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THE SPECIFICS OF CORRECTING CHANGES IN THE COMPOSITION OF THE MICROBIOTA IN THE MICROBIOTA AND VARIOUS NEUROLOGICAL DISEASES

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Abstract. The intricate relationship between gut microbiota and mental health is becoming more and more evident in recent research, which also highlights the involvement of the microbiota–gut–brain axis (MGBA) in the pathophysiology of mental and neurodevelopmental diseases. Disorders like depression, schizophrenia, bipolar disorder, attention deficit hyperactivity disorder, autism spectrum disorders, and neurodegenerative diseases like Parkinson's and Alzheimer's are linked to dysbiosis, or changes in the gut microbiota's composition. These microbial imbalances can affect brain function through a variety of mechanisms, including activation of the immune system, alteration of intestinal permeability, modulation of the digestive and central nervous systems, and changes in the production of neuroactive metabolites such as short-chain fatty acids, serotonin, and tryptophan derivatives.An increasing amount of research indicates that a number of neurological illnesses are associated with notable alterations in the relative abundance and composition of the gut microbiota. We conducted a comprehensive analysis of the various microbiota that are changed in a variety of neurological conditions, including stroke, multiple sclerosis, amyotrophic lateral sclerosis, Parkinson's disease, and Alzheimer's disease (AD). 52 trials totaling 5496 patients were included. The most commonly implicated bacteria at the genus level are *Prevotella, Faecalibacterium* and *Akkermansia*. With eight genera (*Akkermansia, Butyricicoccus, Bifidobacterium, Coprococcus, Dorea, Faecalibacterium, Parabacteroides* and *Prevotella*) shared by MS and PD and six genera (*Enterococcus, Faecalibacterium, Lactobacillus, Parabacteroides, Prevotella* and *Roseburia*) shared by PD and stroke, the overlap between the pathologies was greatest. The question of whether AD, PD, and MS share a shared origin or, more accurately, a common outcome is raised by the identifying markers for these diseases overlapping. The low number and poor power for AD, ALS, and stroke make interpretation difficult and provide a lot of room for false positive and false negative results.

Keywords. Gut microbiota, multiple sclerosis, atrophic lateral sclerosis, Parkinson's disease, Alzheimer's disease, stroke.

Introduction. In recent years, there has been a growing interest in the role and significance of the bidirectional interactions between the brain and the gut, often known as the brain–gut axis, in the development of many central neurological illnesses. This is likely one of the most

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promising areas of research. Approximately 1000 bacterial species and 7000 bacterial strains have been found, reflecting a total of 1013–1014 distinct microorganisms in the gut, making up the gut microbiome. The intestinal microbiota, the intestinal barrier, intestinal inflammation, and the intestine/systemic/brain immune systems are some of the components that make up the gut–brain axis, which is a bidirectional communication channel. Both disease and normal central nervous system function are influenced by the gut-brain axis. The findings in transgenic animal models for AD and PD have fueled clinical studies, identifying the gut microbiome as a key determinant of dementia risk and a potential target for preventive interventions. These findings also strongly support the interaction between gut microbiota and AD and PD in the brain. It has been demonstrated that modifications to the gut microbiota in AD transgenic mice can modify the amount of amyloid that is deposited in the brain. α-synuclein protein (αSyn) overexpression in mice causes motor impairment and is a characteristic of Parkinson's disease (PD) and other synucleinopathies [1-5]. It has been demonstrated that the gut microbiota affects αSyn pathology, microglial activation, and motor impairments and seems to play a crucial role in pathogenesis. While microbial re-colonization increases pathophysiology, antibiotic treatment reduces it in adult animals, indicating that postnatal communication between the gut and the brain regulates illness.

