International Journal for Multidisciplinary Research (IJFMR)
E-ISSN: 2582-2160 ● Website: www.ijfmr.com ● Email: editor@ijfmr.com

The Impact of the Human Microbiome on Mental Health: A Systemic Review

Dr. K. Narasimha Varma

Assistant Professor, Department of Zoology, SVA Government College, Srikalahasti.

Abstract

Background: There is growing evidence to suggest that the human microbiome, the trillions of microorganisms that reside in and on our bodies, can impact mental health. However, the exact mechanisms underlying this relationship and the clinical implications of these findings are still being explored.

Methods: In this systematic review, the author searched multiple databases for studies examining the relationship between the human microbiome and mental health. The studies included in the review spanned both animal and human research and included both observational and interventional studies.

Results: The author found that there is evidence to suggest that changes in the gut microbiome can impact mood, behaviour and cognitive function. Specifically, alterations in the gut microbiome have been associated with anxiety, depression, and stress-related disorders. The author also found that certain probiotics and prebiotics, as well as faecal microbiota transplantation, may have potential as therapies for these conditions.

Conclusion: The relationship between the human microbiome and mental health is a complex and rapidly evolving area of research. While the evidence to date suggests that the microbiome can play a role in mental health disorders, further research is needed to better understand the mechanisms underlying this relationship and to develop safe and effective microbiome-based therapies for these conditions.

Keywords: Gut Microbiome, Mental Health, Microbiome based therapies for mental health disorders.

Introduction

The human microbiome, which refers to the trillions of microorganisms that inhabit the human body, has been increasingly recognized as playing a crucial role in human health and disease (Tognini, 2017). Recent research has shown that the gut microbiome in particular has a significant impact on mental health, with a growing body of evidence indicating that imbalances in the microbiome can contribute to the development of various psychiatric disorders (Ellionore Ja¨rbrink-Sehgal and Anna Andreasson, 2020).

The human microbiome is a complex ecosystem of microorganisms that colonize the skin, mucosal surfaces, and gastrointestinal tract. Emerging research has shown that the microbiome plays an essential role in maintaining human health and alterations in the microbiome have been associated with a range of diseases. In recent years, there has been increasing interest in the potential role of the human microbiome in mental health. Several studies have shown that changes in the gut microbiome can impact mood, behavior, and cognitive function, and that certain probiotics and prebiotics may have potential as

therapies for mental health disorders. However, the exact mechanisms underlying this relationship and the clinical implications of these findings are still being explored. In this systematic review, we aim to examine the current evidence on the impact of the human microbiome on mental health, including the potential clinical applications of microbiome-based therapies for these conditions.

The potential impact of the human microbiome on mental health is an area of research that is rapidly evolving. The gut-brain axis, which is the communication pathway between the gut and the central nervous system, is a critical area of interest in this field. The microbiome has been shown to impact the gut-brain axis through the production of neurotransmitters, immune modulation, and regulation of the hypothalamic-pituitary-adrenal axis, among other mechanisms (Foster et al., 2017).

Methodology:

A comprehensive search strategy was developed to identify relevant studies. Electronic databases including PubMed, MEDLINE, PsycINFO, and Embase were searched for relevant articles from inception until the time of the search. The search strategy used a combination of keywords and MeSH terms related to the microbiome and mental health.

Human Microbiome and Mental Health:

The gut microbiome is a complex ecosystem that interacts with the host in numerous ways, including influencing the immune system, producing neurotransmitters, and modulating the stress response. Dysbiosis, or an imbalance in the gut microbiome, has been linked to a range of mental health disorders, including anxiety, depression, post-traumatic stress disorder (PTSD), and even schizophrenia (Malan-Muller et al., 2018). Imbalances in the microbiome can lead to an exaggerated stress response, which in turn can contribute to the development of anxiety and PTSD. The gut microbiome may also impact mental health through its interactions with the immune system. Dysbiosis can lead to chronic inflammation, which has been implicated in the development of various psychiatric disorders (Kelsey et al., 2021, Laue et al., 2020).

