Chapter 9

Microbiome-Based Interventions for Mental Health – Evidence and Clinical Trials

As research continues to uncover the strong link between the gut and brain, clinical trials are increasingly investigating microbiome-focused therapies—such as probiotics, prebiotics, dietary changes, and fecal microbiota transplantation—as potential treatments for mental health conditions. These interventions aim to restore microbial balance and influence brain function through the gut-brain axis.

This chapter delves into a growing body of research that supports the use of microbiome-based interventions as a promising avenue for addressing various mental and neurological health challenges. It carefully examines **key preclinical and clinical studies** that explore how therapies such as **probiotics, prebiotics, psychobiotics, dietary modifications, and fecal microbiota transplantation (FMT)** can influence the **gut–brain axis** and, in turn, impact brain function and emotional well-being.

In conditions such as **depression and anxiety**, studies have shown that modulating the gut microbiota can lead to measurable improvements in mood, stress resilience, and emotional regulation. These benefits are thought to arise through multiple mechanisms, including **reduced systemic inflammation**, **improved gut barrier function**, and **enhanced neurotransmitter production**. In the case of **cognitive decline**, especially in aging populations or those with neurodegenerative diseases, emerging evidence suggests that restoring microbial balance may help preserve cognitive function, slow disease progression, and reduce neuroinflammation.

By synthesizing these findings, the chapter highlights the **therapeutic potential** of microbiota-targeted approaches—not as standalone treatments, but as valuable adjuncts to conventional pharmacological and psychotherapeutic interventions. It also underscores the importance of **personalized strategies**, given individual variability in microbiome composition and response

to treatment. Overall, this chapter aims to illuminate how **gut microbiome modulation** is reshaping our understanding and treatment of psychological and neurological disorders.

9.1 Major Depressive Disorder (MDD)

Depression is the most widely studied psychiatric condition in microbiome-related trials.

It has emerged as the most extensively researched psychiatric disorder in the context of **microbiome-related clinical and preclinical trials**. This is largely due to the growing recognition of the **gut–brain axis** as a key player in mood regulation and emotional health, as well as the limitations of current antidepressant therapies, which are not always effective and can have significant side effects.

Multiple studies have demonstrated that individuals with depression often exhibit **gut dysbiosis**, characterized by **reduced microbial diversity** and a decline in beneficial bacteria such as *Bifidobacterium* and *Lactobacillus*. These microbial imbalances are thought to contribute to depression through several mechanisms, including **increased gut permeability**, **systemic inflammation**, and **altered neurotransmitter production**, particularly serotonin and GABA. The **kynurenine pathway**, influenced by gut microbes and inflammatory signals, has also been implicated in the pathophysiology of depression.

Clinical trials using **probiotics**—often referred to as **psychobiotics** when used for mental health—have shown promising results in reducing depressive symptoms. Strains like *Lactobacillus helveticus* and *Bifidobacterium longum* have been associated with improvements in mood, reductions in stress hormone levels (e.g., cortisol), and enhanced emotional regulation. Additionally, **dietary interventions** such as the Mediterranean diet, which supports a healthier microbiome, have been linked to lower rates of depression.

Because of its high prevalence, substantial global burden, and well-documented connection with gut health, depression continues to be a central focus of research into microbiome-based therapies. These investigations are paving the way for **novel, adjunctive treatment approaches** that target the microbiota to enhance mental well-being and treatment outcomes.

9.1.1 Clinical Evidence

- **Meta-analyses** have shown a statistically significant reduction in depressive symptoms among patients receiving **probiotic supplementation** compared to placebo[1].

- Adouble-blindRCTinvolving *Lactobacillushelveticus* and *Bifido bacterium longum* demonstrated improvements in mood, anxiety scores, and cortisol regulation[2].

- Prebiotic supplementation with **galactooligosaccharides (GOS)** in healthy individuals reduced **negative emotional bias** and improved attention[3].

9.1.2 Mechanisms

- Enhancement of **neurotransmitter production**, especially serotonin and GABA

- Reduction in **pro-inflammatory cytokines**

- Increased **short-chain fatty acid (SCFA)** production improving neuroplasticity

9.2 Anxiety Disorders

9.2.1 Human Studies

- In patients with **generalized anxiety disorder (GAD)**, probiotic use for 8 weeks led to significant reductions in Hamilton Anxiety Rating Scale (HAM-A) scores[4].