According to new research, probiotic therapy may help people with moderate cognitive impairment think better by regulating their gut bacteria. Dietary changes can also alter the gut flora; a ketogenic diet has shown very encouraging outcomes in treating a number of neurological disorders. There is a dearth of quantitative data regarding the different microbiota implicated in neurological disorders, despite an increasing amount of evidence. There are still many unresolved issues. From a physiopathological standpoint, it is critical to ascertain whether certain gut microbiota are consistently associated with a particular disorder across studies in order to comprehend their mode of action in a particular disease [6-11]. Additionally, from a research standpoint, it is imperative to assess whether findings are consistent. Determining if the correlations and alterations are linked to several neurological conditions is also of interest. This could indicate a shared pathophysiology or a shared course of the illness, meaning that gut microbiota changes may result from brain diseases or vice versa. You might be interested in either path. If the neurological condition causes alterations in the gut flora, a causal pathway might present chances for intervention and prevention. Therefore, in order to improve management through precision medicine and individualized treatment, it is critical to detect the changes in microbiota in the various illnesses and to ascertain the direction of these changes. In order to find the literature for the review, databases were searched with an emphasis on original publications and clinical trials, followed by meta-analyses and literature reviews. Some articles of particular or historical relevance were included in the review even though they exceeded the 10-year time limit for the period range of publications solicited for the review [12-19]. The research's keywords are mentioned above. Articles that were out of date, unavailable in English, or unrelated to the subject matter were excluded. The gut-brain axis interrelationships are schematically represented in this paper, which offers a thorough review of the current literature on the relationship between gut microbiota and psychiatric disorders. It also briefly discusses a few neurodegenerative diseases where psychiatric symptoms are prevalent, providing a broader context and suggesting possible directions for future research in this quickly developing field. The results of research on the relationship between microbiota and neurodegenerative diseases, including as AD, PD, and ALS, are compiled in this overview. We also contrast these with the results of microbiome research on stroke, which frequently co-occurs with AD and PD, and multiple sclerosis, a neuroinflammatory disease [20-28].

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The main purpose of the presented manuscript is a brief interpretation of the specifics of correcting changes in the composition of the microbiota in microbiota and various neurological diseases based on the results of reputable scientific papers.

Gut Microbiota: *Crucial Information.* By carrying out vital physiological tasks, such as preserving the integrity of the gut barrier, affecting epithelial homeostasis, protecting against infections, generating energy, and controlling the immune system as well as the host's mental processes and behavior, the human gut microbiota offers its host many advantages. *Proteobacteria, Firmicutes, Actinobacteria* and *Bacteroidetes* make up the majority of its composition. It changes over the course of a person's life, impacted by things including birth type, nutrition, lifestyle, infections, illnesses, and therapies. While C-section babies develop a skin-like microbiota dominated by *Staphylococcus, Corynebacterium* and *Propionibacterium spp.,* vaginally delivered babies acquire a microbiota similar to their mother's vaginal and fecal flora, rich in *Lactobacillus spp.* Later on, dietary variables have a major role in shaping its diversification. We cannot ignore the mouth cavity, the initial segment of the digestive tract, when discussing it [5-13]. Although bacteria like *Streptococci, Gemella, Granulicatella* and *Veillonella* prevail in this area, some illnesses like periodontitis can induce a dysbiosis and gradually shift the majority to Gram-negative species. *Porphyromonas gingivalis*, an anaerobic, Gram-negative bacterium that exclusively causes gum tissue destruction and is associated with Alzheimer's disease, is the ideal example. Seyedmoalemi's narrative assessment of recent research highlights the impact of oral health on cognitive decline in addition to the reciprocal association between periodontitis and Alzheimer's disease. The findings indicate that, especially in people over 65, periodontitis considerably raises the risk of dementia and death. Numerous gastrointestinal illnesses have also been linked to changes in the composition of the gut microbiota. Pro-inflammatory taxa like Actinobacteria and Proteobacteria have been found to increase in Crohn's disease (CD) patients, while beneficial anti-inflammatory bacteria like *Firmicutes, Bacteroidetes, Akkermansia muciniphila* and *Faecalibacterium prausnitzii* have been found to decline significantly. Increased Firmicutes:Bacteroidetes ratio at the phylum level, decreased Bacteroidetes levels, and increasing Firmicutes levels are among the changes associated with irritable bowel syndrome (IBS). Lower taxonomic levels showed a decrease in *Bacteroidia* and *Bacteroidales* and an increase in *Clostridia* and *Clostridiales* [24-31].

