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Review Article

Promising Role of FMT in Schizophrenia Therapeutics

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Abstract

Schizophrenia is the resultant of the cumulative effect of a complex and dynamic bidirectional interaction of genetic expression and the accumulation of prenatal and postnatal environmental risk factors. Earlier treatments for schizophrenia include cognitive behavioral therapy (CBT), which can help people learn how to avoid acting on their thoughts. FMT is likely to strongly improve the efficacy of microbiota-orientated treatments. FMT is a promising treatment for schizophrenia and other psychiatric disorders that may help improve symptoms and restore behavioral impairments: FMT helps to restore the recipient's gut microbiota and reverse dysbiosis. Current FMT is still a relatively new area of research, and there are several limitations to the current evidence

Keywords

Neurodevelopmental Disorder, Cognitive Behavioral Therapy, Antipsychotics.

Introduction

Schizophrenia is a heterogeneous neurodevelopmental disorder of unknown aetiology; identified by a collection of signs and symptoms, predominantly defined by signs of psychosis [1] In its most common form, schizophrenia presents a paranoid delusions and auditory hallucinations late in adolescence or in early adulthood. This disorder is the resultant of the cumulative effect of a complex and dynamic bidirectional interaction of genetic expression and the accumulation of prenatal and postnatal environmental risk factors [2]. The development of the neural circuitry underlying social, cognitive and emotional domains requires precise regulation from molecular signalling pathways, especially during critical periods, when the brain is particularly sensitive to the influence of environmental input signalling [3].

The first episode of psychosis is important to recognize the symptoms of schizophrenia usually diagnosed between the ages of 16 and 30 fortunately rare in younger children. However, research evidences shows that gradual changes in thinking, mood, and social functioning often appear before the first episode of psychosis. Though, the expression of this disorder can differ from person to person, but they generally fall into three main categories: psychotic, negative, and cognitive [4].

However, as such studies are limited in their ability to provide knowledge that can be used to develop preventative interventions, it is important to shift the focus to individuals with increased vulnerability for psychosis (i.e., high-risk groups). Current treatments for schizophrenia focus on helping people manage their symptoms, improve day-to-day functioning, and achieve personal life goals, such as completing education, pursuing a career, and having fulfilling relationships. Patients who get regular psychosocial treatment are less likely to have symptoms reoccur. Patients receiving antipsychotics such as high-potency first-generation antipsychotics, clozapine, or quetiapine should undergo proper evaluation and intervention to minimize the disease burden and life-threatening outcomes of treatment. However, the risk of gastrointestinal hypomotility (GIHM) with the use of antipsychotic medications in patients with schizophrenia remains inadequately recognized. The aim of this study was to explore the incidence of GIHM and its risks in patients with schizophrenia treated with antipsychotics [5].

Promising role of FMT in treatment

Microbiology and neuroscience have converged to understand the role of microbes in brain development and function and the imbalance of the gut microbiota responsible for the prognosis of many human diseases. The gut microbiota plays an important role of in the pathophysiology of neurodegenerative disorders shown by us as well by many other authors [6-10] implying

that alteration of the gut microbiota serves as a most effective treatment strategy.

In the recent past due to technical advancement to study the microbial system enough proof for its link to human health has been accumulated. The administration of specific lactic acid bacteria strains (*Lactobacillus* and *Bifidobacterium*), or those combined with vitamin D and selenium, maintain the integrity of the gut flora, preventing antagonistic effects including inflammation, antipsychotic-related body weight gain (olanzapine) and other metabolic dysfunctionalities was in vogue. But later it was found that there are multiple antipsychotics that exert a potent effect upon gut flora, influencing a plethora of pathways and creating a dysbalance ratio between beneficial and opportunistic pathogens as well [11]. Among the thousands of new human microbiome species discovered *Firmicutes*, *Actinobacteria*, and *Bacteroidetes* dominate, with lower relative abundances of *Verrucomicrobia* and *Proteobacteria* at phylum level dominated in faecal samples [12]. Some are beneficial for example *Bacteroides fragilis* corrects gut permeability, alters microbial composition, and ameliorates defects in communicative, stereotypic, anxiety-like and sensorimotor behaviours [13] and some are observed to be the causal factor for many diseases in humans.

Prognosis for schizophrenia

The intricate microbial signalling system communicating with the brain via the vagus nerve, immune system, enteric nervous system, enteroendocrine signalling and production of microbial metabolites, such as short-chain fatty acids are involved in the prognosis of nerve disorders. Scientific based evidences as well clinical data demonstrates that microbiota-gut-brain MGB axis signalling influences the neurotransmission, neurogenesis, myelination, dendrite formation and blood brain barrier development, modulating cognitive function and behaviour patterns, such as, social interaction, stress management and locomotor activity.In addition, altered gut microbiota profiles in schizophrenia has been observed.