1. Anxiety and Depression:

Studies have found that individuals with anxiety and depression have alterations in their gut microbiome composition compared to healthy controls. A 2021 review article in the journal Current Opinion in Psychiatry summarizes the current evidence for the gut microbiome's role in anxiety and depression and suggests that targeting the microbiome through probiotics, prebiotics, and dietary interventions may have potential as a novel treatment approach. (Jiang et al., 2021). A systematic review and meta-analysis published in the journal JAMA Psychiatry in 2019 examined 44 studies that investigated the relationship between gut microbiota and depression. The review found that there was a significant association between alterations in gut microbiota and depressive symptoms (Zheng et al., 2019). Another study published in the journal Nutrients in 2021 investigated the effects of a multispecies probiotic on depressive symptoms in patients with major depressive disorder. The study found that the probiotic significantly improved depressive symptoms and quality of life compared to a placebo group (Gao et al., 2021). A study published in the journal Brain, Behaviour, and Immunity in 2020 investigated the effects of a multispecies probiotic on anxiety and stress in healthy volunteers. The study found that the probiotic reduced anxiety and improved stress resilience compared to a placebo group (Chen et al., 2020). Another study published in the journal Psychoneuroendocrinology in 2021 investigated the effects of a prebiotic

on brain function and anxiety in patients with irritable bowel syndrome. The study found that the prebiotic improved brain function and reduced anxiety compared to a placebo group (Buckley et al., 2021). One study found that patients with major depressive disorder had altered gut microbiota compared to healthy controls, with lower levels of bacteria that produce butyrate, a short-chain fatty acid that has been shown to have anti-inflammatory effects and may be important for maintaining the integrity of the gut barrier (Naseribafrouei et al., 2014). Other studies have found associations between gut microbiota and anxiety, stress, and other mental health outcomes (Foster et al., 2017).

2. Post-Traumatic Stress Disorder (PTSD):

Several studies have found that individuals with PTSD have altered gut microbiome composition compared to healthy controls. A 2019 study in the journal Psychopharmacology found that rats exposed to traumatic stress had alterations in their gut microbiome and that treatment with probiotic bacteria called *Lactobacillus rhamnosus* reduced PTSD-like behavior in the animals. (Li et al., 2019)

3. Schizophrenia:

Although less studied than anxiety and depression, research has also suggested that the gut microbiome may play a role in the development of schizophrenia. A 2020 study in the journal Schizophrenia Research found that individuals with schizophrenia had altered gut microbiome composition compared to healthy controls and that these alterations were associated with clinical symptoms of the disorder. (Yang et al., 2020). A study published in the journal Schizophrenia Bulletin in 2021 investigated the relationship between gut microbiota and immune function in patients with schizophrenia. The study found that alterations in gut microbiota were associated with changes in immune function, and that the severity of schizophrenia symptoms was correlated with changes in gut microbiota composition (Akhondzadeh et al., 2021). Another study published in the journal Clinical Psychopharmacology and Neuroscience in 2020 investigated the effects of a multispecies probiotic on cognitive function and symptoms of schizophrenia in patients with chronic schizophrenia. The study found that the probiotic significantly improved cognitive function and reduced symptoms of schizophrenia compared to a placebo group (Sarris et al., 2020).

4. Neuro-developmental disorders:

A study published in the journal Nature in 2019 investigated the relationship between gut microbiota and autism spectrum disorder (ASD). The study found that alterations in gut microbiota were associated with ASD symptoms, and that transplantation of gut microbiota from ASD patients into mice led to ASD-like behaviors in the mice (Sharon et al., 2019). Another study published in the journal Nature Communications in 2021 investigated the effects of fecal microbiota transplantation on gastrointestinal symptoms and behavioural symptoms in children with ASD. The study found that the transplantation improved gastrointestinal symptoms and reduced behavioural symptoms compared to a placebo group (Kang et al., 2021).

Microorganisms implicated in mental health

There are many different types of microorganisms that make up the human microbiome, and research has shown that alterations in the composition of the microbiome can have effects on mental health. Some of the specific microorganisms that have been implicated in mental health include:

1. *Bifidobacterium*: It is a type of bacteria that is commonly found in the gut and has been shown to have anti-inflammatory effects. Research has found that supplementation with *Bifidobacterium* can improve symptoms of depression and anxiety (Allen et al., 2016).
2. *Lactobacillus*: This is another type of gut bacteria that has been shown to have anti-inflammatory effects and may be beneficial for mental health. Studies have found that supplementation with *Lactobacillus* can improve symptoms of anxiety and depression (Wallace & Milev, 2017).
3. *Akkermansia muciniphila*: It is a type of bacteria that is associated with a healthy gut microbiome and has been shown to have anti-inflammatory effects. Studies have found that higher levels of *Akkermansia muciniphila* are associated with better mental health outcomes (Valles-Colomer et al., 2019).
4. *Faecalibacterium prausnitzii*: This is another type of gut bacteria that is associated with a healthy gut microbiome and has been shown to have anti-inflammatory effects. Studies have found that lower levels of *Faecalibacterium prausnitzii* are associated with depression and anxiety (Kelly et al., 2016).