Drug reaction and gut microbiota. Drug response, which is primarily defined by pharmacokinetic (PK) and pharmacodynamic (PD) characteristics, is known to vary from person to person due to a variety of factors, including age, gender, and genetic differences. But only recently have scientists recognized the importance of microbiota in medical therapy as a modulator of drug response. As a current area of study, we describe here how the gut microbiota modulates the action of drugs. Numerous compounds are known to be metabolized by the gut flora, which may have an impact on how well drugs are absorbed. In particular, the GI tract can alter the stability of medications taken orally before they enter the bloodstream. It was recently proposed that the microbiota in the small intestine might also significantly affect the physiological processes of the host. Given that the small intestine is a key location for medication absorption, this study brought attention to the possible drug-microbiota interaction. In fact, a number of investigations have documented altered medication PK with therapeutic implications that is mediated by gut microbiota [13-18]. For instance, Sun et al. found that rats' aspirin absorption was enhanced by a hypoxic environment, which can alter the gut microbiota's makeup. Matuskova et al. found that the PK of the antiarrhythmic medication amiodarone in male rats was impacted by concurrent oral administration of the probiotic E. coli strain Nissle 1917 (EcN). Remarkably, a recent study by Klünemann et al. found several new interactions

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between drugs and bacteria, and over half of these were attributed to bioaccumulation—a process that allows bacteria to store drugs without undergoing chemical changes, changing the host's reaction to the medication. In particular, bioaccumulating bacteria like S. salivarius reduced the behavioral response of Caenorhabditis worms to the antidepressant duloxetine. Numerous studies have demonstrated that the gut microbiota can significantly influence medication PK and, in turn, drug responsiveness in clinical settings. To create successful treatment plans, a deeper comprehension of this interplay is necessary [21-29].

Elements that affect the gut microbiome. There are many factors that can affect the makeup of the human gut microbiota. Early human birth is when the first colonization of gut bacteria takes place, with the infant's developing gut microbiota being established via microbial transmission from the mother's birth canal, skin, and breast milk. Following weaning, the gut microbiota of infants goes through a transitional phase before stabilizing in childhood. It becomes the original bacteria when its variety, composition, and function progressively resemble those of adults. According to certain perspectives, the placental microbiome during a mother's pregnancy may have an impact on the human microbiota, exposing it earlier. Prior research has demonstrated a two-way communication between the brain and the human gut microbiota, referred to as the microbiota–gut–brain axis (MGBA). Through neurotransmitters, immunological modulation, and metabolic pathways, the MGBA affects the host's nervous system development, emotional regulation, and cognitive performance [17-24]. The makeup of the gut microbiota is influenced by a variety of factors, including environment, genetics, nutrition, and lifestyle. The majority of studies have looked at how the gut microbiota controls host physiology and how it may be used to prevent and cure neurological conditions. It is still necessary to investigate the individual variability of gut microbiota, strains that are implicated in neurological disorders, and how these microbial metabolites interact with the central and peripheral neural systems. Notably, the gut microbiota is influenced by hundreds of external and intrinsic factors. Gut microbes and various influencing factors interact, and the results of this interplay are probably complicated. Individual differences may also affect the relative significance and degree of influence of these elements. More research is required to completely comprehend the development and regulation processes of the gut microbial population, which is a very complex ecosystem [26-35].