A large epidemiological study (n = 1,015,447), showed that treatment with anti-infective agents such as antibiotics were found to increase the risk of developing schizophrenia by a hazard rate ratio of 1.37. Alteration in the immune system along with pathogen exposure may amplify susceptibility to schizophrenia [13].

PET studies shows that subjects at high risk of psychosis, and as well as schizophrenia patients had altered microglial activation compared to healthy controls. The gut microbiota has the capability to involve in the maturation and activation of microglia in the brain [14,15].

Stress can reshape gut microbiota composition and alter gut barrier permeability. Preclinical evidence suggests that the gut microbiota signature acquired and maintained during the pivotal early developmental stage may also affect stress sensitivity and may turn to be a causal factor for the development of this disorder [13].

Fecal microbiota transplantation (FMT) is currently the most effective gut microbiota intervention and an accepted treatment for recurrent *Clostridioides difficile* infections. To evaluate indications of FMT for patients with neurological disorders, we summarized the available literature on FMT. In addition, we provide suggestions for future directions.

Dysregulation of synaptic structure and function is also responsible for the development of schizophrenia since, the gut microbiota plays a role in developmental programming of the brain, specifically, synapse maturation and synaptogenesis. Reduced levels of synaptophysin a marker of synaptogenesis have been demonstrated in the cerebral cortex of post-mortem samples from schizophrenia subjects [16].

Dopaminergic dysfunction is a key manifestation of psychotic symptoms (hallucinations and delusions). A primary circuit involved in psychosis includes the thalamus and prefrontal cortex feeding into the associative striatum. Preclinical studies using germ free (GF) rodents, antibiotics and probiotics have given evidence that dopaminergic circuits are sensitive to changes in gut microbes. Preclinical studies, suggests that the dopaminergic system, is having a direct relevance to the pathophysiological path to of psychosis, is under the partial influence of the gut microbiota. The risk factors associated with psychotic disorders and its association with the gut microbiota has been listed earlier [13].

Gut microbiome transfer from individuals with schizophrenia to GF mice modulated the glutamate-glutamine-GABA cycle associated with increased responses and locomotor hyperactivity [17]. Glutamate-glutamine-GABA cycle known to be dysfunctional in schizophrenia [18] and was increased in the hippocampus in GF mice that received the FMT from schizophrenia patients [17].

Neurotrophin a brain-derived neurotrophic factor is a key regulator of synaptic strengthening and pruning, maintaining appropriate levels of BDNF and other neurotrophins, especially during critical neurodevelopmental windows is vital for schizophrenia. In addition preclinical studies show that BDNF levels are influenced by the gut microbiota [13].

Serotonin (5-HT)

The indolamine 5-HT has a wide range of physiological functions, including anxiety and fear modulation, stress responsivity, reward, cognition and social behaviour. Results of a meta-analysis of post-mortem schizophrenia studies found an elevation in prefrontal 5-HT1A receptors and a reduction in prefrontal 5-HT2A receptors [19].

Short chain fatty acids (butyrate, acetate and propionate SCFA's) a bacterial metabolites, has the capability to reach the circulation, cross the BBB and have a wide range of physiological functions. These metabolites can increase tryptophan hydroxylase 1 transcription, the rate limiting for mucosal 5-HT synthesis in chromaffin cell cultures and increase colonic and blood 5-HT in GF mice. Under normal physiological conditions, approximately 99% of tryptophan is metabolized to kynurenine in the liver

by tryptophan-2,3-dioxygenaseTDO. In schizophrenia patients indoleamine 2,3-dioxygenase IDO induce the metabolism of tryptophan along the kynurenine pathway. Abnormal Kynurenic acid (KYNA) KYNA levels are implicated in the pathophysiology of schizophrenia and microbial regulation of this pathway is emerging as an important objective in schizophrenia research [13].

The efficacy of *Faecalibacterium*, *Coprococcus* and *Bacteroide*s for producing short-chain fatty acids (SCFAs), which exhibit important anti-inflammatory effects in the host's inflammatory response has been identified earlier was found to be less in these patients. Therefore, the decrease in SCFAs-producing bacteria and the increase of pro-inflammatory bacteria may be involved in the inflammatory response in patients with SCZ [20].

The negative impact of urbanization is also associated with an increased risk of immune and metabolic disorders, obesity as well as reducing microbial diversity and impacting the overall functionality of the gut microbiome. From a recent study migration from a non-Western country to the United States was associated with immediate loss of gut microbiome diversity and function liking. Earlier migration was observed to have a close link with higher rates of schizophrenia.

