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Fecal Microbiota Transplantation as a Tool for Therapeutic Modulation of Neurological and Mental Disorders

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Abstract

Neurological, psychiatric, and psychological disorders are highly prevalent in the world population, but available pharmacological treatments cause numerous side effects, and also there is an elevated rate of treatment-resistant patients. Dysbiosis of the gut microbiome is implicated in several neurological and mental disorders and, consequently, restoring the imbalance of the gut microbiome can improve the symptoms associated with these conditions. One method of achieving the gut homeostasis is through fecal microbiota transplantation. This approach has been successfully applied in the treatment of microbial pathogens, such as *Clostridioides difficile*, and as a therapeutic tool in various gastrointestinal diseases. However, its application for the treatment of neuropsychiatric and psychological disorders has been largely unexplored. This review aims to present a summary of studies that have used fecal microbiota transplantation in order to treat neurological and mental disorders; therefore, the mechanisms underlying this particular technique are reviewed, and its influence on the recipient intestinal microbiome is also analyzed.

Keywords: Fecal microbiota transplantation; Gut microbiome; Neurological disorders; Mental disorders; Treatments.

Introduction

The human Gut Microbiome (GM) contains between 10 and 100 trillion microbial cells, and represents an intricate ecosystem associated with the function of several host physiological, immune, and neurological processes [1]. The gut contributes up to 70% of human immune function, and is the largest microbial ecosystem within the host. The human GM is mainly represented by four bacterial phyla: Bacillota, Bacteroidota, Pseudomonadota, and Actinomycetota, whose composition reaches a state of homeostasis among all its members, establishing complex trophic relationships with each other and their human host [1].

Dysbiosis constitutes a change in the autochthonous bacteria within the human gut that is often associated with several disorders, some of which cannot be treated with the established clinical treatments [2]. In this sense, the transfer of fecal matter from a healthy donor into the intestinal tract of a recipient, named Fecal Microbiota Transplantation (FMT), may represent a therapeutic procedure to change the recipient's microbiota with subsequent health benefits. However, while the FMT strategy has achieved clinical success in treating infections caused by *Clostridioides difficile*, it has not achieved the same results in other conditions such as inflammatory bowel disease or multidrug-resistant bacterial infections [2]. These conflicting results have been explained by the no consideration of ecological principles in clinical trials, or by problems in the efficacy of FMT [3]. The latter factor can be avoided by FMT augmentation strategies, consisting of repeated introductions from multidonors [4] or of synthetic microbial communities (SynComs); both approaches aimed to increase the diversity of microbiota in recipients [5]. Strain engraftment is also an important factor for the success of FMT and depends on the propagule pressure, a measure of introduction intensity that will increase the likelihood of establishing the bacterial allochthonous population. The size of the initial microbial population and its influence on

the autochthonous gut bacteria can directly or indirectly facilitate strain engraftment in the recipient's GM [6,7]. Greater donor strain GM colonization rate is achieved in antibiotic-treated patients prior to FMT administration; the antibiotic treatment reduces the colonizing resistance in the recipient GM and favors the ulterior engraftment [8]. In addition, Ianiro et al. [2] reported a greater strain engraftment after single-route FMT administration in patients suffering an infectious disease. This so-called "invasional meltdown" is the ability of non-autochthonous bacterial species to facilitate each other's establishment, and may explain why in *C. difficile* infection cases have been found a greater FMT engraftment in recipients.

This review examines human studies that have assessed the effects of FMT on symptoms associated with a variety of neurological, psychiatric, and psychological disorders. Comorbid conditions associated with poor mental health outcomes, such as gastrointestinal and non-gastrointestinal diseases, were also included in this review.

Therapeutic applications of FMT in gastrointestinal and non-gastrointestinal diseases

Bacterial dysbiosis leads to a decline in the immune functions of the GM, which increases the risk of developing various gastrointestinal disorders, such as irritable bowel syndrome (IBS), Ulcerative Colitis (UC), and Crohn's disease [9,10], as well as non-gastrointestinal disorders like metabolic syndrome, non-alcoholic fatty liver disease, cardiovascular inflammation, and refractory melanoma [11,12].

