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Perspectives on Fecal Microbiota Transplantation: Uses and Modes of Administration

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Abstract Fecal microbiota Transplantation (FMT), often referred to as stool transplantation, fecal transfusion, and fecal bacteria therapy, is considered one of the most medical innovations of the 20th century. Fecal microbiota Transplantation entails filtering and dilution of a healthy donor's feces before injecting it into the recipient's digestive system. In China, it was first administered orally in the fourth century for diarrhea and food poisoning under the name "Yellow Soup." It has recently been widely employed in a variety of clinical settings, including cases of *Clostridium difficile* infection that are recurring and resistant. By replacing the unhealthy intestinal microbiota with a healthy bacterial community, the FMT treatment aims to enhance the intestinal flora. It also looks at neurological conditions where alterations in gut microbiota are prevalent. We have discussed FMT in the context of its use in conditions affecting the nerve system, such as neurological and other conditions (multiple sclerosis, Parkinson's disease, Alzheimer's disease, stroke, epilepsy, Amyotrophic lateral sclerosis, Tourette syndrome, neuropathic pain, Huntington's diseases, etc.), as well as the role of gut microbiota in many neurological disorders.

Keywords Gut-brain axis, Neurological Diseases, Applications of FMT, Delivery methods of FMT

Introduction

The gut-brain axis, referring to the reciprocal interaction between the digestive system and the central neurological system, has attracted a lot of attention during the past ten years [1]. Numerous studies suggest that the pathophysiology of disorders in the neurological system is significantly influenced by gut bacteria [1 - 9]. Several neurological disorders, including Parkinson's disease, neuromyelitis optica, Rett syndrome, spinal cord injury, multiple sclerosis, amyotrophic lateral sclerosis, epilepsy, autism spectrum disorder, cerebral infarction, Alzheimer's disease, and multiple system atrophy have been known to benefit from a specific individual comparison of the composition of participants' gut microbiota in good health. However, the information on microbiome composition is frequently inconclusive and there are a number of potential confounders. Oddly enough, individuals with all of these neurological disorders

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frequently have digestive symptoms [6], which may indicate that the GI system is involved in illness pathogenesis. The onset of these neurological diseases, their clinical features, and their course may potentially be influenced by modification of the gut microbiota. Gut microbiota interventions may potentially impact the availability and pharmacokinetics of drugs for neurological illnesses, which could result in improved efficacy and a new set of side effects. The administration of antibiotics, probiotics, and prebiotics, symbiotic relationships, or faecal microbiota transplantation are only a few examples of gut microbiota therapies. In a few neurological illnesses, antibiotic treatment has been shown to alter the course of the disease [3, 4]. Probiotics and Fecal Microbiota Transplantation (FMT) are methods designed to enhance gut health, but they vary considerably in composition and function. Probiotics are specific live microorganisms, usually bacteria or yeasts, that are taken in controlled doses to deliver health benefits by improving the diversity and functionality of the gut microbiome. Commonly found in fermented foods and dietary supplements, probiotics can help prevent or alleviate gastrointestinal issues, bolster immune function, and promote overall well-being. More precise details on the kinds of bacteria that offer health benefits, together with recommendations for doses and combinations, could be extremely beneficial for FMT compounds. Particular bacterial strains have been linked to a range of health consequences, and the gut microbiome is a complex ecology. To improve the effectiveness of FMT preparations and target certain illnesses, it may be helpful to identify beneficial strains, such as *Lactobacillus rhamnosus*, *Bacteroides fragilis*, and *Faecalibacterium prausnitzii*. Similarly important is standardizing the dose; current methods differ greatly in this regard, using as little as 30 grams or as much as 100 grams of donor feces in certain cases. To achieve consistent and successful treatments, the best doses should be determined based on clinical outcomes. Furthermore, investigating synergistic pairings of bacterial strains may optimize advantages. For example, a combination of strains known to improve mucosal integrity and anti-inflammatory ones may be more helpful in treating inflammatory bowel illnesses. Prebiotics or metabolites added during the FMT procedure may also improve the engraftment and performance of the microorganisms that are transplanted.

In contrast, FMT involves transferring a wide range of gut microbiota from a healthy donor to a recipient, typically through enema, colonoscopy, or oral capsules. This procedure seeks to restore a balanced microbial community in individuals experiencing severe dysbiosis, particularly those suffering from recurrent *Clostridium difficile* infections or other gastrointestinal disorders. While probiotics introduce beneficial strains into the gut, FMT offers a more thorough restoration of microbial diversity, making it a more effective treatment for conditions where the microbiome has been significantly disrupted [5 - 9]. Fecal microbiota transplantation, which involves introducing a solution of fecal matter from a donor into a recipient's digestive system, is the most effective method for altering the gut microbiota (Figure 1). Recurrent infections with *Clostridioides difficile* can be successfully treated with FMT [5].

Additionally, Gastrointestinal (GI) symptoms are frequently seen in patients with neurological dysfunction [6]. Some of the current medicines targeting the intestinal microbiota include FMT, antibiotics, probiotics, prebiotics, and symbiotics, which involve transferring functional microbiota from healthy individuals into the GI tracts of patients. FMT has the ability to improve gut microbiota health and lessen symptoms. FMT has been demonstrated to ameliorate psychiatric and neurological symptoms by altering the gut- brain axis as well as exerting its direct therapeutic activity in GI diseases [7]. We have covered the role of gut microbiota in a number of neurological and psychiatric illnesses in this review, along with the current uses of FMT in these settings. We have also emphasized potential processes and directions for further study.

Microbiome-gut-brain Axis

The bidirectional contact between the brain and the intestinal microbiota is known as the Microbiome-gut-brain (MGB) axis. The gut microbial environment can have an impact on neuropsychiatric health, according to a growing body of preclinical and clinical research. A growing body of evidence supports the involvement of the MGB axis in regulation and two-way communication between the brain and the gut microbiota [8]. According to recent investigations, there are five different communication pathways, which are defined as follows:

The Neuronal Pathway

The gut and brain share neuroanatomical features, and the intestinal wall contains a large number of intestinal nerves. Through the vagus nerve and intestinal nerves, the brain can receive information from the gastrointestinal tract [9]. Through the descending vagus nerve, the brain, the physical center of the organism, can control intestinal processes. The vagus

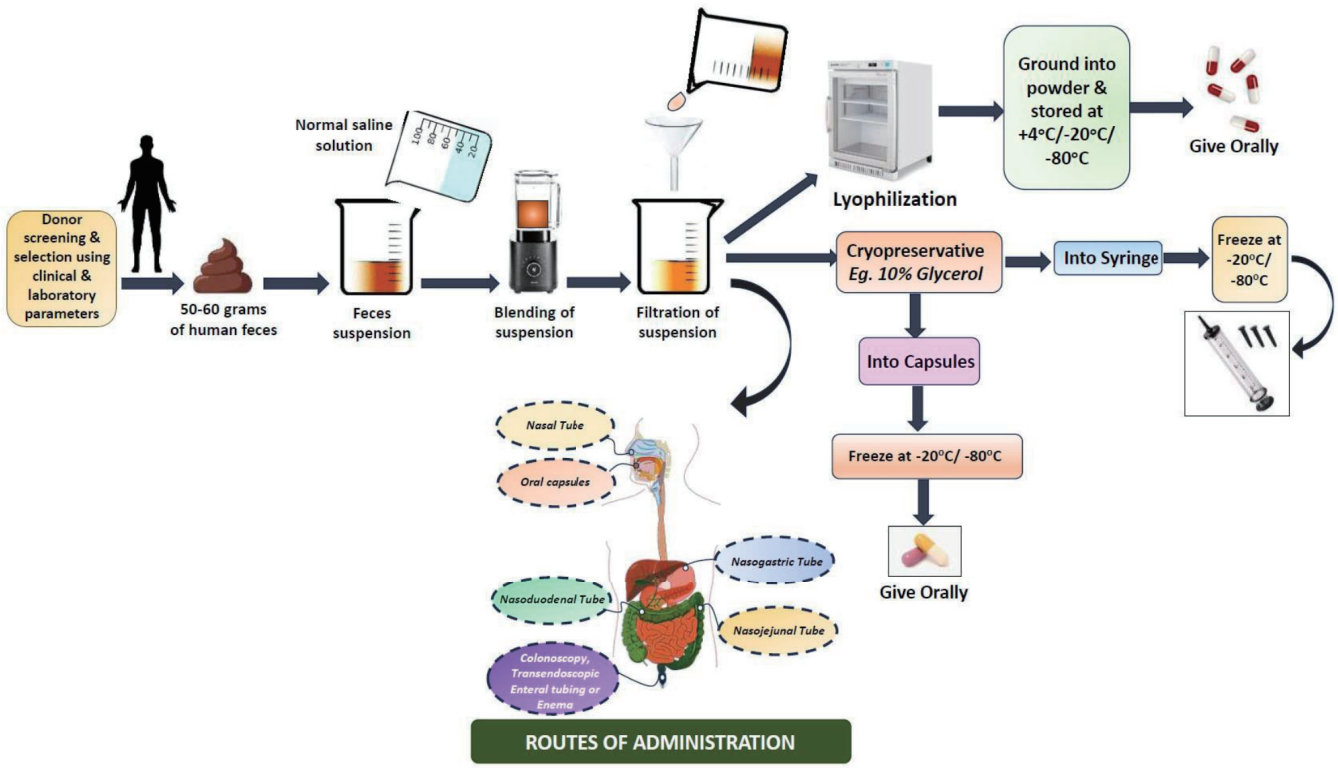

Figure 1: The schematic diagram of the fecal microbiota transplantation procedure.

nerve, a crucial hub for information exchange between the brain and the stomach, is a crucial component of the MGB axis.