Bacterial enzymes associated with plant fiber degradation, and a displacement of *Prevotella* with *Bacteroides* strains occurs over time was linked with the elevated incidence of this disorder [21]. Zheng and colleagues [22] showed that individuals with schizophrenia had reduced gut microbiota alpha diversity compared to healthy controls advocating the concept that a more diverse ecosystem may be a health promoting factor [22].

Impaired social cognition is just one of the multiple cognitive domains that are witnessed in schizophrenia. During neurodevelopment cognitive activity is modulated by microbiota and its metabolic outputs such as combination of acute stress and infection [23].Neruroscientist have observed the reduced Hippocampal volume which takes the responsibility of a pivotal process in learning and memory consolidation during neurogenesis. It is interesting to observe that this role played by Hippocampus regulated by the gut microbiota, mediated at least partially via the vagus nerve. Patients with schizophrenia (n = 63) had lower alpha (within-sample) diversity compared to healthy controls (n = 69), and that several species *ccaceae*, *Bifidobacteriaceae*, *Brucellaceae*, *Pasteurellaceae*, and *Rikenellaceae*) reportedly discriminated individuals from healthy controls [22]. Zheng, P. *et al.,* 2019 [22] gave a clue from their studies in GF mice that received the FMT from a random sample of five schizophrenia patients that gut microbiota has an influence over amino acid pathways in schizophrenia (discussed above) was well as altered lipid metabolism in serum and hippocampus. Kelly *et al.,* [13] has given a consolidated report of the Microbiota and clinical schizophrenia studies. Zhu *et al*.[24] transferred fecal microbiota from drug-free SCZ patients into pathogen-free models and to their surprise abnormal phenotypic peculiarities, such as psychomotor hyperactivity, alongside impaired memory and learning capacity, were noted [24].He *et al*., [25] observed increased abundances of *Clostridiales*, *Prevotella* and *Lactobacillus ruminis,* in fecal samples, in an ultra-high-risk (UHR) group (n = 19) compared to healthy controls. In people diagnosed with FEP(FEP: First Episode Psychosis,) (n = 28), who were medicated with antipsychotics, harboured significantly increased *Lactobacillaceae* and decreased *Veillonellaceae* at the family level and increased *Lactobacillus* at the genus level compared to healthy controls (n = 16). The authors also observed that the number of *Lactobacillus* group correlated positively with severity of psychotic symptoms measured using the Brief Psychiatric Rating Scale, but negatively with global assessment of functioning scale. *Lactobacilli* and *Lactobacilli phage phiadh* were also found in greater abundances in the oropharyngeal microbiome in people diagnosed with schizophrenia [25].

In SCZ patients, Bifidobacterium, Blautia and Shigella were mainly dominated in gut microbiome while Faecalibacterium, Blautia and Roseburia were mainly dominated in gut microbiome of healthy control. In addition,only two genera including Shigella and Collinsella were increased, while eight genera including *Faecalibacterium, Coprococcus, Prevotella, Haemophilus, Ruminococcaceae_Ruminococcus, Bacteroides, Oscillospira and Alistipes* were depleted in SCZF Compared with HCF [26]. Moreover, it has been reported that *Collinsella* and *Escherichia-Shigella* mainly exhibit pro-inflammatory effects in various disease [27].

The efficacy of *Faecalibacterium, Coprococcus* and *Bacteroides* for producing short-chain fatty acids (SCFAs), which exhibit important anti-inflammatory effects in the host's inflammatory response has been identified earlier. Furthermore, we analyzed the correlation of predicted Differential metabolism pathway correlated with gut bacteria studies prove that twelve metabolism pathways were significantly associated with the relative *abundances Nesterenkonia, Bacteroides, Acinetobacter, Shigella, Burkholderia, Brevundimonas, Pseudomonas, Agrobacterium, Cupriavidus,* and *Acidovorax* From MetagenomeSeq analysis significant enriched species belonging to Bifidobacterium, Collinsella, Blautia, Shigella, and Acinetobacter at the genus level were observed [26].

Szeligowski et al.,[28] has given a consolidated report of the complete taxa of the microme based on 6 studies implicating dysbiosis in schizophernia in humans. Class Clostridia was found to be enriched as a whole to be in schizophrenia [28]. A significant elevation of Lactobacilli in schizophrenia and higher risk group for this disorder is perplexing because are common components of probiotics, thought to confer benefits for mental health [29].