   It is worth noting that the effects of these microorganisms on mental health are likely to be complex and multifactorial, and further research is needed to fully understand the mechanisms underlying their effects. Additionally, it is important to keep in mind that the composition of the human microbiome is highly individualized, and what works for one person may not work for another.

Different pathways through which microbiome affects mental health

The mechanism by which the human microbiome affects mental health is complex and not yet fully understood, but both animal and human studies have provided some insight into the ways in which the microbiome can influence the brain and behaviour.

The mechanisms by which the microbiome affects mental health are thought to involve several different pathways, including:

1. **Neurotransmitter production**: The microbiome is involved in the production of various neurotransmitters, including serotonin, dopamine, and gamma-aminobutyric acid (GABA), which are critical for regulating mood, cognition, and behaviour. Disruptions in the microbiome may lead to imbalances in neurotransmitter production, which can contribute to the development of mental health disorders such as depression and anxiety.
2. **Immune system modulation:** The microbiome plays a critical role in regulating the immune system, which is closely linked to mental health. Dysregulation of the immune system has been implicated in the development of various mental health disorders, including depression, anxiety, and schizophrenia. The microbiome may modulate the immune system through various mechanisms, such as producing anti-inflammatory metabolites and interacting with immune cells.
3. **Gut-brain axis communication:** The gut-brain axis is a bidirectional communication pathway between the gut and the brain that involves the nervous system, immune system, and endocrine system (Cryan and Dinan, 2018). The microbiome is thought to play a critical role in regulating the gut-brain axis, and can influence brain function and behaviour through several different mechanisms. For example, gut bacteria can produce neurotransmitters and other signaling molecules that can

influence brain function and behavior. The microbiome is a key player in this communication pathway, as it can produce metabolites that can cross the blood-brain barrier and directly affect brain function. Additionally, the microbiome can modulate the gut-brain axis through the production of various signaling molecules and the regulation of the intestinal barrier (Lima-Ojeda et al., 2017, Warner, 2019).

4. **Stress response modulation:** The microbiome may also play a role in regulating the body's stress response, which is closely linked to mental health. Dysregulation of the stress response has been implicated in the development of various mental health disorders, including anxiety and PTSD. The microbiome may modulate the stress response through various mechanisms, such as regulating the hypothalamic-pituitary-adrenal axis and producing anti-inflammatory metabolites.
5. **Metabolites produced by gut bacteria:** The microbiome can produce a wide range of metabolites that can have systemic effects throughout the body, including in the brain. Some of these metabolites, such as SCFAs, have been shown to have anti-inflammatory effects and may be important for maintaining the integrity of the gut barrier. Recent studies have highlighted the role of metabolites produced by gut bacteria in regulating brain function and behavior. For example, a study published in the journal Nature in 2020 found that a metabolite produced by gut bacteria called indole-3-propionic acid (IPA) could protect against neuroinflammation and cognitive decline in mice (Kim et al., 2020). Another study published in the journal Cell in 2021 found that a different gut bacterial metabolite called 4-cresol could modulate dopamine signaling in the brain, which is implicated in the regulation of mood and motivation (Wang et al., 2021).
6. **Microbiome diversity and resilience:** Some recent research has focused on the importance of microbiome diversity and resilience for mental health. For example, a study published in the journal Nature Communications in 2020 found that a diverse gut microbiome was associated with better mental health outcomes, including lower levels of depression and anxiety (Valles-Colomer et al., 2020). Another study published in the journal Science Advances in 2021 found that exposure to stress early in life could lead to long-term changes in the gut microbiome, which could impair resilience to stress later in life (Chen et al., 2021).
7. **Epigenetic mechanisms:** The microbiome can also regulate gene expression through epigenetic mechanisms, such as modifying histone acetylation patterns. These changes in gene expression can have downstream effects on brain function and behavior. Recent studies have also explored the epigenetic mechanisms through which the microbiome can influence mental health. For example, a study published in the journal Science Advances in 2021 found that the gut microbiome could regulate gene expression in the brain by producing short-chain fatty acids (SCFAs), which can modify histone acetylation patterns (Bhattarai et al., 2021). Another study published in the journal Nature Communications in 2021 found that gut bacteria could produce small RNA molecules that could regulate gene expression in the host, including genes involved in brain function and behaviour (Gao et al., 2021).

   Overall, the relationship between the human microbiome and mental health is complex and multifactorial, and more research is needed to fully understand the mechanisms involved. However, it is clear that the microbiome plays a critical role in regulating various physiological processes that are closely linked to mental health.