The Neuroendocrine Pathway

It is made up of the Hypothalamic-pituitary-adrenal (HPA) axis, and is a major part of the neuroendocrine system and a key route for communication between the brain and the gut [10]. Through the activation of the HPA axis, stress affects the makeup and function of the bacteria in the gut [11]. An essential factor in the pathophysiology of neuropsychiatric disorders is HPA axis dysfunction.

The Inflammatory Signaling Pathway

Tumor Necrosis Factor-alpha (TNF-α), Interferon-gamma (IFN-g), and Interleukin-6 (IL-6) are examples of gut-derived inflammatory substances that can impair blood-brain barrier integrity and contribute to the emergence of brain disorders [12] after crossing a compromised gut mucosal barrier. Inflammation triggers the HPA axis by promoting the release of glucocorticoids, which in turn stimulates intestinal function and boosts the production of pro-inflammatory chemicals. Moreover, activated enteric immune cells, such as Th17 and natural killer cells, can penetrate the brain and cause inflammation. The gut microbiota's composition is changed by the stress response to neuroinflammation, which in turn increases enteric immune cells in this two-way flow of inflammatory signals. Additionally, intestinal inflammation is regulated by afferent vagus nerve signals from enteric immune cells, while efferent vagus nerve signaling transmits intestinal inflammatory information, thereby activating brain processes [13]. These inflammatory signaling pathways that traverse the MGB axis are crucial for controlling brain illnesses linked to the gut microbiota.

There are numerous ways in which metabolites generated from microbes might control host brain activity [14]. Short- chain Fatty Acids (SCFAs), which regulate host immunity and metabolism, are the most frequently researched metabolites in microbe-host interactions. Butyrate, propionate, and acetate are a few SCFA examples. Gut-derived SCFAs have the ability to protect the Blood-brain Barrier (BBB) and modify the activity of the HPA axis, neuroinflammation, and peripheral inflammatory responses. They may also affect the integrity of the intestinal barrier and regulate enteric immunity (Figure 2). These pathways could play a role in how SCFAs affect brain shape and function, either directly or indirectly [15]. The most researched amino acid is tryptophan, and tryptophan's downstream metabolites, such as indole, 5-hydroxytryptophan, and kynurenine, have a big influence on how the body works. The gut microbiota modifies bile acids, which help to regulate a number of

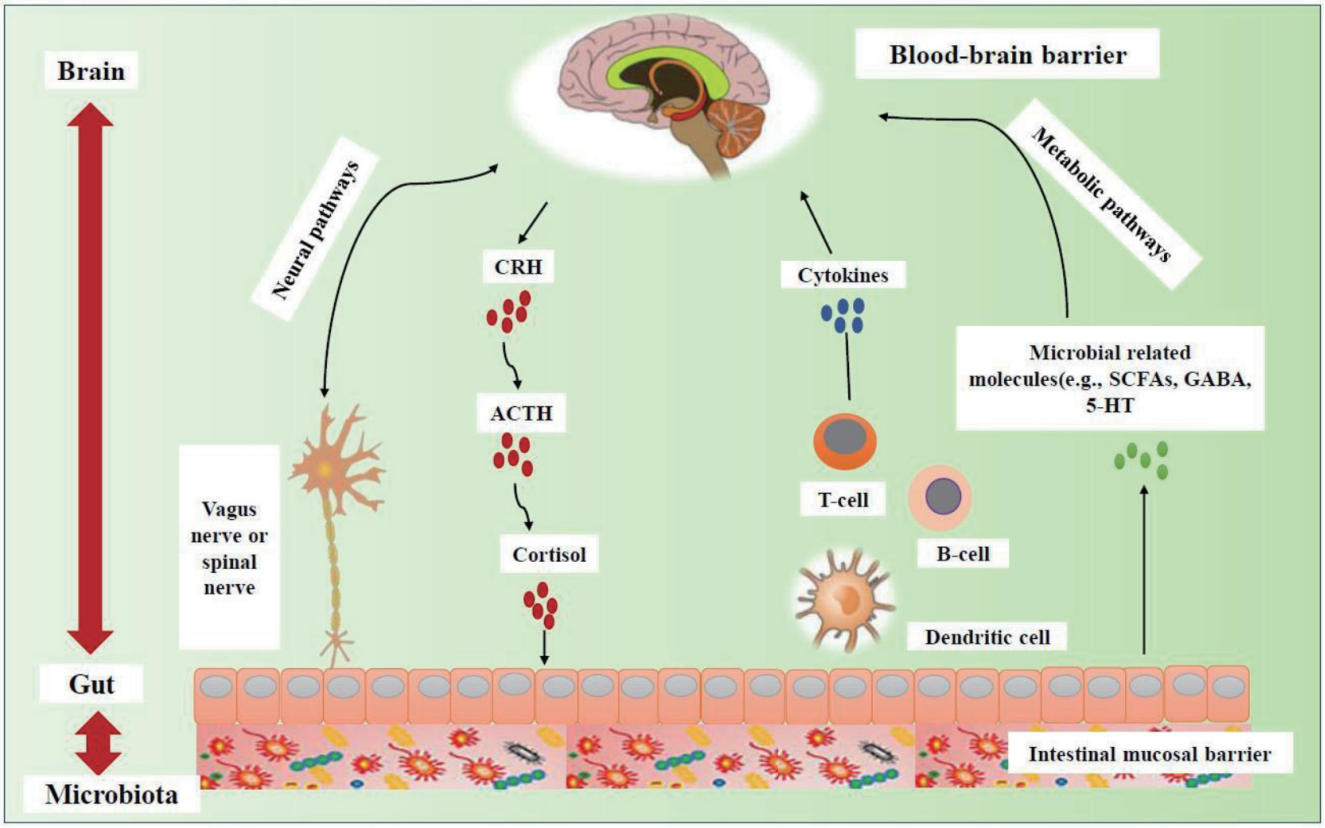

Figure 2: Microbiome-gut-brain axis [Short Chain Fatty Acids (SCFAs)].

aspects of host function. Through bile acid- activated receptors, bile acids altered by the microbiota may result in intestinal inflammation, fuelling neuroinflammation associated with brain diseases [16]. Neurotransmitters, including serotonin, GABA, and catecholamines, which are generated in the gut are important modulators of the gut microbiota-host relationship.

The gut mucosal barrier and BBB are examples of natural barriers in the MGB axis. The gut mucosal immune system and commensal microbiota are housed in the many layers that make up the gut mucosal barrier, which also serves as the functional and physical interface between the host and the gut microbiome [17]. For the maintenance of brain homeostasis, the BBB is necessary. The BBB integrity and brain function are significantly impacted by the gut bacteria and chemicals that they produce [18]. Stress, along with certain chemical and physical elements, can impair barrier functioning and increase permeability, allowing dangerous substances to reach the brain and ultimately advance the onset of disease. Technologies provide essential research resources for a full understanding of the role of the MGB axis in illness. Currently, fecal microbiota transplantation into animals using antibiotics or Germ-free (GF) animals (often rats) are the main methods used in gut microbiota research. An essential model organism for understanding host-gut microbiota interactions is the GF animal [19]. Since GF animals are not exposed to any bacteria after birth, this model offers an invaluable resource for a thorough comprehension of how germs affect the host's physiology, behavior, and neurology. We may assess how the gut microbiome affects brain function and behaviors from the perspectives of “no microbiota” and “full of microbiota” by contrasting GF animals with Specific Pathogen-free (SPF) animals. Second, the animal model exposed to antibiotics is a useful pharmacological tool for investigating the effects of intestinal microbiota dysbiosis on mental processes and behavior. Antimicrobial treatment is possible at any point in the life of the GF animal model, offering better temporal adaptability and specificity for microorganisms [20]. The ability of antibiotic therapy to more closely resemble clinical human situations is another benefit. The adaptability and specificity of antibiotic therapy make this model a crucial tool for assessing the MGB axis's functionality as well as a foundation for further study in this area. Third, the oral gavage technique is used to transplant the fecal microbiota from one person into another, establishing the FMT animal model. FMT has been used successfully

in preclinical investigations to create animal models for a variety of mental illnesses, such as schizophrenia, Major Depressive Disorder (MDD) [21, 22], and Autism Spectrum Disease (ASD) [23]. As a result, FMT offers a useful technique for learning more about how the host's functions are affected by the gut bacteria (Figure 3).