Irritable Bowel Syndrome (IBS) is a chronic gastrointestinal disorder characterized by recurrent abdominal discomfort associated with abnormal defecation, such as constipation and/or bloating [13], resulting in impaired quality of life. The precise pathogenesis of IBS is still unknown, but several psychological and physiological factors seem to be related to its development and persistence, including inflammation, GM dysbiosis, genetic predisposition, dietary habits, to name the most important [14]. The use of FMT treatment has shown strong positive effects on IBS symptoms in several studies [15,16]. Members of the phylum Bacillota increased in IBS patients treated with FMT, while members of the phyla Pseudomonadota and Actinomycetota showed a lower abundance [17], although increases in the members of the orders Clostridiales and Bacteroidales were reported in another study [18]. Körner and Lorentz [19] reported that the most important factors influencing FTM treatment success were the efficacy of delivery methods (oral capsules, gastroscopy, or colonoscopy), fecal material content and processing, and the selection of different donors. The two most important types of IBS are ulcerative colitis and Crohn's disease, the former affecting the mouth, esophagus, stomach, small and large intestine, and the anus, while the latter affects the colon and the rectum [20].

UC is a chronic inflammatory disease of the colon and rectum associated with defects in colonic epithelial cells, mucus barrier, and epithelial barrier, and its development is influenced by genetic, immunological, bacterial, and environmental factors [21]. UC is accomplished by a GM dysbiosis with an abnormal distribution and reduced biodiversity of intestinal commensal microorganisms, characterized by a decrease in the abundance of members of Bacillota and an increase in the levels of Pseudomonadota members [22]. Recently, FMT has been investigated as a promising treatment for UC, and although the majority of studies have proven a high efficacy, its safety remains a critical issue [23,24]. In addition, the efficacy of FMT was also dependent on the duration and route of administration [25-29]. Analysis revealed an increase in microbial diversity after FMT in patients with remission, who presented an enrichment of *Eubacterium hallii* and *Roseburia inulivorans*, and increased levels of SCFAs [30]. Instead, patients who did not achieve remission had an increase in *Escherichia* spp., *Fusobacterium gonidiaformans*, and *Sutterella wadsworthensis*, as well as Lipopolysaccharide (LPS) levels [24,30]. In summary, some studies have established several aspects to optimize the safety of FMT in UC, including strict screening and management of donors [31], ensuring the quality of the FMT product during preparation, and selecting the appropriate matching between donors and recipients [32].

Crohn's disease is a chronic relapsing IBS related to an abnormal activation of the gastrointestinal immune system against the GM in genetically susceptible hosts and under the influence of environmental factors [33]. Sokol et al. [34] found that the gut microbiota in patients with this disease was altered compared to healthy individuals, with an increased abundance of pro-inflammatory bacteria such as *Escherichia coli*, and a decrease in the anti-inflammatory bacteria *Faecalibacterium prausnitzii*. Current therapeutic strategies used in Crohn's disease are based on immunosuppressive treatments, which may be potentially associated with complications such as opportunistic microbial infections [35]. For this reason, Sokol et al. [9] applied FMT to Crohn's disease patients in a randomized pilot study. The primary endpoint of donor microbiota colonization at the end of the intervention was not met, with enrichment in different members of the Gammaproteobacteria class (Pseudomonadota phylum), such as *Klebsiella, Actinobacillus*, and *Haemophilus*. The low similarity between donor and recipient microbiota suggests that a single FMT is not sufficient to induce significant changes in the GM of patients.