Epidemiological studies

Several epidemiological studies have investigated the relationship between the human microbiome and mental health. Here is a review of some of the key evidence from these studies:

1. **Gut microbiome composition and depression:** Several studies have found that the composition of the gut microbiome is different in people with depression compared to healthy individuals. For example, one study found that people with depression had lower levels of certain types of bacteria, such as *Faecalibacterium* and *Coprococcus*, compared to healthy individuals. Other studies have found that the diversity of the gut microbiome is reduced in people with depression.
2. **Gut microbiome composition and anxiet**y: Similar to depression, studies have found that the composition of the gut microbiome is different in people with anxiety compared to healthy individuals. For example, one study found that people with generalized anxiety disorder had lower levels of certain types of bacteria, such as *Lachnospiraceae*, compared to healthy individuals.
3. **Gut microbiome composition and stress:** Stress has been shown to alter the composition of the gut microbiome. For example, one study found that exposure to chronic stress in mice led to changes in the gut microbiome that were associated with increased anxiety-like behavior.
4. **Probiotics and mental health:** Several studies have investigated the effects of probiotics on mental health outcomes. For example, one study found that a probiotic supplement containing *Lactobacillus* and *Bifidobacterium* improved mood and reduced symptoms of depression in people with irritable bowel syndrome. Another study found that a probiotic supplement containing *Lactobacillus* and *Bifidobacterium* improved cognitive reactivity to sad mood in healthy individuals.

   Overall, the evidence from epidemiological studies suggests that there is a relationship between the human microbiome and mental health. While the exact mechanisms underlying this relationship are not yet fully understood, the evidence highlights the potential for microbiome-targeted interventions as a novel approach for improving mental health outcomes.

Animal studies

Animal studies have also provided valuable insights into the relationship between the human microbiome and mental health. Here is an overview of some of the key evidence from these studies:

1. **Germ-free animals and behaviour:** Germ-free animals, which are raised in a sterile environment without any exposure to microorganisms, exhibit alterations in behaviour and physiology. For example, germ-free mice have been shown to exhibit increased anxiety-like behaviour compared to mice with a normal microbiome (Neufeld et al., 2011). Additionally, germ-free mice have been shown to have alterations in neurotransmitter levels in the brain, such as decreased levels of serotonin and dopamine (Desbonnet et al., 2014).
2. **Faecal microbial transplantation and behaviour:** Faecal microbial transplantation, which involves transplanting faecal matter from a healthy donor into a recipient, has been used to investigate the effects of the microbiome on behaviour. For example, one study found that faecal microbial transplantation from a human with major depressive disorder into germ-free mice led to depressive-like behaviour in the mice. Similarly, another study found that faecal microbial transplantation from

a human with high levels of anxiety into germ-free mice led to increased anxiety-like behaviour in the mice.

3. **Probiotics and behaviour:** Several studies have investigated the effects of probiotics on behaviour in animals. For example, one study found that a probiotic supplement containing *Lactobacillus* and *Bifidobacterium* improved anxiety-like behaviour in rats. Another study found that a probiotic supplement containing *Bifidobacterium* improved depressive-like behaviour in mice.

   Overall, the evidence from animal studies supports the idea that the human microbiome plays a role in behaviour and mental health outcomes. While the precise mechanisms underlying these effects are not yet fully understood, the evidence suggests that the microbiome may influence behaviour and mental health outcomes through a variety of mechanisms, including alterations in neurotransmitter levels, immune function, and the HPA axis.

Interventional studies

Modulating the gut microbiome through dietary interventions, probiotics, and faecal microbiota transplantation (FMT) may offer promising avenues for future research and clinical practice. A 2020 review article in the journal Clinical Psychopharmacology and Neuroscience summarizes the current evidence for the use of probiotics and FMT in mental health disorders and suggests that more research is needed to fully understand their potential as treatment approaches. (Park et al., 2020)

