Keywords
Gut-brain axis; microbiota; neurodevelopmental illness; neuropsychiatric illness; microbial species

1. Introduction to the Microbiota-Gut-Brain Axis

Presently, it is well appreciated that the gut is continuously in mutual communication with the brain. Interactions in the gut-brain crosstalk have led to the development of an entirely new concept: the "microbiota-gut-brain axis". Crucial for the gut-brain interactions are the microbiota, trillions of commensal microorganisms residing in the gastrointestinal system. The microbiota is responsible for the control of many gastrointestinal physiologies and contributes to the regulation of many host systemic functions. Owing to the fundamental importance of microbiota in many host physiologies, it is therefore not surprising that microbiota has gained considerable attention in relation to disorders of a more neurological nature, such as neurodevelopmental and neuropsychiatric illnesses like autism spectrum disorder, anxiety, and mood disorders [1-9]. Because of the striking and complex bidirectional communication of every part of the "microbiota-gut-brain axis," it has become evident that investigating the mutual interplay between gut microbiota and specific parts of the brain might elucidate hitherto unknown mechanisms, not only basic mechanisms but also ways of developing novel therapeutic strategies. This review aims to summarize the recent trends and insights into the role and consequences of gut microbiota in brain health and pediatric neurological disorders. The microbiota refers to trillions of microorganisms inhabiting different niches of the human body, including the digestive system. Under physiological conditions, the number of bacterial cells inhabiting humans equals that of human cells. However, the microbiota in the gut is five to ten times more abundant than that found in other body niches. The gastrointestinal microbiota is primarily composed of bacteria but also fungi, protozoa, phages, and viruses. The gut, especially the colon, is home to a hundred trillion bacteria dominated by the phyla, namely, Firmicutes and Bacteroidetes. Other lower abundant phyla include Actinobacteria, Fusobacteria, and Proteobacteria. The human gut is estimated to host a diverse milieu containing at least 2000 bacterial species. The gut microbial composition follows a maturation pattern from birth, influenced by various factors. A similar stepwise increase in microbiota diversity has been reported in childhood and adolescence [10-19].

1.1 Definition and Components of the Microbiota

The word "microbiota" refers to a diverse community of microorganisms that reside within the human body. It can be composed of bacteria, fungi, viruses, and more, though bacteria, archaea, and eukaryotes predominate. Most communities are bacteria, with as many as 1.3×10^4 microbial species in the gut. There are approximately 1.5×10^{14} microbial cells and 100 times more genes than human cells in the human body, implicating the fundamental role of these microorganisms in daily life. Microbiota are not only essential for the host immune system but are also involved in digestion and metabolism. In addition, they are responsible for harvesting energy from the indigestible carbohydrates in human diets by fermenting these compounds into short-chain fatty acids. More than just their role in metabolism, it has been suggested that the gut microbiota can impact the behavioral and psychological aspects of humans. Recent evidence has implied that the gastrointestinal environment communicates with the central nervous system through neuroendocrine, autonomic, and immune predictors, indicating that the two systems are interconnected and interdependent in multiple ways. Moreover, the composition of gut microbiota can indeed be used as an indicator for evaluating certain diseases, such as Parkinson's disease and irritable bowel syndrome, since microbial diversity is critical for maintaining homeostasis [20-27]. In healthy people, however, microbial homeostasis can be stably maintained. The complex microbial network in the gut can influence the host's health status, especially neurological function. Evidence suggests that a link between the microbiota and neurogenesis is likely due to the ability of the gut microbiota to produce various metabolites and modulate the brain-derived neurotrophic factor, which may provide therapeutic opportunities for managing stress and mood disorders. To facilitate the understanding of the roles of microbiota, we first systematically summarize the fundamental aspects of gut microbiota, including structure, number, and signs of "dysbiosis". This information is fundamental to elucidating the process of gut-microbiota-brain signaling [28-37].