Metabolic syndrome is a group of conditions that increase the risk of atherosclerotic cardiovascular disease, Type 2 Diabetes Mellitus (T2DM), and stroke. These factors may produce central obesity, dyslipidemia, insulin resistance, and arterial hypertension; disturbances that have been associated with GM dysbiosis [36,37]. Healthy GM use their respective metabolic pathways to produce molecules, Such As Short-Chain Fatty Acids (SCFAs), which act as energy sources for colonocytes, and as signaling molecules. SCFAs increase insulin sensitivity and stimulate fatty acid oxidation and lipolysis [38]. In addition, gut bacteria transform primary bile acids into secondary bile acids that act on the farnesoid X receptor, a regulator of host glucose and lipid homeostasis [39]. Several FTM interventions have been performed in humans with metabolic syndrome, and the results showed that after FMT from donors, the GM diversity was increased and the most abundant bacterial species found were butyrate or propionate producers: *Akkermansia muciniphila, Bacteroides* spp*., E. hallii, E. ventriosum,* and *Roseburia intestinalis*. The increased SCFAs are thought to reduce the translocation of endotoxins (i.e., LPS) into the bloodstream, which drives to insulin resistance [40-42]. However, several studies found no differences between the intervention and placebo groups despite the engraftment of donor bacteria [43,44]. These negative results could be explained by the small group size and by the lack of dietary intervention. In this sense, Mocanu et al. [45] found increased insulin sensitivity in patients with severe obesity and metabolic syndrome treated with a single oral encapsulated FMT combined with adjunctive daily fiber. The treatment with FMT plus fiber increased bacterial alpha and beta diversities, inducing an increase in the abundance of members

of the family *Christensenellaceae* and the species of the genera *Akkermansia, Bacteroides,* and *Phascolarcobacterium*, and a decrease in *Dialister* and *Ruminococcus* genera. Zhou et al. [37] proposed a series of procedures to improve the use of FMT in T2DM, concluding that FMT modulates the GM, improves glucolipid metabolism, and reduces weight of T2DM patients. In diabetic patients, the composition of GM is significantly altered, as the bacterial genera *Akkermansia, Blautia, Faecalibacterium, Fusobacterium, Peptostreptococcus,* and *Roseburia* are associated with T2DM [46-48], and members of the family *Rikenellaceae* and the genera *Anaerotruncus, Escherichia, Lactobacillus,* and *Streptococcus* may also serve as potential biomarkers to select patients with T2DM for FMT [49,50].

The therapeutic applications of FMT to non-gastrointestinal disorders have been reviewed by Liptak et al. [11], who found that several microbial metabolites stimulate the enteric nervous system and contribute to disease relief. Specifically, metabolic syndrome and obesity appear to be modulated by microbial SCFAs and secondary bile acids. LPS and other bacterial components enter the blood system affecting the liver health. Cardiovascular health has been found to be regulated by bacterially produced Trimethylamine N-oxide (TMAO) and by systemic inflammation induced by circulating bacteria.

Therapeutic applications of FMT in neurological and mental disorders

It is known that GM dysfunction produces neurochemical changes that may be involved in several neurological, psychiatric, and psychological disorders. Various theories have been proposed as to how the human GM modulation affects the Central Nervous System (CNS), resulting in host changes, including serotonin production, immune response, and metabolism [51]. Serotonin transmission is altered in depression, and GM dysbiosis affects serotonin production through the SCFAs' regulation of tryptophan hydroxylase involved in the serotonin synthesis in enterochromaffin cells [52]. SCFAs have anti-inflammatory properties in intestinal macrophages and dendritic cells, and also regulate the maturation and function of microglia in CNS [53]. Numerous neuropsychiatric disorders and mental conditions are associated with an enhanced immune response and inflammatory processes, as observed by increased levels of cytokines [54]. A more direct network by which GM affects the CNS is via the vagus nerve, which is affected by SCFAs through the production of neurotransmitters [55].

Many people refuse available pharmacological treatment for mental disorders because to its side effects, stigma-related reasons, treatment-resistance, or inefficiency regarding to improve the disease symptoms. The repopulating of the patients' GM with bacteria from healthy individuals through FMT may have beneficial neurological, immune, and metabolic effects that could improve the course of the mental condition. However, because this is a relatively new area of research, there are few human studies of FMT as a treatment for neurological, psychiatric, and psychological disorders [56-58].

Several FMT treatments for neurological and mental disorders are described in Table 1. In total we have reviewed 28 studies from 2017 to 2023, of which 35.7% corresponded to depression (MDD) and anxiety disorders [61,63,65,66,68,71,74,75,81,85]; 17.8% to Parkinson's Disease (PD) [69,76,77,79,83]; 10.7% to Multiple Sclerosis (MS) [64,72,80]; 7.1% to Alzheimer's Disease (AD) [73,78]; 7.1% to Autism Spectrum Disorder (ASD) [60,70]; 3.7% to amyotrophic lateral sclerosis (ALS) [86]; 3.7% to Anorexia Nervosa (AN) [67]; 3.7% to bipolar disorder [82]; 3.7% to epilepsy [59]; 3.7% to insomnia [84]; and 3.7% to Tourette Syndrome (TS) [62].