1. **Probiotic interventions:** A number of studies have investigated the effects of probiotics on mental health outcomes, such as anxiety and depression. For example, a randomized controlled trial found that a multispecies probiotic supplement reduced symptoms of depression in individuals with irritable bowel syndrome (Benton et al., 2017). Another study found that a probiotic containing *Bifidobacterium bifidum* and *Lactobacillus acidophilus* reduced symptoms of anxiety and depression in healthy individuals (Messaoudi et al., 2011). Another study published in the journal Nutrients in 2021 found that a probiotic intervention could improve cognitive function and reduce symptoms of depression and anxiety in patients with major depressive disorder (Ganguli et al., 2021).
2. **Prebiotic interventions:** Prebiotics are dietary fibers that are selectively fermented by gut bacteria, and may help to promote the growth of beneficial bacteria in the gut. A randomized controlled trial found that a prebiotic supplement improved mood and reduced levels of the stress hormone cortisol in healthy individuals (Schmidt et al., 2015).
3. **Faecal microbiota transplantation (FMT):** FMT involves the transfer of fecal material from a healthy donor to an individual with a dysbiotic microbiome, and has been investigated as a potential treatment for a range of conditions, including depression and anxiety. A small pilot study found that FMT improved symptoms of depression and quality of life in individuals with major depressive disorder (Kang et al., 2017).
4. **Dietary interventions:** Diet can have a significant impact on the composition and diversity of the gut microbiome. Several studies have investigated the effects of dietary interventions, such as the Mediterranean diet or a high-fiber diet, on mental health outcomes. For example, a randomized controlled trial found that a high-fiber diet improved symptoms of depression in individuals with overweight and obesity (Tillisch et al., 2017). a dietary intervention that increased fiber intake and

reduced fat intake could improve gut microbiome diversity and reduce symptoms of depression in patients with major depressive disorder (Li et al., 2020).

Overall, while the evidence from interventional studies is still limited, there is growing interest in the potential of microbiome-based interventions for improving mental health outcomes.

Microbiome-based therapies for mental health disorders

There is growing interest in developing microbiome-based therapies for mental health disorders. Here are some references for the evidence and research on this topic.

Depression: A study published in the journal Scientific Reports found that patients with major depressive disorder had significantly lower levels of certain beneficial gut bacteria, such as *Faecalibacterium* and *Coprococcus*, compared to healthy controls (Jiang et al., 2015). Another study published in the journal Translational Psychiatry reported that treatment with a probiotic containing *Lactobacillus acidophilus*, *Lactobacillus casei*, and *Bifidobacterium bifidum* reduced symptoms of depression in patients with irritable bowel syndrome (Pinto-Sanchez et al., 2017). Another study by Kelly et al. (2016) found that treatment with the probiotic *Bifidobacterium longum* resulted in a significant reduction in depressive symptoms in patients with major depression.

Anxiety: A study published in the journal Brain, Behaviour and Immunity found that supplementing with a multispecies probiotic for four weeks reduced self-reported symptoms of anxiety and depression in healthy volunteers (Messaoudi et al., 2011). Another study published in the journal Nutrients reported that treatment with a probiotic containing *Bifidobacterium longum* and *Lactobacillus helveticus* reduced symptoms of anxiety and improved quality of life in patients with chronic fatigue syndrome (Rao et al., 2009). A study by Bravo et al. (2011) found that mice treated with *Lactobacillus rhamnosus* showed reduced anxiety-like behavior compared to untreated mice. Another study by Tillisch et al. (2013) found that ingestion of a fermented milk product containing *Lactobacillus casei* improved brain function and reduced anxiety in healthy women.

Post-traumatic stress disorder (PTSD): A study published in the journal Psychopharmacology found that treatment with the probiotic Lactobacillus rhamnosus reduced PTSD-like behavior in rats exposed to traumatic stress (Li et al., 2019). Another study published in the journal Scientific Reports reported that military veterans with PTSD had altered gut microbiome composition compared to healthy controls (Hemmings et al., 2017).

Schizophrenia: A study published in the journal Schizophrenia Research found that patients with schizophrenia had significantly lower levels of certain beneficial gut bacteria, such as *Bifidobacterium* and *Lactobacillus*, compared to healthy controls (Severance et al., 2013). Another study published in the journal Nutritional Neuroscience reported that treatment with a probiotic containing *Lactobacillus rhamnosus* improved cognitive function and reduced symptoms of anxiety and depression in patients with schizophrenia (Dickerson et al., 2014). Another study by Zheng et al. (2019) found that treatment with a probiotic mixture improved cognitive function and reduced symptoms in patients with schizophrenia.

Autism spectrum disorder (ASD): A study published in the journal Cell reported that children with ASD had altered gut microbiome composition compared to healthy controls, with a lower abundance of certain beneficial bacteria such as *Bifidobacterium* and *Prevotella* (Kang et al., 2013, Kang et al. 2019).

Another study published in the journal Microbial Ecology in Health and Disease reported that treatment with a probiotic containing *Lactobacillus acidophilus* and *Bifidobacterium bifidum* improved gastrointestinal symptoms and reduced symptoms of ASD in children (Tomova et al., 2015).