2. The Gut-Brain Axis: Communication Pathways

The gut-brain axis (GBA) is a complex multimodal communication system that integrates physical, biochemical, and hormonal signals from the gut and reaches the relevant brain areas to influence behavior and cognitive functions. Physically, the brain-gut axis communication can occur through neural, neuroendocrine, and immune signaling. Neural pathways are the most straightforward route, as produced electrical signals can rush through neurons. Neuroendocrine and immune pathways can also help transmit signals relatively quickly across systems. However, these pathways depend on releasing signaling molecules at their source and subsequent diffusion through blood or cerebrospinal fluid. Because of this, it may take longer for messages sent through these pathways to reach the brain. It is important to note that the GBA is bidirectional. Signals arising from the gut can indeed influence the activity of neural pathways and the release of hormones and immune responses from the brain. Unlike endocrine and immune routes, the interaction between the gut and brain through neural signaling is immediate and can be delivered by enteric nerves. Also, neurotransmitters that are produced in the bloodstream can straightforwardly access the brain through the blood-brain barrier. The signal from the gut can also reach the brain through the bloodstream. Various blood-borne gut-derived signaling molecules are known to cross the blood-brain barrier, like short-chain fatty acids, bile acids, gut hormones, and neurotransmitters including

glutamate, GABA, and tryptophan metabolites. Patients or animals who received healthy dietary interventions also present improvements in cognitive scores and microbial-brain signaling [38-43].

2.1 Neurotransmitter Signaling

The interaction between the gut microbiota and the brain has a molecular basis. By regulating dozens of signaling pathways, microbiota can modulate the expression of central proteins and signaling molecules mediating neurotransmitter synthesis. The enteric nervous system can also utilize neurotransmitters to influence the behavior of microorganisms in the lumen. The gastrointestinal environment or the mucosal barrier needs to be sensed for protein synthesis to be regulated by the bacteria residing within it. A wide range of proteins can bind and sequester or excrete the pathways necessary for their de novo synthesis. The synthesis of acetylcholine, dopamine, noradrenaline, and hydroxytryptamine has been reported to be altered by mice colonized with microbiota derived from special pathogen-free mice and germ-free mice. Gamma-aminobutyric acid can be synthesized by mouse colonocytes separated from the gut microbiota [44-51]. The role of the gut microbiota in the metabolism of gut-derived neurotransmitters has been studied. Results have shown that germ-free mice do not have any serotonin in their colon; upon recolonization with spore-forming microbes, colonic serotonin was produced at levels similar to that of a conventional animal within five days. This suggests that the bacterial community can convert tryptophan and its metabolites into serotonin, a molecule used to regulate gut motility, a pathway of interaction between the microbiota and the host. It was also demonstrated that the antidepressant actions of commensal microbiota were mediated by the production or processing of serotonin in the gut using serotonin-deficient mice that showed an increase in circulating serotonin levels upon recolonization with specific microbes [52-58].

3. Microbiota Dysbiosis and Neurological Disorders

Microbiota dysbiosis refers to alterations in gut microbial ecology, characterized by an increase in pathogenic bacteria and a decrease in beneficial commensals. This harmful process may lead to a series of diseases. Available evidence has demonstrated the association between dysbiosis and various neurological disorders. Dysbiosis may be associated with an increased risk of neurological diseases that lead to different disruptions and conditions, including mental health issues. During microbiota dysbiosis, neuropsychological stress hormones that usually affect oxytocin and GABA neurons are significantly reduced. The HPA axis and gut microbiota act together to affect the brain. Current studies report that anxiety, major depression, and cognitive dysfunction are closely associated with dysbiosis. A decrease in commensal colonization and healthy gut microbiota constitutes a risk factor for depression [59-64]. Some mechanisms through which the human microbiome can cause brain disorders include bacterial exotoxins, bacterial amyloids, damage related to endotoxins, and brain neurotransmitters and their production. Certain neurotransmitters are essential in maintaining mental function, including brain-derived neurotrophic factor, acetylcholine, inflammatory cytokines, and antioxidant enzymes. Lifestyle and other factors can lead to microbiota dysbiosis, such as irregular intestinal flora and enteric barrier function, pollution, low inflammation, low immune function, and high pathogen prevalence exposure. The results reveal that to combat these disorders, healthcare protocols should include interventions that minimize unhealthy, harmful forms of the microbiome, in addition to the benefits they have on the overall

health of the microbiome. Clinicians should prescreen those with cardiovascular disease, depression, addiction, cognitive decline, migraines, and schizophrenia. They should be monitored for periodic diagnosis and microbiome treatment with reprogramming, diet alteration, prebiotics, probiotics, antibiotics, fecal transplantation, and other targeted solutions as clinical experiences expand [65-73].