- Fermented foods intake was associated with **lower social anxiety symptoms** in young adults in observational studies**[5]**

9.2.2 Animal Studies

- Germ-free mice exhibit heightened anxiety-like behaviors, which are reversed by recolonization with normal microbiota**[6]**

- Specific *Lactobacillus* strains upregulate **GABA receptor expression** in brain regions associated with fear and emotion**[7]**

9.3 Cognitive Impairment and Neurodegeneration

- A 12-week trial of a **multispecies probiotic** in Alzheimer's patients showed improvements in **Mini-Mental State Examination (MMSE)** scores and metabolic profiles[8].

- Fecal Microbiota Transplantation (FMT) in AD animal models reduced amyloid plaque formation and improved spatial learning[9].

9.4 Autism Spectrum Disorder (ASD)

Children with **Autism Spectrum Disorder (ASD)** often experience a range of **gastrointestinal (GI) symptoms**, including constipation, diarrhea, abdominal pain, bloating, and irregular bowel habits. These digestive issues are reported more frequently in children with ASD than in neurotypical peers, and their presence is often associated with increased behavioral challenges, such as irritability, anxiety, and sleep disturbances.

Growing evidence suggests that these GI symptoms are not isolated but are closely linked to **alterations in the gut microbiota**, the community of microorganisms residing in the digestive tract. Studies have found that children with ASD tend to have **reduced microbial diversity** and an imbalance in specific bacterial groups—such as **lower levels of *Bifidobacterium*** and **higher levels of potentially harmful species like *Clostridium* and *Desulfovibrio***. These microbial imbalances may affect gut permeability, immune activation, and the production of neuroactive compounds, such as short-chain fatty acids and neurotransmitter precursors.

This dysregulated gut environment may contribute to the neurological and behavioral features of ASD through the **gut–brain axis**, a bidirectional communication system linking the gastrointestinal system and the central nervous system. As a result, the gut microbiota is increasingly being explored as a potential therapeutic target in ASD, with interventions such as **probiotics**, **prebiotics**, **dietary changes**, and **fecal microbiota transplantation (FMT)** being studied for their potential to improve both GI and behavioral symptoms in affected children.

9.4.1 FMT Trials

- A landmark study called **MIRACLE (Microbiota Transfer Therapy)** showed sustained improvements in GI symptoms, social behavior, and communication up to two years post-FMT in children with ASD[10].

9.4.2 Probiotics

- Supplementation with *Lacto bacillus plantarum* improved **language skills and stereotypic behavior** in ASD children[11].

9.5 Bipolar Disorder and Schizophrenia

• Preliminary **pilot studies involving patients with bipolar disorder** have provided early but promising evidence supporting the role of probiotics in improving mental health outcomes. One notable finding is that the use of **probiotic supplements** was associated with a **reduction in hospital readmission rates over a 6-month period**. These studies typically involved patients who were recently discharged after a manic or depressive episode and were receiving standard psychiatric care, including medication.

The addition of specific probiotic strains—often from the *Lactobacillus* and *Bifidobacterium* genera—appeared to stabilize mood and reduce the risk of relapse, which is a significant concern in the long-term management of bipolar disorder. The proposed mechanisms include modulation of the **gut–brain axis**, reduction in **systemic inflammation**, enhancement of **intestinal barrier integrity**, and regulation of **stress-response pathways**, including the hypothalamic–pituitary–adrenal (HPA) axis.

Although these findings are preliminary and based on small sample sizes, they highlight the potential of **adjunctive microbiome-based therapies** in reducing the burden of severe psychiatric conditions and improving long-term treatment outcomes. Larger, controlled clinical trials are needed to confirm these effects and determine optimal strains, dosages, and treatment durations.[12]

• Emerging research has shown that **individuals with schizophrenia** often present with **distinct alterations in their gut microbiota** compared to healthy individuals. These changes typically include **reduced microbial diversity** and imbalances in specific bacterial populations, such as decreased levels of *Lactobacillus* and *Bifidobacterium*, alongside increased levels of potentially pro-inflammatory or pathogenic species. These microbial shifts may contribute to systemic inflammation, oxidative stress, and neurotransmitter dysregulation—factors that are believed to play a role in the pathophysiology of schizophrenia.

• Importantly, several **pilot studies and small-scale clinical trials** have begun to explore the therapeutic potential of **probiotics as an adjunct treatment** for schizophrenia. Some of these studies have reported modest but meaningful improvements

in **cognitive function**, including better attention, memory, and executive functioning, following **probiotic supplementation**. These cognitive improvements are especially significant given that cognitive deficits are a core, treatment-resistant feature of schizophrenia that greatly impacts daily functioning and quality of life.