Table 1: Human clinical studies of FMT as a therapeutic tool for neurological, psychiatric, and psychological disorders.

Study	Design type	Intervention	Donor	Receptor	Findings
He et al. [59]	Case report, pre- and post- intervention assessment.	Single FMT through mid-gut by gastroscopy.	Fresh fecal microbiota suspension from a fecal microbiota bank system.	A girl with CD and with a 17-year history of epilepsy.	- Decreased CD symptoms after 12 months. - The patient showed sustained improvement of her quality of life.
Kang et al. [60]	Open-label clinical trial with 8 week follow-up.	FMT treatment through oral and rectal administration, followed by orally maintenance for 7-8 weeks.	Standardized Human Gut Microbiota (SHGM).	N=18. Children with ASD. Age: 7-16 years old.	- FMT led to significant improvements in both GI- and ASD-related symptoms, and the improvements were sustained at least 8 weeks after the treatment. - Both microbiota and phage from the donors appear to have engrafted, at least partially, in the recipients.
Mizuno et al. [61]	Open-label nonrandomized study with 12 week follow-up.	Single FMT via colonoscopy.	Healthy relatives in second-degree relationship. Mean age: 52 years old.	N=10. Refractory IBS patients. Mean age: 40.1 years old.	- The HAM-D score significantly improved 4 weeks after FMT, but returned to the baseline level at 12 weeks. - GI symptoms significantly improved from before FMT to 12 weeks after. - Significant relationship between diversity and response to treatment at week 4, but not before treatment.
Zhao et al. [62]	Case report, pre- and post- intervention assessment.	Small intestine FMT via gastroscopy and via colonoscopy under anesthesia.	Healthy volunteers (between 10 and 40 years old).	A 9-year-old boy with TS.	- Eight weeks after treatment, total tic severity, motor severity and vocal severity scores decreased, shifting from severe to mild.
Kurokawa et al. [63]	Nonrandomized open label observational study.	Single FMT via colonoscopy.	Healthy relatives in second-degree relationship. Mean age: 51.4 years old.	N=17. IBS patients. Mean age: 43.41 years old.	- Significant improvement in HAMD, sleep subscale score, HAM-A, and QIDS, after FMT, even without GI symptoms improvement. - Significant increase in microbiome diversity after FMT.