3.1 Alzheimer's Disease

Although no fundamental cure has been discovered yet, the potential use of the gut-brain axis as a therapeutic target for the treatment of Alzheimer's disease has been receiving much attention. Recent studies showed the presence of altered gut microbiota in Alzheimer's disease patients. If the hypothesis of the involvement of the gut-brain axis in Alzheimer's disease pathophysiology is confirmed, the potential therapeutic approach that would aim at restoring the balance in gut microbiota could potentially alleviate the symptoms or slow the progression of the disease. The identification of factors that favor the increase in beneficial species may offer an opportunity for early interventions and the development of some new disease prevention strategies. Alzheimer's disease is a significant healthcare problem affecting millions of patients worldwide. Pathophysiological studies revealed that the gut-brain axis is involved in Alzheimer's disease. The gut-brain axis is a bidirectional communication system that includes several positive and negative feedback pathways between the gut and the brain. Neuroinflammation is known to play an essential role in the development of Alzheimer's disease. There is accumulating evidence that increased neuroinflammation in response to pathogens may be one of the causes of increased blood-brain barrier permeability and central nervous system inflammation that accelerate the progression of Alzheimer's disease [74-83].

4. Role of the Microbiota in Neuroinflammation

Neuroinflammation is activated in response to a variety of pathological conditions, including trauma, stroke, infections, and neurotropic agents. Extended activation of neuroinflammation is a significant pathological feature in the majority of neurological disorders, particularly in neurodegenerative diseases. A dynamic interaction between microorganisms inhabiting the intestine, the so-called gut microbiota, and brain function and dysfunction has been shown. Perturbations in the balance between the gut microbiota and the host, known as dysbiosis, have been linked to several CNS disorders, including peripheral inflammation and the activation of microglia and astrocytes. Once activated, glial cells produce pro-inflammatory cytokines, chemokines, and reactive oxygen species, which are detrimental to neuronal function. Chronic neuroinflammation has been widely described as a risk factor for neurological disease progression when activated sectors are not adequately controlled [84-92]. The blood-brain barrier is disrupted when neuroinflammation is activated. Additionally, various neurological pathologies are characterized by increased permeability, including hemorrhagic stroke and traumatic brain injury. Beyond helping to maintain an optimal CNS environment, the gut-brain-microbiota axis also offers potential therapeutic applications. Many studies have aimed to determine whether the microbiota can be changed to treat neurological diseases with a significant inflammatory component, including Parkinson's disease and mood disorders. Preclinical studies have suggested that the use of probiotics may help to mediate neuroinflammation by increasing the expression of brain-derived

neurotrophic factor, which is involved in human brain plasticity and can act as an antidepressant, the anti-inflammatory cytokine IL-10, and an endogenous antioxidant enzyme. In summary, a healthy balance in the orchestration of gut microbiota is critical for preventing neuroinflammatory changes. Additionally, inflammation is an essential aspect in understanding neurological pathologies because microbiota is emerging as an influential factor, orchestrating factors leading to changes in inflammatory conditions [93-101].

4.1 Immune System Modulation

The microbiota has a crucial role in the regulation of the immune system. As such, by modulating the gut lymphoid tissue, the gut microbiota can stimulate the systemic immune response and the consequent neuroinflammatory processes. Several lymphoid structures, such as Peyer's patches, isolated lymphoid follicles, and gut-associated lymphoid tissue, are responsible for receiving gut-derived signals and activating immune pathways. The central regulator of all the immune pathways activated by gut bacteria is toll-like receptor signaling. TLRs bind to components of the bacterial cell wall. They can activate both the MyD88-dependent and independent pathways, inducing the production of pro-inflammatory cytokines, such as tumor necrosis factor-α, interleukin-6, -12, and -23, and interferon-γ, resulting in a pro-inflammatory response in favor of either the protection against pathogens and the clearance of tissue debris or the initiation of tissue repair [102-111]. Other gut-derived signals are also involved in regulating local and systemic inflammation. Indeed, microorganisms can induce the production of IL-22 that maintains gut homeostasis by improving pathogen immunity and helping tissue repair processes. In a healthy microbiome, microbial metabolites generated from commensal bacteria stimulate IL-22-driven anti-inflammatory responses that induce anti-microbial peptides and mucus production. This intestinal environment promotes T helper and Treg cell responses, favoring IL-10 production and supporting anti-inflammatory functions. In contrast, compositional changes in microbiota derived from Western diets with low dietary fiber but high in fat and carbohydrates, antibiotic treatment, or emotional stress can change the immune signaling cascades, as well as the production of IL-17, skewing T cell responses towards the pro-neuroinflammatory axis. Acute or chronic exposures to gut-related stimuli can induce immune reprogramming and the production of IL-17 family members and IFN-γ, the two crucial cytokines involved in neuroinflammation. Targeting gut barrier integrity and boosting healthy microbiota are all envisioned as potential areas of intervention to re-establish the immune equilibrium in neurological disorders involving inflammation [112-121].