Several methods are presently available to identify the gut microbiota, including metagenomics, meta transcriptomics, meta proteomics, and microbial microarrays. These methods include metagenomics, 16S ribosomal RNA amplicon sequencing, and fluorescence-based quantitative polymerase chain reaction. The aforementioned techniques can be used to expose the gut microbiota's makeup and potential, but it is still unknown how the microbiota actually works in the body. The *in vitro* production of about 70% of gut microbes is challenging, which limits our knowledge of their microbiology. A unique *in vivo* labelling approach for microbiota, fluorescent-amino acid labelling, enables the detection of the internal and external variables influencing metabolic activity and *in situ* assessment of geographic distributions of the gut microbiota that cannot be created *in vitro* [24]. The native gut microbiota can be quantitatively imaged in three dimensions, which may aid in our knowledge

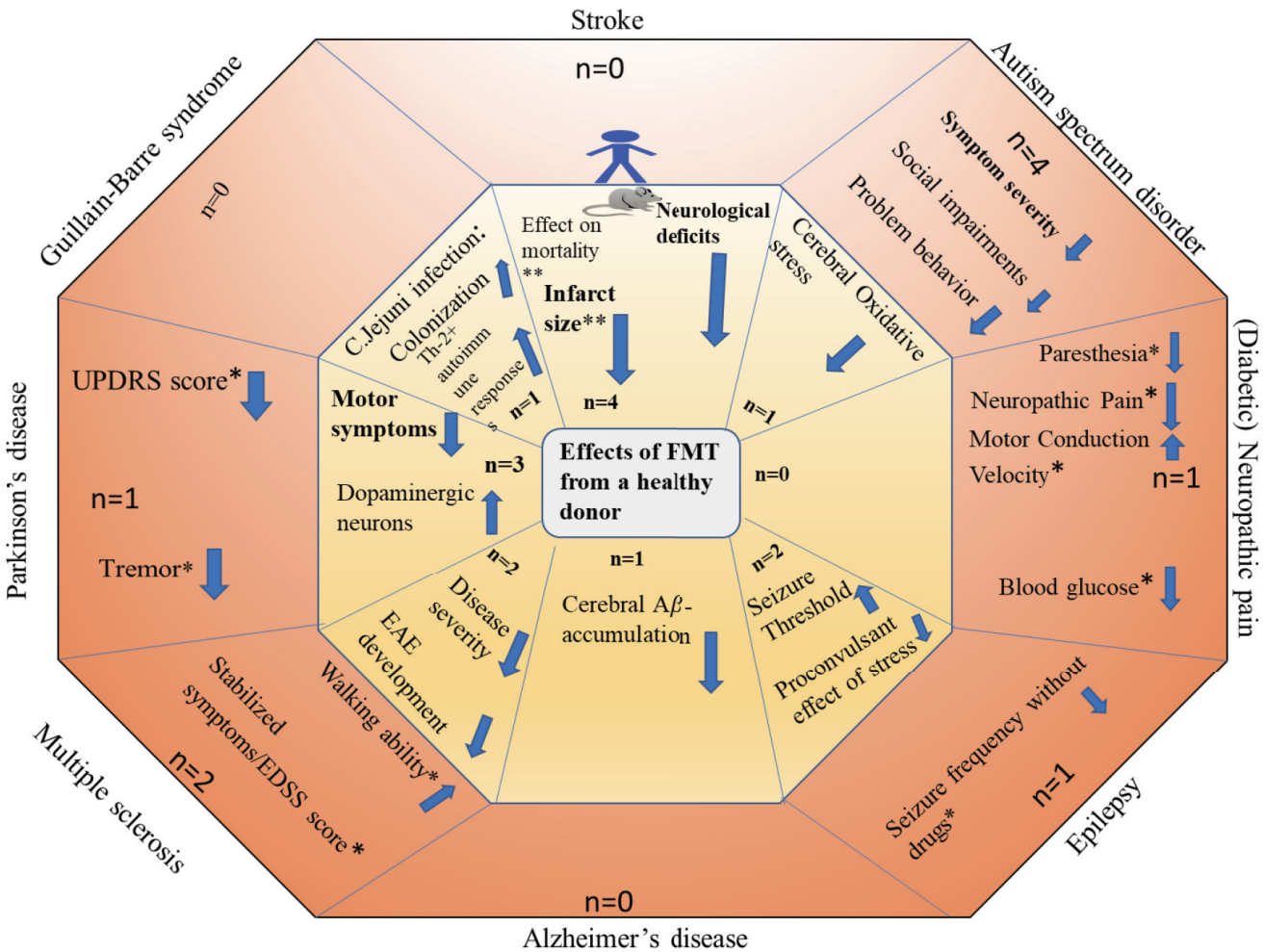

Figure 3: Possible outcomes of Fecal Microbiota Transplantation (FMT) in neurological disease models and people with neurological illnesses. In the research displayed, FMT from healthy donors was given to patients or animal models. Tourette syndrome was not included since there was just one case report for it. The orange portions denote additional effects, the yellow sections deal with motor and sensory symptoms or effects, and the blue sections reflect cognitive problems. The outside circles show the results of research on humans, while the inner rings show the results of research on animals. Bold statements denote conclusions that have been verified by several studies, with the exception of case reports. The letter "N" stands for the total number of research studies, both human and animal, that have been found for each neurological condition.

* Represents case reports or series with scant evidence, and ** indicates inconsistent outcomes.

of host-microbiome interactions. Additionally, microfluidic technology-based gut-on-a-chip models can be used to recreate the three-dimensional structure of the gut [25], elucidate the role of the intestinal microbiome in real-world settings, and offer fresh perspectives on how the host's function is affected by gut bacteria [26].

Neurological Diseases

Numerous serious neurological conditions, including migraine, Alzheimer's Disease (AD), Parkinson's Disease (PD), Multiple Sclerosis (MS), Myasthenia Gravis (MG), Neuromyelitis Optica Spectrum Disorders (NMOSD), epilepsy, autism spectrum disorder (ASD), and Major Depressive Disorder (MDD), have been proven to be impacted by gut microbial dysbiosis (Table 1) [27]. Destroying the intestinal epithelial barrier, losing intestinal neurons, and overproducing pro-inflammatory cytokines have a negative impact on the gut- brain axis. Additionally, during neurological illnesses, there are notable alterations in the variety and abundance of gut microorganisms, particularly those that produce anti- inflammatory substances. FMT is increasingly being explored for the treatment of neurological illnesses because of its ability to drastically alter the number of anti-inflammatory bacteria and increase the diversity of gut species (Figure 3).

Parkinson's Disease (PD)

Increased levels of synuclein lead to the formation of Lewy bodies and neuronal death in the mesencephalic substantia nigra, the conditions that underlie Parkinson's disease, a generalized neurodegenerative disorder. The result is a clinical condition characterized by both motor and non-motor symptoms, including stiffness, bradykinesia, resting tremor, depression, dementia, and difficulties related to the gastrointestinal tract, particularly constipation [28]. It has historically been assumed that PD starts in the gut and spreads to the brain due to vagotomy and appendectomy, for example, the existence of constipation years before symptoms appear and other factors. These factors include increased levels of synuclein in the appendix and enteric nervous system, the relationship between synuclein expression and certain infections, the retrograde transport of synuclein through the vagus nerve, and possible protective benefits [29, 30]. According to the breath test, PD has also been linked to small intestine bacterial overgrowth. This discovery has been associated with unexplained fluctuations, slower response to levodopa or dosage failure, longer off periods, and worse motor function, and is more common in patients with PD. Furthermore, eliminating small intestine bacterial overgrowth has no effect on the pharmacokinetics of levodopa and is linked to improvements in motor fluctuations [31, 32]. In patients with PD, *Helicobacter pylori* infection is more common, and patients with the infection have worse clinical outcomes (as determined by the UPDRS); eradicating *H. pylori* was found to be associated with clinical improvement [33]. The majority of all neurological illnesses have been examined in metagenomics in relation to PD [34]. Only two of the twelve meta-genomic studies that have been conducted to date have reported changes in the number of bacterial taxa (diversity); the findings, however, are inconclusive because one study found that patients with Parkinson's disease had more diversity than controls [35], while the other found the opposite [36].