Oral administration of organisms such as,prebiotic, probiotic, or synbiotic, and especially the treatment with fecal microbiota transplantation (FMT), are methods still in their early research phase for patients with psychiatric disorders, therefore an exploration of data regarding the potential benefits and adverse events of FMT is worth consideration. Vasiliu [30] has reviewed seven clinical trials, 16 preclinical studies, three meta-analyses/ systematic reviews, and six case reports, all of these representing

ten distinct categories of psychiatric disorders or manifestations. According to him clinical trials with sound methodology and more participants are needed to clarify FMT's benefits and risks in psychiatric disorders are dispensable to standardise as well as advocate FMT in therapeutics [30-33].

In summary cleaning up the gut microbiota by transplanting a totally new human gut microbiota in one shot in FMT, is likely to strongly improve the efficacy of microbiota-orientated treatments in schizophrenia and maintain the effect over time. Collectively, these studies suggest that subtle alterations in gut microbiota acquisition and development, by regulating neuro-inflammatory processes, may act as additional vulnerability factors that predispose to schizophrenia. However, if future studies confirm that dysbiosis predicts schizophrenia, then it could link a number of observations in schizophrenia patients, such as raised inflammatory markers or altered brain-derived neurotrophic factor and kynurenate levels, and thus contribute to the increasingly complex picture of its etiology and improve FMT in treatment.

References

1. Insel T. Rethinking schizophrenia. Nature. 2010; 468: 187-193.
2. Wahbeh MH, Avramopoulos D. Gene-Environment Interactions in Schizophrenia: A Literature Review. Genes (Basel). 2021; 12(12): 1850.
3. Howes OD, Bukala BR, Beck K. Schizophrenia: from neurochemistry to circuits, symptoms and treatments. Nat Rev Neurol. 2024; 20(1): 22-35.
4. Developmental Mechanisms and Trajectories of National Institute of Mental Health (NIMH) (.gov) https://www.nimh.nih.gov › about › organization › dtr *Branch* Programs. Risk *and* Early Onset *of* Psychosis Spectrum Disorders. Attention Deficit, Disruptive Behaviors, and *Disorders* of Behavioral Dysregulation.
5. Grant RK, Brindle WM, Donnelly MC, McConville PM, Stroud TG, Bandieri L, et al. Gastrointestinal and liver disease in patients with schizophrenia: A narrative review. World J Gastroenterol. 2022; 28(38): 5515-5529.
6. Gupta PD, Pushkala K. Fecal Transplant Technology: An Effective Therapeutic Method for Many Diseases. J Clinical and Medical Case Reports and Reviews. 2023; 2(2).
7. Pushkala K. Faecal transplant technology in therapeutics of Alzheimer's. J Cell Tissue Res. 2023; 23(20): 73-7325.
8. Pushkala K, Gupta PD. Management of Huntington's disease by Faecal Microbiota Transplant (FMT) Technology. J Infect Dise Treat. 2023; 1(1): 1-3.
9. Pushkala K, Gupta PD. Faecal microbiota transplantation (FMT): An effective therapeutic agent for Parkinson's disease. J New Medical Innovations and Research. 2023; 4(4).
10. Pushkala K, Gupta PD. Promising role of Faecal transplant therapy on Sclerosis. Clinical Trials and Case Studies. 2024; 3:5.
11. Nita IB, Ilie OD, Ciobica A, Hritcu LD, Dobrin I, Doroftei B, et al. (2022). Reviewing the Potential Therapeutic Approaches Targeting the Modulation of Gastrointestinal Microflora in Schizophrenia. Int J Mol Sci. 23(24): 16129.
12. Zhernakova A, Kurilshikov A, Bonder MJ, Tigchelaar EF, Schirmer M, Vatanen T, et al. Population-based metagenomics analysis reveals markers for gut microbiome composition and diversity. Science. 2016; 352(6285): 565-569.
13. Kelly JR, Minuto C, Cryan JF, Clarke G, Dinan TG. The role of the gut microbiome in the development of schizophrenia. Schizophr Res. 2021; 234: 4-23.
14. Bloomfield PS, Selvaraj S, Veronese M, Rizzo G, Bertoldo A, Owen DR, et al. Microglial Activity in People at Ultra High Risk of Psychosis and in Schizophrenia: An [(11)C]PBR28 PET Brain Imaging Study. Am J Psychiatry. 2016; 173(1): 44-52.
15. van Berckel BN, Bossong MG, Boellaard R, Kloet R, Schuitemaker A, Caspers E, et al. Microglia activation in recent-onset schizophrenia: a quantitative (R)-[11C]PK11195 positron emission tomography study. Biol Psychiatry. 2008; 64(9): 820-822.
16. Hu W, MacDonald ML, Elswick DE, Sweet RA. The glutamate hypothesis of schizophrenia: evidence from human brain tissue studies. Ann N Y Acad Sci. 2015; 1338(1): 38-57.
17. Zheng P, Zeng B, Liu M, Chen J, Pan J, Han Y, et al. The gut microbiome from patients with schizophrenia modulates the glutamate-glutamine-GABA cycle and schizophrenia-relevant behaviors in mice. Sci Adv. 2019; 5(2): eaau8317.
18. Schmidt MJ, Mirnics K. Neurodevelopment, GABA system dysfunction, and schizophrenia. Neuropsychopharmacology. 2015; 40(1):190-206.
19. Selvaraj S, Arnone D, Cappai A, Howes O. Alterations in the serotonin system in schizophrenia: a systematic review and meta-analysis of postmortem and molecular imaging studies. Neurosci Biobehav Rev. 2014; 45: 233-245.
20. He Y, Kosciolek T, Tang J, Zhou Y, Li Z, Ma X, et al. Gut microbiome and magnetic resonance spectroscopy study of subjects at ultra-high risk for psychosis may support the membrane hypothesis. Eur Psychiatry. 2018; 53:37-45.
21. Vangay P, Johnson AJ, Ward TL, Al-Ghalith GA, Shields-Cutler RR, Hillmann BM, et al. US Immigration Westernizes the Human Gut Microbiome. Cell. 2018; 175(4): 962-972.e10.
22. Zheng P, Zeng B, Liu M, Chen J, Pan J, Han Y, et al. The gut microbiome from patients with schizophrenia modulates the glutamate-glutamine-GABA cycle and schizophrenia-relevant behaviors in mice. Sci Adv. 2019; 5(2): eaau8317.