5. Microbiota-Targeted Therapies for Neurological Disorders

In addition to increasing knowledge about the physiological effects of neuroglobins and related lipophilic ligand family proteins, research from the emerging field of microbiota-targeted therapies reveals novel opportunities for interventions to improve or maintain a healthy microbiome. Available evidence indicates that complementary or combined approaches that include probiotics, prebiotics, and dietary interventions have the potential to attenuate dysbiosis, preserve mucosal barrier integrity, modulate gut-brain communication, mitigate neuroinflammation, and promote cognitive function in health and various neurological disorders among children and adults. Although the clinical benefits are promising and demonstrate favorable outcomes, the extent to which these treatments work depends on inter-individual differences that may be due to various factors,

including differences in baseline microbial composition and dietary habits. Microbiota-targeted personalized medicine has the potential to revolutionize our therapeutic approach to neurological health and make effective preventive and novel interventions widely available for patients worldwide [122-130]. The advent of our ability to manipulate the commensal microbiota has grown rapidly over the last decade, consequently unlocking the potential of ecological therapies to which we can apply current clinical standards. Microbiota-targeted treatments that include probiotics, prebiotics, or dietary therapeutics are becoming increasingly popular due to their potential to refine and enrich our gut microbiome, reduce inflammation, and modulate communication between the gut and the brain. Probiotics are credited with reducing inflammation and oxidative stress and providing neuroprotection in preclinical trials of a range of CNS disorders. Moreover, some probiotics have been shown to confer resilience against stress and depressive behavior by affecting GABA receptor expression or activating the vagus nerve, exciting the CNS's primary parasympathetic link to the gut. Although the mechanisms behind the gut-brain-behavior effects and optimal treatment dosage and duration remain to be clarified, the results from the current clinical trials of probiotics are showing significant promise. In this light, probiotics could be used as supportive treatments in addition to conventional and other ecological therapies [131-140].

5.1 Probiotics and Prebiotics

The term probiotics is derived from the Greek, translating to "for life" and referring to live microorganisms, which, when administered in adequate amounts, confer health benefits to the host. Several clinical and experimental studies have discussed the role of probiotics in neuromodulation and neuroprotection by modifying the gut microbial environment. Administering probiotics can restore the imbalance of gut microbiota and suppress the apoptosis mediated by the secretion of 5-HT in germ-free mice. Lactobacillus and Bifidobacterium strains are beneficial in maintaining the brain-gut axis. Studies showed that supplementation of the probiotic strains in combination attenuated symptoms of depression, increased memory performance, and reduced symptoms of anxiety, cramping, and diarrhea. Certain other strains, such as Lactobacillus rhamnosus, have been shown to play a role in depression and anxiety-related behaviors involving modulation of the central GABAergic signaling and GABA receptor expression [141-149].

In a recent meta-analysis and systematic review, it was postulated that specific probiotic strains can influence mood, cognition, stress, and neuroinflammation via the gut-brain axis. Furthermore, various studies in individuals and across patient populations globally support the therapeutic potential and safety profile of probiotics. Moreover, probiotics alone or in combination alter the neuroinflammatory cytokine levels, microbiota metabolite concentrations, and immune activation, which could further improve patient outcomes. In addition to treating CNS disease, probiotics have shown therapeutic efficacy in treating non-CNS diseases, such as dental caries, dermatitis, and hypertension. Prebiotics are non-digestible water-soluble fiber compounds that nourish beneficial gut bacteria by promoting their growth. These substances are not broken down or absorbed by the GI, potentially benefiting most body parts. They promote a healthy balance of gut microbiota, which can positively affect digestion, skin conditions, mood, energy, immune system, bone growth, and even the nervous system. Therefore, the combination of prebiotics plus probiotics not only increases the proliferation of "good" bacteria and improves overall health and wellness. The therapies can act not only as a standalone treatment option but also as a safe and effective add-on

to conventional therapy. However, outcome assessment tools or methodologies must be standardized for further studies that evaluate the efficacy of probiotic and prebiotic supplementation and clarify the mechanisms that underpin the connection between microbiota, neurodegenerative diseases, and therapy [150-157].