The initial meta-genomic study, conducted in 2015, revealed a reduction in the frequency of *Prevotellaceae* and a positive correlation between the abundance of *Enterobacteriaceae* and the motor phenotype, including postural instability and abnormalities in gait. It made a comparison of 72 patients and 72 controls [37]. A year later, another study discovered changes in these bacterial families; patients with PD had lower levels of SCFAs and *Enterobacteriaceae* were more prevalent than controls. *Prevotellaceae* were also less prevalent in PD patients (considered to be anti-inflammatory) [38]. Between 2015 and 2017, four research studies demonstrated a relationship between PD and specific gut microbiota compositions. The results showed that some microbes that produce SCFAs (and so have an anti-inflammatory character) were more prevalent in controls' feces than in patients', while other microbes with a stronger pro-inflammatory profile were more prevalent in PD patients' mucosa [36, 39, 40]. In individuals with Parkinson's disease, other researchers have also noted a decline in the number of hydrogen-producing bacteria and decreased serum levels of lipopolysaccharide-binding proteins, increasing intestinal permeability to lipopolysaccharides [41]. It has been shown that people on various drugs have varied gut microbiomes, which may change the toxicity and efficacy of therapy. The makeup of the microbiota in Parkinson's Disease (PD) has been linked to many bacterial metabolic pathways that impact the breakdown of xenobiotics [42].

Numerous studies attempting to correlate symptoms with the composition of the gut microbiota have discovered that symptoms are more severe

Table 1: Effects of FMT on neurological illnesses, its characteristics, and its scope of use.

Kinds of Diseases	Alteration of the Intestinal Flora	Alterations to Substances brought on by Microbial Dysbiosis	FMT Application Level
Huntington's disease	An increase in Bacteroidetes and a decrease in *Firmicutes*, *Lachnospiraceae*, and *Akkermansiaceae*	Glycine, methionine	Animal
Multiple sclerosis	An increase in *Firmicutes*, *Proteobacteria*, *Clostridium*, *Cronobacter*, *Akkermansia*, *Ruminococcus*, *Coprobacillus*, *Clostridium* XVIII, *Atopobium*, *Holdemania*, and *Dorea*, and a decrease in *Bacteroides*, *Faecalibacterium*, *Eubacterium rectale*, *Corynebacterium*, and *Fusobacteria*	Proinflammatory cytokines, butyrate, lipid 654	Animal and patient
Epilepsy	A decrease in *Bacteroidetes*, *Actinobacteria*, *Prevotella*, *Bifidobacterium Saccharibacteria*, *Delftia*, *Paraprevotella*, *Gemmiger*, *Neisseria*, *Coprococcus*, *Fusobacterium*, *Methanobrevibacter*, *Phascolarctobacterium*, and *Roseburia*	Dopamine receptors D1 and D2 and proinflammatory cytokines (TNFα, IL-6, IL-1β)	Animal and patient
Parkinson's disease	A decrease in *Firmicutes*, *Prevotellaceae*, *Coprococcus*, *Bacteroides fragilis*, *Blauti*, *Roseburia*, *Faecalibacterium Christensenellaceae*, *Lactobacilli*, *Akkermansia*, and *Ralstonia*, and an increase in *Verrucomicrobiaceae*, *Ruminococcaceae*, *Proteobacteria*, *Clostridiaceae*, *Enterobacteriaceae*, *Bifidobacteriaceae*, *Lactobacillaceae*, *Pasteurellaceae*, *Christensenellaceae*, *Lactobacilli*, *Akkermansia*, and *Ralstonia*	LPS, SCFAs, α-synuclein, hydrogen production	Animal and patient
Alzheimer's disease	An increase in *Escherichia*, *Shigella, Chlamydia pneumoniae, Borrelia burgdorferi, Treponema pallidum, Burkholderiaceae, Staphylococcaceae, Porphyromonas gingivalis, Propionibacterium acnes*, and a decrease in *Eubacterium rectale* and *Bacteroides fragilis*	Aβ, GABA, BDNF, DHA, inflammatory cytokines	Animal and patient
Tourette syndrome	An increase in *Bacteroidetes*; in particular, *Bacteroides*, *Odoribacter*, and *Oscillospira* were identified as potential microbial biomarkers	D-alanine, tyrosine, dopamine, and SCFAs	Animal and patient
Stroke	Amyotrophic lateral sclerosis	Trimethylamine N-oxide	Animal
	An increase in *Bacteroidetes* and a decrease in *Butyrivibriosss fibrisolvens*, *Firmicutes*, *Peptostreptococcus, Escherichia coli, Oscillibacter, Anaerostipes*, and *Lachnospira*	Butyrate	Animal
Neuropathic pain	*Lactobacillus fermentum* KBL374 and KBL375, *Bacteroides fragilis*, *Escherichia coli*, *Lactobacillus, Streptococcus spp., Enterococcus spp., Corynebacterium glutamicum, Peptostreptococcus, Clostridium sporogenes*	LPS, bacterial flagellin, indole, SCFAs, PUFAs, BAs	Animal and patient

in those with worse clinical profiles, more severe cognitive impairment, altered gait, postural instability, depression, and issues with REM sleep behaviour. They have also discovered differences in the prevalence of certain taxa [43]. The abundance of particular taxa at the beginning of the follow-up period was shown to be correlated with lower UPDRS scores, hallucinations, delusions, and a lack of desire or initiative, in addition to the previously described cross-sectional research study. This second study had a 2-year follow-up period. Based on their research, the scientists concluded that some bacteria might be able to foresee how quickly a disease will spread [44]. Finally, an investigation of Levodopa-free patients observed lower overall virus abundance than controls, but there were no appreciable differences in the abundance of plasmids and prophages in the virome of 31 patients and 28 controls [45] (Figures 4 and 5).

Alzheimer's Disease

Aside from the existence of amyloid plaques and neurofibrillary tangles made of phosphorylated tau protein, little is known about the pathophysiology of Alzheimer's disease, despite the fact that it is the primary cause of dementia [46]. Based on data from autopsy research, numerous microorganisms have historically been linked to the pathophysiology of AD; these infections include *Chlamydophila pneumoniae*, *Borrelia burgdorferi*, various spirochaetes, and herpes simplex virus type 1 [47]. Additionally, a link has been hypothesized between periodontal disease and the buildup of amyloid in vulnerable areas of the brain as shown by amyloid PET imaging [48]. *H. pylori* infection has been connected to the pathophysiology of AD, just like it has been with PD. Verbal memory tests, serial digit learning tasks, and the Mini-Mental State Examination have all shown worse performance in patients with the infection. The infection also induces inflammation and even tau hyperphosphorylation [49]. Investigations have been conducted on certain bacterial taxa with pro- or anti-inflammatory profiles and on specific cytokines in individuals with cognitive