Gut microbiota modulation for therapeutic intervention. Currently, FMT, dietary modification, and probiotic and prebiotic supplementation are the most popular therapeutic strategies that regulate gut microbiota. The majority of research has tried to show that by altering gut microbiota, various treatment approaches can either treat or postpone neurological illnesses. ***Either prebiotics or probiotics.*** Over the last ten years, probiotics, prebiotics, metabiotics, and synbiotics have all been defined and discussed by the International Scientific Society for Probiotics and Prebiotics (ISAPP). With the exception of undefined FMT, probiotics are "living microorganisms that, when consumed in sufficient amounts, confer health benefits to the host." Prebiotics are health-promoting substrates that help beneficial bacteria (Bifidobacterium and Lactobacillus) proliferate and are selectively used by host microorganisms. As discussed in Section 4, neurological disorders frequently exhibit gut microbiome dysbiosis, which is typified by the reduction of anti-inflammatory and beneficial bacteria. Bifidobacterium and Lactobacillus are the most extensively researched probiotics in neurological illnesses, including the symptoms of ASD, ADHD, AD, PD, depression, and anxiety [5-13]. ***Microbiota transplantation of the feces.*** In order to influence the symptoms or course of neurological illnesses through gut microbiota-mediated immunological, endocrine, metabolic, and/or brain pathways, fecal microbiota transplantation (FMT) involves introducing gut microbiota derived from the feces of

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healthy donors into the GI tract of patients. FMT is currently a recognized method for restoring the gut flora. FMT may be a promising treatment option for a number of neurological illnesses, according to preliminary research. For instance, FMT reduced mild stress-induced intestinal inflammation, intestinal mucosal degradation, and neuroinflammation in rats, improved depression-like behaviors, and changed the gut microbiota imbalance. Additionally, FMT has demonstrated efficacy in treating depression in older patients. Mice [14-25]. ***Dietary measures***. The effect of nutrition on gut flora has already been briefly covered. Therefore, eating a balanced diet is essential for controlling gut microbiota, and dietary intervention therapy is a crucial therapeutic strategy to take into account. A diet that is high in fiber, low in fat, high in vegetables, low in meat, and high in antioxidants is associated with a lower chance of developing neurological conditions like AD, PD, stroke, and migraine, among others.298 There is a link between inflammation and food. Anti-inflammatory components such as omega-3 fatty acids, polyphenols, vitamins, critical minerals, and probiotics can be found in fruits, vegetables, nuts, herbs, spices, and legumes, which contribute to a balanced diet and promote a positive brain environment [27-34].

Limitations, Difficulties, and Prospects. There are some restrictions on this review. There is little data on the topic, and because the science is still in its infancy, the results are frequently contradictory. Numerous research rely on animal models or have small sample sizes. Furthermore, it is challenging to draw firm conclusions because different research use different diagnostic standards, microbiota sequencing technologies, and data processing techniques. Standardized biomarkers are obviously needed in this field of inquiry to guarantee the reliability, comparability, and consistency of research. The inability to completely regulate elements like heredity, environment, or food is another drawback. To find out how alterations in the microbiome affect the emergence of mental illnesses, more investigation is required, especially in the areas of immunology and metagenomics [14-22]. The role of medication must also be taken into account, albeit few research have examined its relationship to microbiota to yet. The effects of current patients' drugs are not considered in a sizable portion of studies. Antipsychotics, antidepressants, analgesics, and anticonvulsants are examples of psychiatric medications that might alter gut microbiota, usually by decreasing the variety of microbes present. The importance of the gut microbiota in the pathogenesis and management of neurological and psychiatric illnesses is well supported by data. Future research should be focused on larger groups of people in order to further expand our understanding and investigate novel therapeutic approaches. This is because prior studies have only included a small number of patients, which severely limits the ability to draw conclusions about causality. The significance of integrative multi-omics analyses, including metagenomics, metabolomics, transcriptomics, and proteomics, should also be emphasized. These analyses will be crucial for deciphering intricate host-microbiome interactions and identifying particular microbial metabolites, signaling pathways, and molecular mechanisms that affect behavior and brain function. Individual differences in the makeup of the microbiota and customized treatment based on these differences could also be an intriguing path. Prognosis and therapy monitoring would be greatly aided by the discovery of biomarkers for diagnosis [25-32].