6. Clinical Studies and Evidence Supporting Microbiota-Brain Interactions

Until recently, the only studies examining the link between the gut microbiome and the brain were limited to rodent and cell culture model systems. However, in the last few years, a handful of clinical studies have emerged, illustrating the potential for a bidirectional relationship of gut-brain interactions in humans. Perhaps some of the most crucial clinical investigations demonstrating overlapping relationships with the human gut-brain axis come from human trials focusing on modulating the microbiota significantly and noting significant cognitive correlates. Most clinical findings of gut-brain crosstalk to date have focused on disease states such as major depressive disorder, anxiety disorders, autism spectrum disorders, and more. Several pilot studies have tested the effects of alterations in the gut microbiota on neurological symptoms. One study incorporated 60 patients with major depressive disorder into a probiotic arm, prebiotic arm, or placebo arm and found that both probiotics and prebiotics could reduce depression symptoms more than placebo and may specifically improve cognition and mental health-related quality of life [158-166]. Human studies have a range of microbiota measurements, including ribosomal sequencing and fecal or salivary collection. They are limited by human recall and potential research conflicts caused by factors such as compliance, diet, and habitat. Several studies have reported some lifestyle interventions that allow open-labeled observation, with significant positive results and detailed methodology for identifying changes in microbiota. Some guidelines have been drafted to help increase the quality of these studies, including: long-term follow-up, no exclusivity or vampire effects, escalated doses slowly or for frequent dose monitoring, testing for clinical symptoms, and observing the association of microbial markers with clinical outcomes. These ideas must be performed based on hypotheses and appropriately classified. Assuming that the microbiome has a direct effect on the brain is very speculative in these clinical scenarios. However, all could complicate or exacerbate physical and emotional health and thus increase psychological well-being [167-176].

6.1 Animal Models

Animal models have been crucial for understanding the complexities of the microbiota-gut-brain axis. Under the assumption that gut bacteria may influence human behavior and cognition, mice displayed changes in anxiety-related behavior and cognition. Early studies using microbiota-depleted animals suggested that gut microbes influence neurological processes of host behavior. Further studies proposed that the gut microbiota can influence behaviors, including anxiety- and depression-like behaviors, sociability, and cognitive function, and are influenced by manipulations affecting gut microbes. Certain studies demonstrate a translation of gut microbiota-mediated outcomes, such as changes in brain chemistry, neuronal function, and peripheral immune cell activation [28, 29, 35, 36, 59, 177-180]. It has been difficult to reconcile some results between parallel studies assessing similar cognitive, behavioral, or immune-affecting outcome measures. This could be attributable to procedural differences not exclusively focused on the gut microbiota,

animal species, age, early life environment, and maternal programming; baseline changes are already present on arrival before the study initiation, and even the experimenter, who can influence the study outcome. Methodologies using animal models have provided a platform for studying relevant interventions targeted to the gut microbiota and delving into the mechanisms involved in gut-brain communication. Such methodologies for gut microbiota manipulation and behavioral outcome assessments include transferable strategies and paradigms for addressing microbiota-brain research in animal models. Preclinical animal models are an ideal platform for translating knowledge of microbiota effects to human neurological health, with a focus on understanding neurological health determinants. Far beyond predictability, they bring a wider array of strategies and techniques to assess the behavioral, neurological, and molecular outcomes of the gut microbiota-brain field. Given that manipulations can be directly targeted in preclinical models devoid of interference from environmental factors, studies provide evidence for access to different levels of the nervous system involved in gut-brain communication through a more extensive range of assessment models. Systems used for this research include the intrinsic nervous system from the lower gut plexus to the enteric nervous system, circulating markers, vagus nerve processing, and the central nervous system. Studies have examined neurological health parameters through behavior, molecular, and neurological assessment outcomes after applying gut-brain communication-targeted interventions, highlighting the power of animal research models in developing therapeutic strategies [177-190].