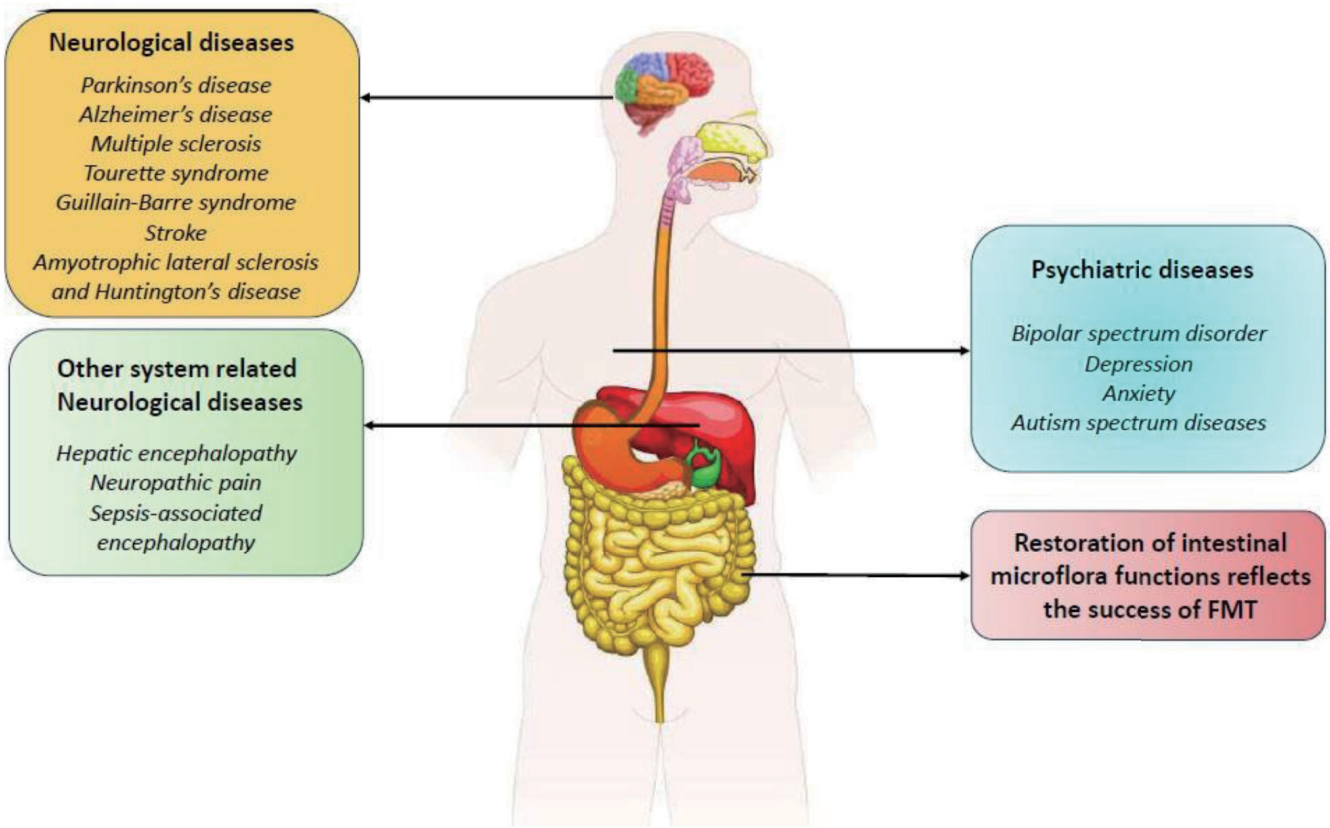

Figure 4: Current applications of FMT in the management of diverse neurological and mental problems. A balanced gut flora is essential for keeping the gut-brain axis functionally stable. Disorders of the gut microbiotme, which can be the cause of several neurological and psychological problems, can be brought on by increased pathogenic bacterial growth or a decline in probiotics. FMT has been employed as an essential therapeutic strategy to address a number of gastrointestinal-brain axis illnesses while working to rebuild the gut microbiota.

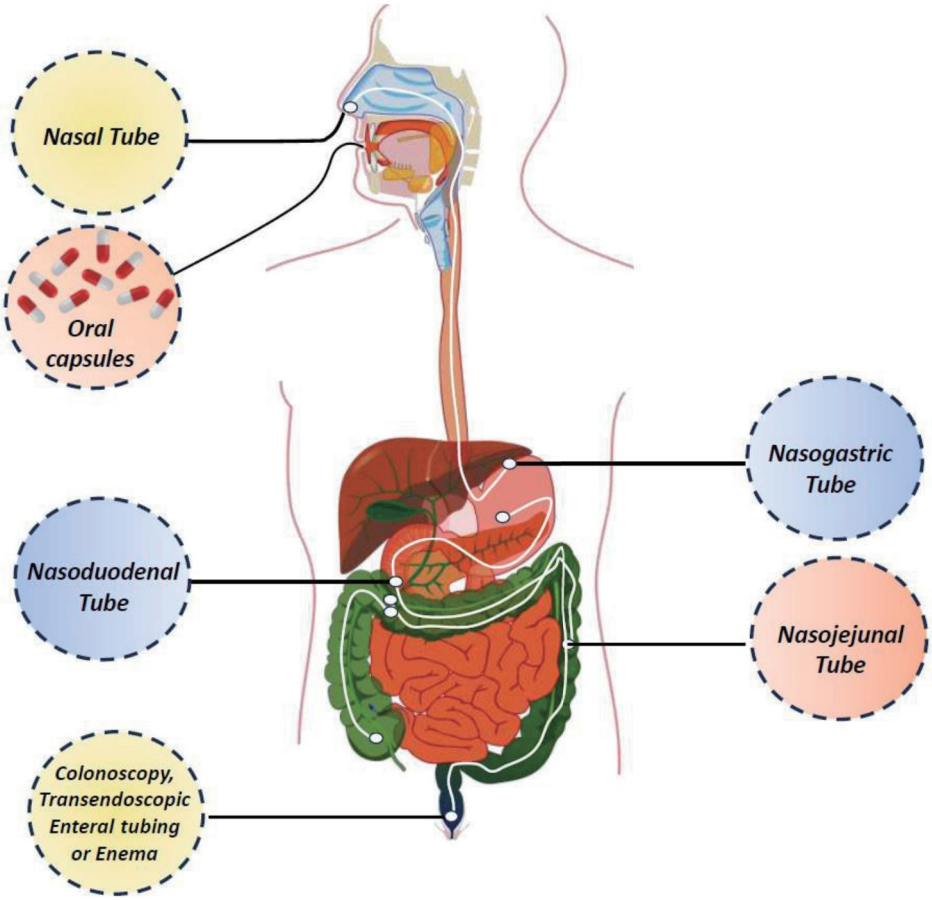

Figure 5: Techniques for fecal microbiota transplant delivery. Lower gastrointestinal routes, such as enema colonoscopy and colonic transendoscopic enteral tubing, and upper gastrointestinal routes, such as nasogastric/nasoduodenal/nasojejunal tubes and capsules, are divided among the delivery techniques.

impairment, categorized based on the presence of amyloid deposition. Reduced levels of two taxa with anti-inflammatory activity, *Eubacterium rectale* and *B. fragilis*, were associated with amyloid deposits, whereas pro-inflammatory taxa, *Escherichia/Shigella*, were associated with pro-inflammatory cytokines [50].

Additionally, the relationship between AD and the gut microbiota has been explored from a metagenomic perspective. In a study on Chinese population, 43 patients and 43 age- and sex-matched controls were examined. Variations were found at many taxonomic levels, from phylum to genus, suggesting that AD patients had changed gut microbiota [51]. In a separate study, 94 age- and sex-matched controls and 25 AD patients were compared. The researchers discovered that the patient group had reduced phylum abundance, higher genera like *Bifidobacterium* and *Bacteroidetes*, and lower *Firmicutes*. They also observed differences in microbial richness and diversity. The 13 most abundant genera in CSF levels were found to be correlated with three AD biomarkers: phosphorylated tau, Aβ42/Aβ40 ratio, and phosphorylated tau/Aβ40 ratio. These results suggest an inverse relationship in controls and a direct correlation in patients between the more abundant species and AD biomarkers [52].

Neuromyelitis Optica

The spinal cord and optic nerve are the two major organs affected by the demyelinating disease known as Neuromyelitis Optica (NMO). In contrast to MS, some NMO patients have a known target antigen that triggers autoimmunity. These patients have been defined to be of three types: those with anti- AQP4 antibodies, those with anti-myelin oligodendrocyte glycoprotein antibodies, and seronegative patients. Due to this, the term "NMO spectrum disorders" has been adopted by researchers [2]. Anti-AQP4 antibody-positive individuals have been shown to react with a similar peptide sequence in a protein of the bacteria *Clostridium perfringens*, which has been found to be more common in NMO patients and capable of eliciting the 17 responses, a factor in autoimmune disorders [53, 54]. Additionally, studies have indicated

that individuals with NMO spectrum diseases have changes in other taxa, most notably a substantial rise in the number of *Streptococcus*, which can be treated with immune-modulating medications. Studies have indicated that these patients have lower stool SCFA levels and that there is a link between higher amounts of acetate and butyrate and a worsening of the condition [55].

Amyotrophic Lateral Sclerosis (ALS)

The rapidly progressive condition known as amyotrophic lateral sclerosis is characterized by the death of the upper and lower motor neurons in the brain and spinal cord. This causes focal weakness that subsequently expands to include the diaphragm and most muscles. Patients pass away from respiratory failure after a typical progression time of three to five years, making the condition deadly [56]. Two research studies employing metagenomics and another using polymerase chain reaction methods have discussed the gut microbiota's function as an environmental influence. In the latter investigation, specific bacterial genera were quantified in 50 ALS patients and 50 age- and sex-matched controls. The patient group had higher levels of *Escherichia* coli and *Enterobacteria* and lower levels of yeast and *Clostridium* [57]. Researchers used metagenomics techniques to look at the microbial diversity in six ALS patients and five controls in a prior study that was published in 2016. A number of taxa that they classified as both beneficial and harmful bacteria were also found, along with differences in the *Firmicutes*/*Bacteroidetes* ratio. With 25 patients and 32 age- and sex-matched controls, the largest investigation on the gut microbiota in ALS only found one taxon (uncultured *Ruminococcaceae*) and the total number of operational taxonomic units as noticeable alterations [58, 59].