23. Kelly JR, Minuto C, Cryan JF, Clarke G, Dinan TG. The role of the gut microbiome in the development of schizophrenia. Schizophr Res. 2021; 234: 4-23.

24. Zhu F, Guo R, Wang W, Ju Y, Wang Q, Ma Q, et al. Transplantation of microbiota from drug-free patients with schizophrenia causes schizophrenia-like abnormal behaviors and dysregulated kynurenine metabolism in mice. Mol Psychiatry. 2020; 25(11): 2905-2918.

25. He Y, Kosciolek T, Tang J, Zhou Y, Li Z, Ma X, et al. Gut microbiome and magnetic resonance spectroscopy study of subjects at ultra-high risk for psychosis may support the membrane hypothesis. Eur Psychiatry. 2018; 53: 37-45.

26. Wei N, Ju M, Su X, Zhang Y, Huang Y, Rao X, et al. Transplantation of gut microbiota derived from patients with schizophrenia induces schizophrenia-like behaviors and dysregulated brain transcript response in mice. Schizophrenia (Heidelb). 2024; 10(1): 44.

27. Liang T, Li D, Zunong J, Li M, Amaerjiang N, Xiao H, et al. Interplay of Lymphocytes with the Intestinal Microbiota in Children with Nonalcoholic Fatty Liver Disease. Nutrients. 2022; 14(21): 4641.

28. Szeligowski T, Yun AL, Lennox BR, Burnet PWJ. The Gut Microbiome and Schizophrenia: The Current State of the Field and Clinical Applications. Front Psychiatry. 2020; 11: 156.

29. Schwarz E, Maukonen J, Hyytiäinen T, Kieseppä T, Orešič M, Sabunciyan S, et al. Analysis of microbiota in first episode psychosis identifies preliminary associations with symptom severity and treatment response. Schizophr Res. 2018; 192: 398-403.

30. Vasiliu O. Is fecal microbiota transplantation a useful therapeutic intervention for psychiatric disorders? A narrative review of clinical and preclinical evidence. Curr Med Res Opin. 2023; 39(1): 161-177.

31. Shen Y, Xu J, Li Z, Huang Y, Yuan Y, Wang J, et al. Analysis of gut microbiota diversity and auxiliary diagnosis as a biomarker in patients with schizophrenia: A cross-sectional study. Schizophr Res. 2018; 197: 470-477.

32. Castro-Nallar E, Bendall ML, Pérez-Losada M, Sabuncyan S, Severance EG, Dickerson FB, et al. Composition, taxonomy and functional diversity of the oropharynx microbiome in individuals with schizophrenia and controls. PeerJ. 2015; 3: e1140.

33. Xu HM, Huang HL, Zhou YL, Zhao HL, Xu J, Shou DW, et al. Fecal Microbiota Transplantation: A New Therapeutic Attempt from the Gut to the Brain. Gastroenterol Res Pract. 2021; 2021: 6699268.