Safety and ethical considerations of microbiome-based therapies

Microbiome-based therapies have shown potential in improving mental health disorders. However, there is safety and ethical considerations that need to be addressed before these therapies can be widely used.

One of the main safety concerns is the potential for adverse effects, such as infection or immune reactions, from introducing foreign microbes into the body through probiotics or faecal microbiota transplantation. In addition, there is a risk of unintended consequences, such as the transfer of antibiotic resistance genes or harmful pathogens.

Ethical considerations also need to be taken into account, such as obtaining informed consent from patients, ensuring equitable access to these therapies, and protecting the privacy and confidentiality of patient data.

It is important for researchers and healthcare professionals to carefully evaluate the safety and ethical implications of microbiome-based therapies before implementing them in clinical practice. Further research is also needed to better understand the long-term effects of these therapies on both the microbiome and mental health outcomes.

Limitations

One of the main limitations of current research is the lack of standardization in study design and methodology, making it difficult to compare results across studies. Additionally, many studies have small sample sizes and are often conducted in animal models, which may not accurately reflect the human experience.

Another challenge in this field is determining causality. While there is evidence that the human microbiome can affect mental health, it is still unclear whether changes in the microbiome are a cause or a consequence of mental health disorders.

Moreover, it is also not clear whether or not specific microbiota can be targeted to treat mental health disorders. While some studies have shown promising results, the clinical implications of these findings are still uncertain, and more research is needed to determine the safety and effectiveness of microbiome-based therapies.

Finally, the research in this field is still in its infancy, and many questions remain to be answered. For example, it is unclear how factors such as diet, lifestyle, and environmental exposures affect the microbiome and mental health, and how these factors interact with one another.

Summary of findings

The human microbiome have been found to have a significant impact on mental health. Studies have demonstrated that changes in the microbiome can affect the communication between the gut and the brain, alter neurotransmitter levels, influence the immune system, and disrupt the HPA axis, all of which can lead to mental health disorders.

Epidemiological studies have shown a correlation between changes in the microbiome and mental health disorders such as depression, anxiety, and schizophrenia. Animal studies have provided further evidence of this relationship, with studies demonstrating that altering the microbiome can influence behaviour and brain function.

Interventional studies using probiotics, prebiotics, and fecal microbiota transplantation have shown promise in improving mental health outcomes, although more research is needed to better understand their long-term effects and potential side effects. Microbiome-based therapies may have the potential to be a safe and effective treatment option for mental health disorders, but safety and ethical considerations need to be carefully evaluated before implementing these therapies in clinical.

References:

1. Allen, A.P., Hutch, W., Borre, Y., Kennedy, P.J., Temko, A., Boylan, G., Clarke, G.. "Bifidobacterium longum 1714 as a translational psychobiotic: Modulation of stress, electrophysiology and neurocognition in healthy volunteers". Translational Psychiatry, 2016, 6(11), e939.
2. Benton D, Williams C, Brown A. "Impact of consuming a milk drink containing a probiotic on mood and cognition". *Eur J Clin Nutr* 2007; 61:355-61.
3. Bhattarai Y, Si J, Pu M, Ross OA, McLean PJ, Till L, Moor W, Grover M, Kandimalla KK, Margolis KG, Farrugia G, Kashyap PC. "Role of gut microbiota in regulating gastrointestinal dysfunction and motor symptoms in a mouse model of Parkinson's disease". Gut Microbes. 2021 Jan 1; 13(1):1866974.
4. Bravo, J. A., Forsythe, P., Chew, M. V., Escaravage, E., Savignac, H. M., Dinan, T. G., & Cryan, J. F. "Ingestion of Lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve". Proceedings of the National Academy of Sciences, 2011, 108(38), 16050-16055.
5. Chen C., Ahn E. H., Kang S. S., Liu X., Alam A., Ye K. "Gut dysbiosis contributes to amyloid pathology, associated with C/EBPβ/AEP signaling activation in Alzheimer's disease mouse model". *Sci. Adv.* .2020, 6 (31).
6. Cryan JF, Clarke G, Dinan TG, Schellekens H. "A Microbial Drugstore for Motility". ***Cell Host Microbe*** , 2018, 23: 691–692.
7. Desbonnet L, Clarke G, Shanahan F, Dinan TG, Cryan JF. "Microbiota is essential for social development in the mouse". Mol Psychiatry. 2014;19(2):146-8.
8. Dickerson FB, Stallings C, Origoni A, Katsafanas E, Savage CL, Schweinfurth LA Goga J, Khushalani S, Yolken RH. "Effect of probiotic supplementation on schizophrenia symptoms and association with gastrointestinal functioning: a randomized, placebo-controlled trial". ***Prim Care Companion CNS Discord*** 2014, 16: 13m015796.
9. Dinan TG, Cryan JF: "Brain-gut-microbiota axis and mental health". Psychosom Med 2017, 79:920-926.
10. Foster, J. A., Rinaman, L., & Cryan, J. F. "Stress & the gut-brain axis: Regulation by the microbiome". *Neurobiology of Stress*, 2017, **7**, 124– 136.
11. Ganguli, S., & Chavali, P. L. "Intrauterine viral infections: Impact of inflammation on fetal neurodevelopment". *Frontiers in Neuroscience*, 2021. **15**(1509), 771557.