Multiple Sclerosis (MS)

The most commonly persistent inflammatory illness of the central nervous system is multiple sclerosis. The immune system, glia, and neurons in this demyelinating disease interact intricately and dynamically to cause intermittent symptoms and progressive neurodegeneration. While the exact etiology of MS is unknown, it is commonly accepted that some environmental variables, such as the gut microbiota's makeup, could induce the condition in people who are genetically predisposed to it [60, 61]. The association between the gut microbiota and immunity is based on research showing that the balance of Th1-Th17/Th2 cells, Treg cells, and humoral immunity is regulated by the gut microbiota. Animal models of MS, such as experimental autoimmune encephalomyelitis, are widely known [28]. Numerous research studies back up the link between MS and the gut microbiota [62]. A brief study involving seven patients and eight healthy controls discovered differences between the two groups at the genus level as well as treatment-related changes [63]. Japanese descriptive research published the same year included twenty Japanese patients and forty controls. While variations in the genus-level taxa involved in SCFA production were not observed, there were alterations in diversity. Similar alterations in a few taxa have also been seen in the population of North America, in adults (31 patients and 36 controls) [64, 65] as well as in children (18 patients and 17 controls) [66], with the latter study focusing on the genera in question. Researchers have shown a clear correlation between overall microbial richness and T helper 17 (Th17) cells [67] as well as an inverse association between Th17 cells and the phylum *Bacteroidetes*, associated with autoimmune diseases, in the paediatric population. A research study including 60 patients and 43 controls discovered a connection between particular taxa and the expression of specific genes in addition to the changes in microbial composition between MS patients and controls. Numerous immune-related genes, including those in circulating T cells and monocytes, are connected to dendritic cell maturation, interferon signalling, and NF-kB signaling [68]. Two genuinely ground-breaking studies have also been published as a consequence of the combination of case-control investigations, *in vitro* studies, and research employing experimental autoimmune encephalomyelitis model studies. In these studies, researchers have colonized animals with specific taxa or with the microbiota collected from patients and controls, and then they have assessed disorder progression. The bacterial taxa that were discovered to be more prevalent in patients with MS exacerbated the inflammatory response both *in vitro* and in mice that were monocolonized with those bacteria in the first of these investigations, which included 71 controls and 71 patients with Multiple Sclerosis (MS). In contrast, bacteria discovered to be less prevalent in patients were able to promote anti-inflammatory T cell development both *in vitro* and in mice with monocolonies. Additionally, animals colonized with the MS microbiota progressed less well than mice colonized with the control microbiota [69]. In the second trial, 34 MS patients and their unaffected twins served as the controls. The abundance of various taxa varied between groups, according to this study. Additionally, animals with spontaneous brain

auto- immunity colonized with patient feces showed decreased IL-10 production (anti-inflammatory) and increased autoimmunity [70]. The most current study, conducted on the Spanish population and published in 2018, compared MS treatment recipients compared to non-recipients. It included 15 participants who received interferon beta-1b, 15 participants who did not receive treatment, and 14 controls. Moreover, there were differences in the abundance of *Prevotella copri*, which has been previously proposed to have a protective effect against MS, between those who received treatment and those who did not have microbiological taxa that are different in patients with and without the disease. The microbial composition of interferon beta-1b recipients was comparable to that of controls; nevertheless, it remains to be shown whether treatment could reverse the dysbiosis linked to MS [71-77].

Epilepsy

The recurring, episodic, and temporary brain dysfunction associated with epilepsy is a frequent persistent neurological condition brought on by excessive synchronous neuronal activity. An etiology of epilepsy may be controlled by the gut microbiome. Among people with epilepsy, there were larger concentrations of the species *Delftia, Lautropia, Campylobacter, Haemophilus*, and *Neisseria* than in healthy controls, although *Blautia*, *Faecalibacterium*, *Parabacteroides*, and *Bifidobacterium* were decreased [72]. In animal models, it has been discovered that a number of antiepileptic medications, including valproate and clobazam, have an impact on the gut microbiota's makeup and *vice versa* [73]. For those with epilepsy, the Ketogenic Diet (KD) is an additional therapeutic diet that is high in fat and low in carbohydrates. Using a mouse model of refractory epilepsy, Olson et al. [74]. found that the KD significantly decreased seizures in mice and immediately changed the gut flora within 4 days. The abundance of *Parabacteroides spp.* and *Akkermansia muciniphila* increased as a result of this modification. However, in mice treated with antibiotics, the anti-seizure benefits of the KD were recovered following co-administration of *Akkermansia muciniphila* and *Parabacteroides spp.* This suggests that the gut microbiota has a modulatory function in the treatment of KD.

Due to epilepsy, SPF mice treated with GF and antibiotics did not experience the anti-epileptic benefits of the KD [74]. The findings of 16S RDNA sequencing of fecal samples from 14 epileptic and 30 healthy newborns showed that the number of *Proteobacteria spp.* was considerably greater in epileptic infants compared to healthy controls [75]. By lowering *Proteobacteria* and *Firmicutes spp.* and raising *Bacteroides*, *Bifidobacterium*, and *Prevotella spp.*, the KD reduced epilepsy symptoms [75, 76]. Moreover, Olson *et al*. found that in faecal samples from children with severe epilepsy, *Escherichia coli* relative abundance rose whereas Escherichia coli relative abundance decreased after 3 months of KD therapy. By introducing healthy volunteer fecal bacteria into the guts of epilepsy patients, it was possible to prevent seizures from recurring [78].

Ischemic Stroke

Stroke was described as a condition that manifests unexpectedly in the brain's cognitive processes for no other reason than vascular ones [79]. It is well documented that cerebral ischemic stroke decreases short-chain fatty acids despite increasing gut permeability by altering the gut microbiota, which is a side effect of the condition [80]. In an experimental investigation, it was found that increasing the amount of short-chain fatty acids at the conclusion of the application of a microbially rich FMT process resulted in a decrease in intestinal permeability, and that these decreases treated ischemic stroke *via* the food-intestinal axis. Butyric acid was unfavourably associated with ischemic stroke. An increase in *Lactobacillus* species has been linked to butyric acid's role in intestinal healing [81]. The risk of stroke is decreased by an increase in *Lactobacillus* species by lowering the volume of cerebral infarction, oxidative stress, and neural cell death. By restoring intestinal epithelial cells, it also prevents barrier dysfunction [82]. After implantation of the FMT-derived microbiota into young mice following stroke, an increase in the *Firmicutes/Bacteroidetes* ratio, a decline in physical performance, and an improvement in ischemic stroke were seen [83]. It has been noted that after colonization with the dysbiotic microbiota, proinflammatory T cells are produced in the ischemic brain and intestine immune compartments. It has been noted that by lowering the dysbiosis that arises as a result of brain injuries, FMT can be employed in the treatment of stroke [84].

Neuropathic Pain

Neuropathic pain is characterized by peripheral or central nervous system damage (such as a nerve injury or chemotherapeutic harm), which causes abnormal feelings or discomfort even after normal stimulations.

The gut microbiota of diabetes patients differs significantly in composition and function from that of healthy individuals [85]. Germ-free mice exposed to FMT from conventionally raised mice exhibited an increase in insulin resistance [86], whereas individuals with metabolic syndrome experienced an increase in insulin sensitivity [87]. Additionally, gut microbiota can indirectly control central and peripheral neurological inflammation or directly control the dorsal root neurons of the spinal cord [88]. Oxaliplatin can produce peripheral neuropathy and discomfort; however, in mice treated with antibiotics or in animals with no gut flora at all, these effects were not readily apparent. Additionally, FMT performed on the appellate mice caused the pain to return, showing that the gut microbiota affects neuropathic pain [89]. *In vitro* paclitaxel-induced neuropathic pain was lessened by probiotics, according to another study [90], albeit the type of neuropathic pain affects how effective they are. For instance, when persistent compression damage caused neuropathic pain in rats, *Lactobacillus reuteri* or *Bifidobacterium* were ineffective [91].