Makkawi et al. [64]	Case report, pre- and post- intervention assessment, 10 years follow-up.	Single FMT infusion via rectal enema.	Feces of her partner.	A 61-year-old woman with MS.	- Improvements in functional system scores and in MMSFC scores over 10 years. - Resolution of *Clostridioides difficile* infection (CDI).
Mazzawi et al. [65]	Open-label pilot study.	Single duodenal FMT via gastroscopy.	Healthy donors (between 20 and 42 years old).	N=13. IBS patients. Mean age: 32 years old.	- Scores of IBS-QOL, EPQ-N-12 and HADS improved up to 28 weeks. - Patients' GM composition became similar to donors.
Cai et al [66]	Case report, pre- and post- intervention assessment.	Single FMT via gastroscopy.	6-year-old grandson.	Female MDD patient. Age: 79 years old.	- Six month after intervention PHQ-9 scores improved. - Increase in Bacillota members (family *Lachnospiraceae*) and decrease in Bacteroidota.
de Clerq et al. [67]	Case report, pre- and post- intervention assessment.	Single duodenal FMT.	Unrelated female with BMI of 25.	Female AN patient. Age: 26 years old.	- Increase in BMI post-intervention. - No significant changes in the GM composition.
Huang et al. [68]	Pre- and post- intervention assessment with a 1,3, and 6 months follow-up.	Two-three FMT via colonoscopy.	Healthy volunteers (between 8 and 35 years old).	N=30. Refractory IBS patients. Mean age: 44 years old.	- Improved IBS symptoms, and also depression and anxiety scores, 1 and 3 months post-FMT. - Increase in *Methanobrevibacter* and *Akkermansia* at the genus level at 1 month after FMT.
Huang et al. [69]	Case report, 3 months follow-up.	FMT via colonoscopy. A transendoscopic enteral tubing tube was inserted into the ileocecal junction through the endoscopy channel and fixed to the intestinal wall.	A healthy male college student. Age: 26 years old.	A 71-year-old PD patient with an intractable constipation.	- The patient successfully improved constipation. - The patient's tremor in legs almost disappeared at 1 week after FMT. - The relative abundance of *Lachnoclostridium, Dialister, Alistipes*, and members of *Ruminococcaceae* increased after 1 week; *Megamonas* increased after 1 month, and *Akkermansia* and *Faecalibacterium* increased after 3 months.
Kang et al. [70]	Longitudinal clinical trial with 2 years follow-up.	Same conditions of those described in Kang et al. (2017).	Same conditions of those described in Kang et al. (2017).	Same conditions of those described in Kang et al. (2017).	- Improvements in GI symptoms and autism-related symptoms after the end of the treatment. - Important changes in gut microbiota at the end of the treatment remained at follow-up, including significant increases in bacterial diversity and relative abundances of Bifidobacteria and *Prevotella*.
Xie et al. [71]	Case report, pre- and post- intervention assessment.	Six rounds of FMT via colonoscopy.	Healthy individual. Age: 22 years old.	An 86-year-old male patient with MDD and GI symptoms.	- Improved depressive symptoms. -Improved appetite, but not abdominal pain or distension. - Increased BMI.
Engen et al. [72]	Single arm, non-randomized, single-subject, longitudinal study.	Two FMT interventions on a single-subject over 12 months.	Taymount Clinic fecal preparations. (FMT implants of frozen liquid form).	A 48-year-old male with active RRMS.	- FMT interventions were associated with increased abundances of beneficial stool bacteria and short-chain-fatty-acid metabolites. -Increased/improved serum brain-derived-neurotrophic-factor levels and gait/walking metrics.
Hazan [73]	Case report, pre- and post- intervention assessment.	FMT infusion (per the Borody method) and follow-up at 2 and 6 months.	Stool from the patient's 85-year-old wife.	An 82-year-old man that presented recurrent CDI and AD.	- Following the procedure, the patient's CDI symptoms resolved, and repeated stool testing 2 months later was negative. - Six months post-FMT, the patient reported a marked improvement in mood; he was more interactive, and showed more expressive affect.
Johnsen et al. [74]	Double-blind, randomized controlled trial, parallel group.	FMT using health donors, or using patient's own feces, via colonoscopy.	Frozen or fresh feces from healthy donors.	N=85. IBS (non-constipated) patients. Age: between 18 and 75 years old.	- Clinical effect on IBS-QoL, and on fatigue, six months after the treatment.
Kilinçarslan & Evrense [75]	Experimental study, pre- and post- intervention assessment.	FMT suspension was infused into the patients through colonoscopy.	Healthy donors without neuropsychiatric or somatic diseases.	N=10. IBS patients. Mean age: 32.7 years old.	- The severity of anxiety, depression and obsession in IBD patients decreased after FMT. - Improvement of GI symptoms.
Xue et al. [76]	Preliminary clinical trial with 2 years follow-up.	FMT using health donors feces, via colonoscopy and nasoduodenal tube.	Healthy donors (between 18 and 24 years old).	N=15. PD patients. Age: 49-72 years old.	- Among 15 PD patients, there were 5 cases that had adverse events, including diarrhea, abdominal pain, and flatulence. - FMT could relieve the motor and the non-motor symptoms with acceptable safety in PD.