Discussion. Among the microbiota associated most frequently, a clear pattern was observed for the genus Akkermansia, which showed a consistent increase in nine studies in PD and four in MS. The last ten years have seen a rapid increase in studies of the role of microbiota in various disorders. In this review, we focus on the consistency of the direction of the relationship found within neurological diseases and between neurologic diseases, including PD, AD, ALS, MS, and stroke. PD has the most consistent microbiome associations, and the results are the most reliable

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because they are based on the largest sample size. The relationship between nutrition and mental health is becoming more and more the subject of current research. These research' conclusions show that mental illnesses are not limited to conditions affecting the central nervous system (CNS). Many highly innervated neural networks, especially those in the enteric nervous system, are also the source of the issue. The microbiome–gut–brain axis (MGBA) has intricate mechanisms that depend on a wide range of factors and are probably based on a reciprocal interaction. We can speculate that the way the gut-brain-microbiome axis functions may be influenced by heredity [5-11]. A balanced diet affects the gut microbiota's composition by encouraging the growth of beneficial bacteria and preventing the formation of harmful ones. Additionally, dietary changes lower inflammation and affect the permeability of the gut wall. Therefore, there is a great chance that an unhealthy diet would impact neurobiological and emotional processes, leading to psychiatric problems, as our diet has a significant impact on the composition of our microbiomes. Given the significance of the immune system, metabolome analysis, and metagenomics, further research is required to precisely identify which alterations in the microbiome affect the emergence of psychiatric diseases. Proposals for novel approaches to treating mental illnesses that center on reestablishing a balanced gut flora are growing. These potential treatments may involve fecal microbiota transplantation, carefully chosen probiotics, or customized diet plans. Preventive interventions should be prioritized in addition to the direct treatment of microbiota abnormalities. Numerous factors, including preterm, mother age, social stress in childhood, breastfeeding, parental smoking, and pet ownership, affect the gut microbiota's makeup at birth. From a young age, parents should be aware of these variables and take the necessary actions to handle them [16-23]. In conclusion, the gut microbiota of people with NDDs shows notable changes, with unique microbial profiles appearing across various illness subtypes, according to this meta-analysis. We found significant differences in microbial composition and beta diversity at several taxonomic levels, but no significant differences in alpha diversity between NDD patients and healthy controls. The continuous dysbiosis pattern, which includes a trend toward a decrease in Escherichia/Shigella and Roseburia and an increase in Peptostreptococcaceae based on preliminary data, indicates that these taxa could be possible microbial markers for NDDs. Probiotic supplements and dietary changes are two examples of microbiome-targeted therapies that show promise in reducing clinical symptoms in afflicted people. To clarify the causal connections between gut microbiota and NDD pathophysiology and to create individualized treatment plans, however, more extensive, long-term research is required [31-39].

Conclusion. The gut microbiota of people with NDDs is significantly altered, according to this meta-analysis, with unique microbial profiles appearing across several illness subtypes. We found notable differences in beta diversity and microbial composition at several taxonomic levels, but no discernible differences in alpha diversity between NDD patients and healthy controls.

The results are most consistent for PD and MS, according to our summary of the data supporting a role of the gut microbiota in and across neurological illnesses. We also discover that the results are frequently not specific to neurological conditions. Further research is necessary to determine whether the significant overlap between PD and AD and MS and PD represents a shared etiology of those disorders and a shared result of neurological dysfunction. The most notable microbiota signature was seen in Parkinson's disease (PD), where the relative abundance of Akkermansia increased significantly across all taxonomic levels. Furthermore, despite the small number of individuals examined, results for MS were frequently comparable across trials.

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From the standpoint of microbiota composition, PD and MS have the most similar signatures. Baseline values and standard reporting templates have been developed for future clinical applications, which should facilitate and disseminate the study of gut microbiota in doctors' daily practice. The microbiome is a viable target for preventive and/or restorative treatment, despite the limitations of the studies that have been done thus far, according to the data gathered from the current studies. The results call for further investigation to see whether specific anti- or probiotic treatments could be useful in preventing neurological conditions or in enhancing patients' quality of life.

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