Tourette Syndrome

Probiotic supplementation decreased tic-like behavior and elevated dopamine and norepinephrine levels in mice. A neurodevelopmental disorder called Tourette Syndrome (TS) causes motor and vocal tics in youngsters [92, 93]. A significant difference in the composition of the gut's microbes was found in a study involving 30 children with *Streptococcal* infections, associated with children's autoimmune neuro- psychiatric diseases and pediatric acute-onset neuropsychiatric illnesses [94]. Another study discovered that medications that successfully lower streptococcal infections might diminish tic symptoms and the problems associated with the disease [95]. It was also revealed that over the course of 8 weeks, FMT reduced involuntary shrugging, abolished involuntary articulation, and improved attention span in a child with TS in an uncontrolled clinical experiment [96].

Guillain-Barre Syndrome

Guillain-Barre Syndrome (GBS) is an autoimmune paralytic neuropathy brought on by immunological activation or infection, particularly GI infection from *Campylobacter jejuni* [97]. The hallmarks of the innate immune response to campylobacteriosis include the accumulation of neutrophils and macrophages, inflammatory damage to the mucosa, anomalies in the gut barrier, and malabsorption that finally results in bloody diarrhoea [98]. Injected mice showed a direct connection between the etiology of GBS and intestinal dysbiosis. In fact, one of the causes of GBS is the cross- reaction between *Campylobacter jejuni* Lipopolysaccharides (LPS) and the peripheral gangliosides [99]. Antibiotics and FMT greatly sped up the removal of *Campylobacter jejuni* from the sick mice [100]. It was observed that in mice infected with *Campylobacter jejuni*, the Th2 and autoimmune response were amplified by human FMT. Finally, the peripheral neuropathic pain linked to GBS can be initiated directly by *Campylobacter jejuni*'s outer core liposaccharides through the promotion of neurotoxic antiganglioside autoantibodies [101].

Huntington's Disease

Huntington's disease, sometimes referred to as Motor Neuron Disease (MND), is a neurodegenerative illness characterized by progressive atrophy following upper and lower motor neuron damage of the leg, trunk, chest, and abdominal muscles [102]. The gut microbiota structure of mice with Amyotrophic Lateral Sclerosis (ALS) was changed compared to healthy mice, with a decrease in the proportion of bacteria that make butyrate, for example [103]. Now, FMT's therapeutic potential is being investigated, despite the lack of a conclusive pathogenic function for the gut microbiota in people with ALS [104]. In most cases, Huntington's disease is inherited and is brought on by an autosomal dominant huntingtin gene mutation. Nevertheless, a number of studies have linked non-genetic variables, such as the gut microbiome, to the onset of Huntington's disease [105]. Through metabonomics research, it was discovered that both healthy controls and patients with pre- and early-onset Huntington's disease had significantly altered levels of the gut microbiota's metabolites [106], suggesting that changes in the microflora affect the progression of the illness. In a mouse transgenic model, intestinal dysbiosis played a role in the etiology of Huntington's disease [107]. To completely comprehend how the gut microbiota and its metabolites contribute to the development, progression, and severity of Huntington's illness, however, more research is required [108, 109].

Delivery Modes for FMT

When the stool material is prepared and processed, it can be given for FMT utilizing a variety of distribution techniques that can be broadly categorized into lower gastrointestinal (capsules) and upper gastrointestinal (nasogastric, nasoduodenal, and nasojejunal tubes) channels (enema, colonoscopy) (Fig. 1).

The first procedure to be used was the traditional enema, sometimes referred to as a clyster, which involved injecting the preparation of the feces via the rectum into the lower bowel. Fecal microbiota transplantation through retainment enema has been demonstrated to be efficacious and well-tolerated in treating the signs of CDI in individuals with several subordinate comorbidities hospitalized with severe or complicated CDI [109]. The benefit of an enema is that the procedure is overseen and guided visually. This technique needs a skilled endoscopist, it is expensive, and there are procedural hazards [110]. Also, it cannot be carried out on patients who have colon inflammation. Colonic Transendoscopic Enteral Tubing (TET), as opposed to the conventional enema or colonoscopy, entails inserting a tube inserted through the anus into the cecum to convey the whole colon. For additional FMTs, the tube might be retained *in situ*. TET has proven to be efficient and less taxing on patients' psychological well-being [111, 112]. Among the ways for delivering feces to the upper gastrointestinal tract, nasal tubes can be used to transport FMT to the stomach (nasogastric tube), the duodenum (nasoduodenal tube), or the jejunum (nasojejunal tubes) [111]. Encapsulated FMT administered orally is the most recent delivery route, which has been proven to be safe and efficacious [112, 113] and is better tolerated by patients. The term "autologous FMT" is used to describe fecal stool that is taken from the patient who will receive it; otherwise, the term "allogenic or heterologous FMT" is used.

Colonoscopy

Fecal matter from a healthy donor is inserted into the colon of the recipient during a clinical procedure called FMT via colonoscopy. This technique is mostly used to treat gastrointestinal illnesses, particularly recurrent CDI, by restoring the balance of the gut microbiota in such patients. The process entails making a fecal suspension from a healthy, screened donor and making sure it is pathogen-free. Usually, processing is done on the suspension to separate the useful microbial component from the solid trash [114, 115].

Patients often undergo bowel preparation before the treatment that clears the intestines, just like a colonoscopy does. Once the rectum is reached, a flexible tube called a colonoscope is used to deliver the donor feces. In order to maintain widespread microbiota dissemination throughout the large intestine, the tube travels to the colon, where the fecal transplant is administered. With direct visibility provided by colonoscopy delivery, a doctor may precisely position a transplant in areas of the colon that may have the most effectiveness. For deeper intestinal locations, this approach is recommended when other approaches, including oral capsules or enemas, may be less successful. FMT via colonoscopy has demonstrated 90% success rates in treating diseases, such as persistent CDI. Furthermore, although additional study is needed to validate these effects, the current data point to possible advantages in other illnesses, such as metabolic disorders, irritable bowel syndrome, and Inflammatory Bowel Disease (IBD) [111, 116].

Enema

To re-establish a normal gut microbiome, a healthy donor's feces can be delivered by enema to the recipient. This process is being investigated for additional illnesses, such as inflammatory bowel disease and neurological problems, and is being utilized more often to treat ailments, like CDI. Fresh or frozen donor feces is collected and checked for germs to guarantee safety while using the enema procedure [70]. Next, in order to get rid of bigger particles, the feces are diluted with a sterile or saline water solution and filtered. Using a rectal enema, the feces solution is administered to the patient's colon once it has been prepared. The operation can be carried out in a clinical environment or at home. Patients are frequently instructed to lie on their left side in order to optimize the retention and absorption of the fecal material, since this position facilitates the material's deeper transit into the colon. It is important to note that patients should hold the solution for a minimum of 30 minutes to an hour, but ideally longer. By doing this, the microbiota is able to disperse throughout the colon and encourage the colonization of helpful bacteria [112, 116].

FMT administered via enema is generally regarded as safe and efficient; however, it may need to be used repeatedly to have long-lasting therapeutic effects. While enemas are less intrusive than other administration modalities, like colonoscopy or oral capsules, they may have a reduced retention rate, particularly in individuals with diarrhea or inflammation that restricts the amount of feces that may be retained. Through altering gut-brain communication pathways, recent research has also shown possible therapeutic advantages for ailments other than gastrointestinal illnesses, such as metabolic and neurological conditions, like epilepsy [117].

Nasoduodenal Tube

In order to treat illnesses, like recurrent CDI and other GI problems, FMT *via* a nasoduodenal tube is a treatment method targeted at restoring gut microbial balance. Using this technique, donor feces can be directly delivered into the upper gastrointestinal system by inserting a nasoduodenal tube, which runs *via* the nasal route, down the esophagus, and into the duodenum. Donors receive comprehensive medical and microbiological assessment, including stool testing for pathogens, to assure safety; rigorous screening of donor feces is essential prior to the treatment to reduce the danger of spreading diseases [118]. In order to make administration easier, the donor feces are turned into a liquid suspension and frequently mixed with saline. Engrafting beneficial bacteria in the small intestine can be facilitated by the fecal solution being infused more gradually and under control through the nasoduodenal tube. Patients who find it difficult to tolerate alternative delivery methods, including a colonoscopy or an enema, can benefit most from this approach. Pre- and post- transplant examinations are carried out to determine the treatment effectiveness and changes in microbiota composition. The patient may be observed during the surgery for any acute adverse effects [119, 120].