Kuai et al. [77]	A prospective single study.	FMT infusion through a nasoduodenal tube.	Frozen fecal microbiota obtained from the China FMT Bank.	N=11. PD patients. All the patients basically followed the traditional Chinese food structure (containing mainly grains and vegetables, and small amounts of meat) before and after the FMT treatment.	- Increased abundance of *Blautia* and *Prevotella* in PD patients after FMT, while the abundance of Bacteroidota decreased. - FMT improved the motor and the non-motor symptoms. - Constipation symptoms were reduced.
Park et al. [78]	Case report, pre- and post- intervention assessment.	Two rounds of FMT via colonoscopy.	Healthy donor (27-year-old man without GI symptoms).	A 90-year-old woman with AD, diabetes mellitus, hypertension, and chronic kidney disease. She was diagnosed with CDI in the hospital.	- Following the first FMT, her severe GI symptoms improved, and a stool test for CDI was negative. - One month after the first FMT, her cognitive functions slightly improved. - FMT improved cognitive function and daily living ability, such as the ADAS-cog or SIB.
Segal et al. [79]	Case report, pre- and post- intervention assessment.	Single FMT via colonoscopy.	A 38-year-old male and a 50-year-old male, both healthy.	N=6. PD patients. Mean age: 52 years old.	- Four weeks following the FMT, motor, non-motor and constipation scores were improved in 5 of 6 patients. At week 24, an improvement in motor scores, non-motor scores, and in constipation scores, were recorded in all patients.
Al et al. [80]	A pilot randomized controlled trial with a follow-up to 6 months.	FMT treatments administered via enema route.	Two donors were selected. Donor 1 provided FMTs to five patients, and donor 2 provided FMTs to four patients.	N=9. MS patients.	- FMT improved elevated small intestinal permeability. - The MS patients had lower bacterial alpha diversity than the healthy donors at baseline, and the diversity did not significantly change in the MS patients over time following multiple FMTs. - FMT decreased the MS-associated taxa *Blautia* and *Subdoligranulum*, and increased *Parabacteroides. Hungatella*, and *Phascolarctobacterium*.
Doll et al. [81]	Double-blind, placebo-controlled, randomized parallel-group design.	FMT capsules.	Two healthy donors.	Two female MDD patients Age: 50-60 years old.	- Symptoms of depression and of GI improved. - The FMT intervention revealed a different effect on the bacterial composition of the two patients. Patient 1 maintained the *Ruminococcus* enterotype over all time points; while patient 2 switched from the *Ruminococcus* to the *Bacteroides*-2 enterotype at 4 weeks post-intervention.
Parker et al. [82]	Case report.	Two high-dose treatments in a clinic; one via colonoscopy and the other via an enema. A second high-dose enema treatment was given on the second day. The remaining treatments were low-dose enemas completed at home.	Not established.	A 28-year-old male with bipolar II disorder.	- Improved hypomanic and bipolar symptoms.
Cheng et al. [83]	Randomized, placebo-controlled trial.	FMT capsules orally, or placebo capsules, once a week during 3 consecutive weeks.	Four healthy donors.	N= 26. Patients with moderate PD. Age: 30-86 years old.	-During the follow-up, no severe adverse effect was observed, and patients with FMT treatment showed significant improvement in PD-related autonomic symptoms compared with the placebo group. - FMT improved GI disorders. - *Blautia* spp., *Clostridiales bacterium*, *Clostridioides difficile*, *Clostridium* spp., *Eubacterium eligens*, *E. ventriosum*, and *Roseburia hominis*, correlated positively with GI performance and PD symptoms.
Fang et al. [84]	Observational study.	FMT treatments administered via the nasoduodenal route.	Healthy stool donors.	N= 17. Chronic insomnia patients. Mean age: 54.3 years old.	- FMT significantly ameliorated the ISI, PSQI, SAS and SDS. - The relative abundance of *Lactobacillus, Bifidobacterium, Turicibacter, Anaerostipes*, and *Eisenbergiella* significantly increased after FMT treatment. - *Eggerthella* may potentially serve as a distinctive genus associated with chronic insomnia.

Green et al. [85]	A pilot randomized controlled trial.	FMT treatments administered via enema route, and 26 weeks phone follow-up.	Active FMT enema comprised of syringes supplied by BiomeBank containing donor feces, normal saline, and 10% glycerol.	N=10. Moderate-severe MDD patients. Mean age: 47.2 years old.	- FMT treatment leads to improvements in GI symptoms and in quality of life, noting that IBS is commonly comorbid with MDD.
Lu et al. [86]	Case report, pre- and post- intervention assessment.	Washed microbiota transplantation (WMT) through a transendoscopic enteral tube during a 12 month follow-up.	WMT from Hospital of Nanjing Medical University (China).	A 48-year-old woman with ALS.	- Clinical symptoms and scores were improved by WMTs in the early stage. However, the evidence based on this period is not enough to confirm the role of WMT on ALS.