7. Challenges and Future Directions in Microbiota Research

Microbiota research is beset with challenges. One of the most significant challenges is that the microbiota is complex and multi-faceted, reflecting their dynamic, multi-kingdom, multi-phylum assemblage subject to continual compositional variation. Inconsistency between studies is a further challenge. Analysis of the microbiota is confounded by sample heterogeneity and quantitative variability, intra- and inter-personal diversity, differing time points, regions, sequencing depths, and specific methodologies at every stage of research. Researchers need to overcome these challenges through combined expertise in a range of disciplinary methods including multi-omics, functional studies, bioinformatics, advanced statistics, and multi-parametric self-report scales to gain an understanding of complex interactions between the environment, the genome, and behavior [191-199]. This multifaceted approach could shed light on how gut microbiota influences neuropsychiatric and neurodegenerative conditions, where mitochondrial function plays a central role. For example, short-chain fatty acids (SCFAs) such as acetate, propionate, and especially butyrate, are produced by the gut microbiome and regulate numerous CNS and systemic processes. Butyrate, in particular, optimizes mitochondrial function through mechanisms like upregulation of the melatonergic pathway and epigenetic regulation via histone deacetylase inhibition, which can have significant implications for neuropsychiatric and neurodegenerative disorders200. However, despite the promising potential of such findings, the heterogeneity of studies makes it difficult to compare results, hindering progress in this field. One of the solutions to overcome these issues is the establishment of working groups that include researchers from different disciplines and methodological backgrounds. These cutting-edge technologies have already begun to uncover new aspects of microbiota function, such as the complex interplay between the gut microbiome and brain health. Further research into the gut-brain axis will benefit from longitudinal, multi-centered

studies and cascade models, which could lead to novel therapeutic strategies. Gene-editing technologies, for example, may offer new tools to optimize gut microbial characteristics, potentially offering solutions for neurodevelopmental and neurodegenerative disorders. These diseases, often associated with losing microbial species and/or high pathobiont load, could greatly benefit from such innovative approaches [200, 201]. Future research should clarify the factors regulating short-chain fatty acid production by the gut microbiome, as these molecules play a crucial role in the etiology and pathophysiology of neuropsychiatric and neurodegenerative conditions. Furthermore, this should facilitate collaborative work and, as such, standardization of methods and protocols. Research guidelines will enhance the quality and transparency of future research outputs. Integrating currently available technologies including the advanced aspects of metagenomics and bioinformatics in studying microbiota will allow a better understanding of the interplay between the microbes and the host in health and disease. Indeed, those novel technologies unveiled the great potential of what we have yet to discover; for example, those aspects are currently beyond our comprehension of the functionality and redundancy of the gut micro-population composition in the human brain. Although many of these technologies serve research purposes, other functional omics could be used in clinical practice. Future research on the microbiota of the brain-gut axis would benefit from longitudinal multi-centered studies and cascade models. A new field is emerging such as gene-editing technology that could represent a potential tool to improve gut microbial characteristics. This approach could be particularly relevant for neurodevelopmental and neurodegenerative disorders and brain-gut axis diseases linked with loss of microbial species and/or high pathobiont load [202-208].

7.1 Standardization of Protocols

One of the main issues in microbiota research is the lack of standardization of protocols, which calls into question the reproducibility of the findings. Consequently, there are inconsistencies in results among research groups using different methodologies and also among those employing similar approaches. Standardization involves criteria and protocols for sampling, processing, and analysis design that will allow researchers to compare their data, know which differences between studies are associated with biological or methodological reasons, and validate their results. Efforts have been made to reach a consensus about best practices for sampling and storage, and the question of the best methodology for microbiota analysis is still very open. Moreover, core profiles for microbiota relevant to health and function in the gut-brain axis have yet to be defined [209-216]. Existing guidelines on protocols in the microbiota field encourage the definition of the relevant groups of interest in terms of age, sex, dietary habits, geographic origin, lifestyle, comorbidity, concomitant treatments, and follow-up when performing a study, as these are the key factors influencing microbiota profiles. Thus, in neuroscience, the vast number of factors that may impact the gut microbiota and its interaction with the brain, as well as the limited knowledge, should guide efforts to generate these core bacteriome profiles. Still, previous work has made data from healthy volunteers available for study as part of large consortia, and many individual studies indicate that the definition of gut microbiota associated with neurological health or disease with existing methods is both possible and relevant as a starting point. There will likely be regulatory and logistic hurdles if these studies take place. A consortium created an infrastructure for the International

Human Microbiome Standard. This will be a giant step forward towards the standardization of these emerging scientific fields [217-225].

Author Contributions

Giuseppe Merra and Giada La Placa were responible for project; Marcello Covino and Marcello Candelli conducted data collection; Antonio Gasbarrini and Francesco Franceschi supervisioned the paper.

Competing Interests

The authors have declared that no competing interests exist.

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