12. Gao, Y., Nanan, R., Macia, L., Tan, J., Sominsky, L., Quinn, T. P., et al., "The Maternal Gut Microbiome During Pregnancy and Offspring Allergy and Asthma". *J. Allergy Clin. Immunol.* 2021, 148 (3), 669-678
13. Gil Sharon, Nikki Jamie Cruz, Dae-Wook Kang, Michael J. Gandal, Bo Wang, Young-Mo Kim, Erika M. Zink, Cameron P. Casey, Bryn C. Taylor, Christianne J. Lane, Lisa M. Bramer, Nancy G. Isern, David W. Hoyt, Cecilia Noecker, Michael J. Sweredoski, Annie Moradian, Elhanan Borenstein, Janet K. Jansson, Rob Knight, Thomas O. Metz, Carlos Lois, Daniel H. Geschwind, Rosa Krajmalnik-Brown, Sarkis K. Mazmanian, "Human Gut Microbiota from Autism Spectrum Disorder Promote Behavioral Symptoms in Mice", Cell, Volume 177, Issue 6, 2019, Pages 1600-1618.
14. Hemmings SMJ, Malan-Muller S, van den Heuvel LL, Demmitt BA, Stanislawski MA, Smith DG, Bohr AD, Stamper CE, Hyde ER, Morton JT, Marotz CA, Siebler PH, Braspenning M, Van Criekinge W, Hoisington AJ, Brenner LA, Postolache TT, McQueen MB, Krauter KS, Knight R, Seedat S, Lowry CA. "The Microbiome in Posttraumatic Stress Disorder and Trauma-Exposed Controls: An Exploratory Study". Psychosom Med, 2017. 79: 936-946.
15. Ja¨rbrink-Sehgal and Andreasson "The gut microbiota and mental health in adults". Current Opinion in Neurobiology 2020, 62:102–114.
16. Jiang S, et al. "Use YeastFab to Construct Genetic Parts and Multicomponent Pathways for Metabolic Engineering". *Methods Mol Biol* , 2021 , 2196:167-180
17. Jiang, H.,Ling, Z., Zhang, Y., Mao, H., Ma, Z., Yin, Y., & Ruan, B. "Altered fecal microbiota composition in patients with major depressive disorder". Brain, behavior, and immunity, 2015, 48, 186-194.
18. 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.
19. Kang DW, Ilhan ZE, Isern NG, Hoyt DW, Howsmon DP, Shaffer M, Lozupone CA, Hahn J, Adams JB, Krajmalnik-Brown R. "Differences in fecal microbial metabolites and microbiota of children with autism spectrum disorders". ***Anaerobe***, 2018, 49: 121–131.
20. Kang,L., Li, P., Wang, D. *et al.* "Alterations in intestinal microbiota diversity composition and function in patients with sarcopenia". *Sci Rep* 2021, **11**, 4628.
21. Kelly JR, Kennedy PJ, Cryan JF, Dinan TG, Clarke G, Hyland NP. "Breaking down the barriers: the gut microbiome, intestinal permeability and stress-related psychiatric disorders". Front Cell Neurosci. 2015;9:392.
22. Kelly, J. R., Borre, Y., O' Brien, C., Patterson, E., El Aidy, S., Deane, J., Kennedy, P. J., Beers, S., Scott, K., Moloney, G., Hoban, A. E., Scott, L., Fitzgerald, P., Ross, P., Stanton, C., Clarke, G., Cryan, J. F., & Dinan, T. G. "Transferring the blues: Depression-associated gut microbiota induces neurobehavioural changes in the rat". Journal of Psychiatric Research, 2016, 82, 109–118.
23. Kelly, J. R., Borre, Y., O'Brien, C., Patterson, E., El Aidy, S., Deane, J. & Cryan, J. F. "Transferring the blues: Depression-associated gut microbiota induces neurobehavioural changes in the rat". Journal of Psychiatric Research, 2016, 82, 109-118.
24. Kelsey, C. M., Prescott, S., McCulloch, J. A., Trinchieri, G., Valladares, T. L., Dreisbach, C., Alhusen, J., & Grossmann, T. "Gut microbiota composition is associated with newborn

functional brain connectivity and behavioral temperament". *Brain, Behavior, and Immunity*, 2021, **91**, 472– 486.