ADAS-cog: AD Assessment Scale-Cognitive Subscale; AD: Alzheimer's Disease; ALS: Amyotrophic Lateral Sclerosis; AN: Anorexia Nervosa; ASD: Autism spectrum disorder; BMI: Body mass index; CD: Crohn's disease; EPQ-N-12: Eysenck Personality Questionnaire-Neuroticism; GI: Gastrointestinal; HADS: Hospital Anxiety and Depression Scale; HAM-A: Hamilton Anxiety Rating Scale; HAM-D: Hamilton Depression Rating Scale; IBS: Irritable Bowel Syndrome; IBS-QOL: Irritable Bowel Syndrome-Quality of Life; ISI: Insomnia Severity Index; MDD: Major Depressive Disorder; MMSFC: Modified Multiple Sclerosis Functional Composite; MS: Multiple Sclerosis; QIDS: Quick Inventory of Depressive Symptomatology; PD: Parkinson's Disease; PHQ-9: Patient Health Questionnaire-9; PSQI: Pittsburgh Sleep Quality Index; RRMS: Relapsing-Remitting-Multiple-Sclerosis; SAS: Zung Self-Rating Anxiety Scale; SDS: Zung Self-Rating Depression Scale; SID: Severe Impairment Battery; TS: Tourette syndrome.

Discussion and future perspectives

FMT is not a procedure exempt of difficulties; in fact, it presents significant challenges regarding its application. Firstly, donor selection constitutes a critical step to ensure the safety and effectiveness of the FMT practice [86]. In this sense, potential donors, who are generally healthy individuals with no recent history of gastrointestinal infections, chronic diseases or prolonged use of antibiotics or other microbiota-disturbing substance, undergo a thorough clinical evaluation aimed at seeking infections and/or as conditions that could compromise the recipient's health (e.g., *C. difficile, Helicobacter pylori*, HIV, enterocolitis, or hepatitis); so any failure to detect an underlying condition in the donor can have serious consequences for the recipient. Furthermore, the need for such a rigorous approach limits the number of suitable donors, which can obliterate the availability of appropriate fecal samples and delay treatment for patients in need. Secondly, sample preparation for FMT is a meticulous process that requires strictly controlled conditions to guarantee the success of the treatment [87]. Once collected, the donor's stool is mixed with a sterile saline solution in order to first homogenize the suspension and later to filter it, removing large particles and unwanted materials, thereby obtaining a purified liquid solution containing the desired fecal microbiota. The main difficulty at this stage lies in maintaining an axenic environment and controlling possible contamination during sample handling and processing. Besides, it must be ensured that the concentration of microbiota is adequate for the treatment, complying with strict biosafety regulations to prevent any risk of infection. Thirdly, a number of delivery routes are in use for conducting FMT, which include upper gastrointestinal routes (i.e., nasogastric/nasojejunal tube, endoscopy), oral capsules, and lower gastrointestinal routes like retention enema, sigmoidoscopy, or colonoscopy [88]. These administration methods comprehend particularities that can be extremely uncomfortable and stigmatizing for patients, affecting both social acceptance and willingness to undergo treatment. Colonoscopy is the most common method; the fecal microbiota suspension is introduced directly into the recipient's colon. This procedure requires prior bowel preparation, similar to that performed before a diagnostic colonoscopy, which itself carries risks such as intestinal perforation, bleeding, and adverse reactions to sedation, demanding a highly trained clinical team and an adequate environment. The enema is another route of administration in which the fecal suspension is introduced into the patient's rectum using an enema bag or syringe. Although less invasive than colonoscopy, the enema may be less precise in terms of ensuring that microbiota reaches the most affected areas of the colon. Additionally, retention of the solution may be quite cumbersome for the patient, and there is a risk of infection if strict sterility standards are not followed. Oral capsules, in turn, represent a traditional (but not so recently used) FMT delivery, whose comparison with ancient coprophagic-related practices for medical purpose is inevitable [89]. These capsules are resistant to gastric acids and contain freeze-dried fecal microbiota. The main advantage of this method is the ease of administration and the relative reduction of discomfort for the patient. However, the production of these capsules is technically complex and expensive, since it requires that lyophilization and encapsulation do not compromise the viability of the bacteria. Additionally, long-term clinical outcomes are still being evaluated to confirm the effectiveness of this method. Thus, the idea of receiving an infusion of fecal material, whether through a colonoscopy, an enema, or even oral capsules, can generate repulsion and anxiety in the patients, exacerbated by the unfamiliarity and cultural taboos associated with excrement. These discomfort factors may not only discourage patients from opting for FMT, but may also affect their adherence to treatment and perception of its effectiveness. The social and personal reluctance towards these procedures highlights the urgent need for instructive campaigns to demystify the process, as well as to continue developing less invasive and more acceptable methods of administration (e.g., Washed Microbiota Transplantation [WMT]) [90]. Only by reducing stigma and by improving the patient experience it can be ensured that FMT reaches its full potential as a revolutionary and promising tool within the treatment of gastrointestinal diseases and mental disorders.