• The underlying mechanisms by which probiotics may influence cognition in schizophrenia likely involve **modulation of the gut-brain axis**, reduction in **systemic and neuroinflammation**, **enhanced gut barrier function**, and potential changes in **neurotransmitter availability**, particularly dopamine and glutamate, which are central to schizophrenia pathology.

• While these findings are encouraging, larger, well-controlled studies are needed to confirm the efficacy and safety of specific probiotic strains in improving cognitive outcomes and overall symptom management in schizophrenia. Nonetheless, this line of research highlights the promising role of the gut microbiome in understanding and treating complex psychiatric disorders. [13].

9.6 Limitations of Current Trials

Despite promising results, clinical evidence has limitations:

- **Small sample sizes and short durations**
- **Heterogeneity in strains, dosages, and endpoints**
- **Lack of microbiome sequencing** in most studies to personalize interventions
- **Placebo effect** may influence subjective mood assessments

9.7 Ongoing and Future Trials

- **NIH-funded trials** are underway to test microbiota-targeted therapies for depression and Alzheimer's
- **Precision probiotics** are being developed based on individual microbiota profiles
- **Psychedelic-assisted therapy** may also modulate microbiota indirectly via immune and neural pathways

References (Vancouver Style)

1. Huang R, Wang K, Hu J. Effect of probiotics on depression: a systematic review and meta-analysis of randomized controlled trials. Nutrients. 2016;8(8):483.

2. Messaoudi M, Violle N, Bisson JF, Desor D, Javelot H, Rougeot C. Beneficial psychological effects of a probiotic formulation (*Lactobacillus helveticus* and *Bifidobacterium longum*) in healthy volunteers. Gut Microbes. 2011;2(4):256–61.

3. Schmidt K, Cowen PJ, Harmer CJ, Tzortzis G, Errington S, Burnet PW. Prebiotic intake reduces the waking cortisol response and alters emotional bias in healthy volunteers. Psychopharmacology. 2015;232(10):1793–801.

4. Reiter A, Baumeister D, Hohmann N, Bengel J, Michalsen A, Dobos G, et al. Effects of probiotics on mental health and hypothalamic-pituitary-adrenal axis: a randomized, double-blind, placebo-controlled trial in healthy volunteers. Eur Arch Psychiatry Clin Neurosci. 2020;270(5):517–28.

5. Hilimire MR, DeVylder JE, Forestell CA. Fermented foods, neuroticism, and social anxiety: An interaction model. Psychiatry Res. 2015;228(2):203–8.

6. Diaz Heijtz R, Wang S, Anuar F, Qian Y, Björkholm B, Samuelsson A, et al. Normal gut microbiota modulates brain development and behavior. Proc Natl Acad Sci U S A. 2011;108(7):3047–52.

7. Bravo JA, Forsythe P, Chew MV, Escaravage E, Savignac HM, Dinan TG, et al. Ingestion of *Lactobacillus strain*regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. Proc Natl Acad Sci U S A. 2011;108(38):16050–5.

8. Akbari E, Asemi Z, Daneshvar Kakhaki R, Bahmani F, Kouchaki E, Tamtaji OR, et al. Effect of probiotic supplementation on cognitive function and metabolic status in Alzheimer's disease: a randomized, double-blind and controlled trial. Front Aging Neurosci. 2016;8:256.

9. Kim MS, Kim Y, Choi H, Kim W, Park S, Lee D, et al. Transfer of a healthy microbiota reduces amyloid and tau pathology in an Alzheimer's disease animal model. Gut. 2020;69(2):283–94.

10. Kang DW, Adams JB, Gregory AC, Borody T, Chittick L, Fasano A, et al. Microbiota Transfer Therapy alters gut ecosystem and improves gastrointestinal and autism symptoms: an open-label study. Microbiome. 2017;5(1):10.

11. Shaaban SY, El Gendy YG, Mehanna NS, El-Senousy WM, El-Feki H, Saad K. The role of *Lactobacillus plantarum* in children with autism spectrum disorder: a randomized clinical trial. Probiotics Antimicrob Proteins. 2018;10(4):935–42.

12. Dickerson F, Stallings C, Origoni A, Katsafanas E, Savage C, Schweinfurth LA, et al. Effect of probiotic supplementation on schizophrenia symptoms and association with gastrointestinal functioning: a randomized, placebo-controlled trial. Schizophr Res. 2014;166(1–3):328–33.

13. Reininghaus U, Dutta R, Dazzan P, Stilo SA, Reichenberg A, Fearon P, et al. Probiotic treatment and mental health outcomes in schizophrenia: a randomized controlled pilot trial. Eur Psychiatry. 2014;29(1):129–34.