Oral Capsules

Fecal Microbiota Transplantation (FMT) has shown promise as a therapeutic approach for reestablishing gut microbiota functioning and diversity in disorders, such as inflammatory bowel syndrome and CDI. Oral capsules are a new way to provide FMT, and they have various benefits over more conventional approaches, like colonoscopy or enema administration. Oral pills make a non-invasive treatment easier, improve patient compliance, and make it simpler to store and transport donor feces. Studies have demonstrated that encapsulated FMT may effectively engraft in the gut, resulting in a notable restoration of the microbiota and clinical alleviation of illnesses, like CDI. For instance, a research study by Kao *et al*. [121] showed that oral capsules containing donor feces were just as successful as traditional FMT techniques in treating recurrent CDI. Moreover, it is possible to build the capsules in a way that shields the microbiota from stomach acid, thus increasing the quantity of live bacteria that enter the intestines. According to research, this approach is safe, well- tolerated, and linked to few side effects, which makes it a competitive substitute for conventional FMT administration techniques [122]. As studies continue, oral FMT capsules might be essential for increasing patient outcomes for a range of gastrointestinal illnesses and increasing access to microbiota-based medicines.

Endoscopy

A successful treatment strategy for a number of gastrointestinal conditions, most notably recurrent CDI, has been observed to be the administration of FMT using endoscopy. The process includes transferring fecal material from a healthy donor into the recipient's digestive system, with the main goal being the restoration of the gut microbiota's equilibrium. In order to achieve optimal dispersion of the transplanted microbiota throughout the intestinal lumen, the doctor usually conducts a colonoscopy during an endoscopic FMT. This gives direct access to the colon. Donors are carefully checked for infections prior to the treatment, and the fecal sample is processed to isolate live bacteria, which are often suspended in saline or other solutions for instillation. Research has demonstrated that, following one or two FMT operations, this approach can successfully limit the recurrence of CDI in up to 90% of patients [123]. Furthermore, endoscopic FMT has been investigated in other disorders, like metabolic syndrome and Inflammatory Bowel Disease (IBD), where it has demonstrated promise in regaining microbial diversity and enhancing clinical outcomes [124, 125]. Potential negative outcomes, including infection or intestinal perforation, are among the safety concerns; however, they are rather uncommon when carried out by qualified medical professionals [126]. In general, endoscopic FMT injection is an essential intervention for the treatment of illnesses associated with dysbiosis.

Jejunostomy Tube

FMT *via* a jejunostomy tube includes the insertion of donor fecal material directly into the jejunum, giving an additional route for delivering FMT, especially in circumstances when typical procedures (*e.g.*, colonoscopy or enema) are not viable. Patients with gastrointestinal problems, such as recurrent infections with *Clostridium difficile*, inflammatory bowel disease, or even neurological conditions, such as epilepsy, whose symptoms may be influenced by gut microbiota regulation, may benefit most from this approach [127]. Through the surgical placement of the jejunostomy tube, the prepared fecal material, which has been processed and screened for pathogens to assure safety and efficacy, can be administered continuously or in boluses. Research has demonstrated that microbial diversity and composition may be efficiently restored in recipients of FMT *via* jejunostomy, which may lead

to a therapeutic improvement in their underlying diseases [114, 128]. Monitoring is essential because consequences might include infections, abnormalities in electrolytes, or dislodgement of the tube. Preliminary results show that jejunal FMT can cause considerable changes in the gut microbiota, with some patients having persistent remission of their diseases. The long-term consequences of this approach are still being investigated [129]. Nonetheless, further research is required to develop standardized procedures for fecal processing, delivery methods, and donor screening in order to optimize patient safety and therapeutic effectiveness.

Lyophilization Techniques

By preserving the viability of the microbial population in fecal samples, lyophilization, also known as freeze-drying, is one novel technique to improve the delivery and stability of FMT. By freezing the fecal material and then vacuum- removing the water, a stable, dry product can be formed by the lyophilization process. This method makes it easier to store and transport FMT goods while also extending their shelf-life. According to several studies, lyophilized FMT retains a level of functioning and microbial diversity that is similar to that of fresh fecal transplants. For example, Haindl *et al*. [130] showed promise for human applications and showed that lyophilized FMT may successfully restore gut microbiota in animal models. Since the drying process can inactivate certain viruses and bacteria that can be present in fresh fecal samples, lyophilization also has the important benefit of reducing the risks of pathogen transmission [125, 130]. Further research is necessary to determine the efficacy of lyophilized FMT in clinical settings, and standard operating procedures for administration and preparation should be followed. All things considered, lyophilization techniques involved in FMT offer a feasible way to enhance the safety and accessibility of microbiota-based treatments for treating a range of illnesses.

Conclusion

Fecal Microbiota Transplantation (FMT) has demonstrated encouraging outcomes in the management of several illnesses, including recurrent *Clostridium difficile* Infections (CDI). Further research indicates that CDI may have therapeutic advantages not just for metabolic diseases, but also for Inflammatory Bowel Disease (IBD), irritable bowel syndrome (IBS), and even neuropsychiatric problems, including autism spectrum disorder and depression. Donor selection, formulations, and delivery techniques continue to provide substantial hurdles. Currently, research is being done to determine the best way to administer FMT.

There are several current procedures with different benefits and drawbacks, including colonoscopy, enemas, oral capsules, and nasogastric tubes. Oral capsules are less intrusive, but they cannot always provide viable microorganisms to the gut, whereas colonoscopy administration, although very successful, is pricey and invasive. FMT formulation presents a significant problem since treatment success depends on preserving microbial viability throughout preparation and administration. Donor selection is a critical factor in the success of FMT, as its effectiveness heavily depends on the diversity and composition of the donor's microbiota. While only a few carefully screened donors typically provide stool for transplantation, differences in their microbiomes can result in varying patient outcomes.

To improve consistency and safety, screening processes must be enhanced to reduce the risk of transferring harmful pathogens or microbiota while ensuring an adequate presence of beneficial microbes. Safety is still a top priority, particularly when it comes to the possibility of spreading diseases or harmful microorganisms through FMT. Severe adverse reactions, including sepsis instances, have been documented; however, they are uncommon. More thorough clinical trials are required to confirm the safety and effectiveness of FMT across a range of patient demographics and illnesses, as the long-term implications of the procedure on the host microbiota and health remain mainly unknown. Although FMT has been shown to be beneficial for a number of illnesses, its precise mode of action remains unclear. It seems to restore microbial variety in some situations, which is important for gut health, but research is still being done on the relationships between the host immune system and transplanted microbiota. Moreover, there might be significant variations in FMT results between individuals, most likely as a result of variations in their current gut flora and general health. There are still uncertainties about the duration of FMT effects. For many diseases, it is unclear how long the benefits persist or if repeated treatments are needed. Moreover, the exact composition of an “ideal” FMT donor is not yet fully understood, highlighting the potential for better donor matching and the advancement of microbiota-based therapies.

There is increasing interest in enhancing FMT with more focused and sophisticated methods as studies on the gut flora progress. In order to mimic the

benefits of FMT in a safer and more regulated manner, the emerging field of probiotics, postbiotics, and microbiome therapies seeks to employ certain strains or consortia of beneficial bacteria. In contrast to FMT, these next-generation probiotics could provide more consistent results, reduced manufacturing hazards, and predictable outcomes. Conclusively, FMT is an innovative treatment that exhibits evident advantages for specific ailments, particularly CDI. However, there remains ample knowledge to be gained regarding its enduring safety, working principles, and ideal use. To fully utilize microbiota transplantation as a therapeutic modality in the future, it will be imperative to refine delivery techniques and donor selection procedures and create next- generation microbiome-based medicines.

Authors' Contribution

It is hereby acknowledged that all authors have accepted responsibility for the manuscript's content and consented to its submission. They have meticulously reviewed all results and unanimously approved the final version of the manuscript.

Abbreviations

FMT = Fecal Microbiota Transplantation
CDI = Clostridioides difficile Infections
IBD = Inflammatory Bowel Disease
IBS = irritable bowel syndrome
TNF-α = Tumor Necrosis Factor-alpha
IFN-g = Interferon-gamma
IL-6 = Interleukin-6
SCFAs = Short Chain Fatty Acids
BBB = Blood-brain Barrier
GF = Germ-free
SPF = Specific Pathogen-free
ASD = Autism Spectrum Disease
AD = Alzheimer's Disease
PD = Parkinson's Disease
MS = Multiple Sclerosis
MG = Myasthenia Gravis
NMOSD = Neuromyelitis Optica Spectrum Disorders
ASD = Autism Spectrum Disorder
NMO = Neuromyelitis Optica
ALS = Amyotrophic Lateral Sclerosis
MS = Multiple Sclerosis
KD = Ketogenic Diet
TS = Tourette Syndrome
GBS = Guillain-Barre Syndrome
LPS = Lipopolysaccharides
MND = Motor Neuron Disease
TET = Transendoscopic Enteral Tubing
CDI = Clostridium difficile Infections

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Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

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