The interaction of the GM with risk factors for mental conditions, such as diet and stress in early life [91], suggests that interventions targeting the GM could be used as prophylactic or therapeutic tools for the symptoms of diverse brain disorders. In neuropsychiatric and psychological disorders, there is an imbalance in the GM homeostasis, which is characterized by changes in the microbial composition, diversity, and abundance of the microbiota [92]. For this reason, procedures to restore the GM homeostasis, such as FMT, may be a promising personalized, alternative, and/or adjunctive method to alleviate symptoms of neuropsychiatric and psychological disorders. FMT has been successfully used for the treatment of *C. difficile* infection,

and as a therapeutic tool in several gastrointestinal disturbances; however, its application for the treatment of mental conditions has been scarcely used. In this study, we have reviewed the application of FMT to several neurological, psychiatric, and psychological disorders, such as epilepsy, bipolar disorder, insomnia, AD, ALS, AN, ASD, MDD, MS, PD, and TS, with generally successful results (Table 1). However, several factors such as the cost of the TMF treatment, time and route of application, efficacy and tolerability, and especially safety and side effects, are limiting factors for a generalized clinical practice of this procedure. According to Borrego-Ruiz and Borrego [89], the FMT protocols currently used for neurological and mental disorders lack of standardization, since there is heterogeneity in the pretreatment, GM analysis, administration route and dose, choice of the fecal infusion, and selection of donors. In later sense, these authors suggested that to achieve this objective should be increased the number and quality of the feces banks, such as OpenBiome and the Netherlands Donor Feces Bank, and should be encouraged their operating at the institutional level, both nationally and internationally.

Other important limitations of human studies of FMT are related to the study design, FMT procedures, follow-up, and control groups. Double-blinded interventions with a control group would be desirable, as would the possibility of publication bias, especially in case reports. Regarding the reported efficacy of FMT, a potential difficulty may be the disease severity fluctuation that occurs in brain disorders; therefore, longitudinal interventions may be most appropriate to evaluate outcomes in neurodegenerative diseases, such as AD or PD. For other of the neurological and mental disorders examined in this review, the results of microbiota analyses present a high heterogeneity, which may be due to the sample collection, DNA extraction and sequencing methods used, and the influence of confounding factors (medications, diet, and age) [93].

However, there are still questions to be answered in the near future. For example, the mechanisms involved in the efficacy of this treatment are unknown, since the content of FMT is complex, including viable and inactivated bacteria, as well as other microorganisms integrated in the virome and in the mycobiome, in addition to chemical metabolites (bile acids, SCFAs, proteins), but it is not known which specific components are necessary for the therapeutic efficacy of FMT. In recent years, FMT technology has evolved, and alternatives have opened up new perspectives on the use of this procedure for the treatment of recurrent infections by *C. difficile* infections: the Washed Microbiota Transplantation (WMT) [90] and the spore transplantation [94]. Preclinical studies have shown that WMT is a safer and a more accurate method with a higher control of quality than the use of FMT with untreated fecal matter. The purified ethanol-treated feces (SER-109) from the Bacillota phylum [95] has already been used in the United States as a new strategy, but comparative controlled studies of these techniques have not yet been conducted, nor have their possible long-term side effects been investigated.

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