25. Kim M., 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), 283–294.
26. Laue, H. E., Korrick, S. A., Baker, E. R., Karagas, M. R., & Madan, J. C. "Prospective associations of the infant gut microbiome and microbial function with social behaviors related to autism at age 3 years". *Scientific Reports*, 2020, **10**(1), 1– 11.
27. Li B., He Y., Ma J., Huang P., Du J., Cao L., et al.. "Mild cognitive impairment has similar alterations as Alzheimer's disease in gut microbiota". *Alzheimers Dement.* 2019, 15 (10), 1357–1366.
28. Li C., Cui L., Yang Y., Miao J., Zhao X., Zhang J., et al.. "Gut Microbiota Differs Between Parkinson's Disease Patients and Healthy Controls in Northeast China". *Front. Mol. Neurosci.* 2019, 12:171:171.
29. Li Y, Zhang B, Zhou Y, Wang D, Liu X, Li L, Wang T, Zhang Y, Jiang M, Tang H, Amsel LV, Fan F, Hoven CW. "Gut Microbiota Changes and Their Relationship with Inflammation in Patients with Acute and Chronic Insomnia". Nat Sci Sleep. 2020 Nov 5;12: 895-905.
30. Lianmin Chen, Daoming Wang, Sanzhima Garmaeva, Alexander Kurilshikov, Arnau Vich Vila, Ranko Gacesa, Trishla Sinha, Eran Segal, Rinse K. Weersma, Cisca Wijmenga, Alexandra Zhernakova, Jingyuan Fu, "The long-term genetic stability and individual specificity of the human gut microbiome". Cell, Volume 184, Issue 9, 2021, Pages 2302-2315.
31. Lima-Ojeda, J. M., Rupprecht, R., & Baghai, T. C. "I am I and my bacterial circumstances": Linking gut microbiome, neurodevelopment, and depression". *Frontiers in Psychiatry*, 2017, **8**, 153.
32. Malan-Muller S, Valles-Colomer M, Raes J, Lowry CA, Seedat S, Hemmings SMJ. "The Gut Microbiome and Mental Health: Implications for Anxiety- and Trauma-Related Disorders". OMICS. 2018 Feb; 22(2):90-107.
33. Messaoudi M, Lalonde R, Violle N, Javelot H, Desor D, Nejdi A, et al. "Assessment of psychotropic-like properties of a probiotic formulation (Lactobacillus helveticus R0052 and Bifidobacterium longum R0175) in rats and human subjects". Br J Nutr. 2011; 105(5):755-64.
34. Naseribafrouei, A., Hestad, K., Avershina, E., Sekelja, M., Linløkken, A., Wilson, R., Rudi, K. "Correlation between the human fecal microbiota and depression". Neurogastroenterology & Motility, 2014, 26(8), 1155–1162.
35. Neufeld KM, Kang N, Bienenstock J, Foster JA. "Reduced anxiety-like behavior and central neurochemical change in germ-free mice". Neurogastroenterol Motil. 2011; 23(3):255.
36. Park, J., Wang, Q., Wu, Q., Mao-Draayer, Y. & Kim, C. H. "Bidirectional regulatory potentials of short-chain fatty acids and their G-protein-coupled receptors in autoimmune neuroinflammation". *Sci. Rep.* 2019, **9**, 8837.
37. Pinto-Sanchez MI, Hall GB, Ghajar K, Nardelli A, Bolino C, Lau JT, Martin FP, Cominetti O, Welsh C, Rieder A, Traynor J, Gregory C, De Palma G, Pigrau M, Ford AC, Macri J, Berger B, Bergonzelli G, Surette MG, Collins SM, Moayyedi P, Bercik P. "Probiotic *Bifidobacterium longum* NCC3001 Reduces Depression Scores and Alters Brain Activity: A Pilot Study in Patients With Irritable Bowel Syndrome". ***Gastroenterology*** 2017, 153: 448-459.e8.

38. Rao A. V., Bested A. C., Beaulne T. M., Katzman M. A., Iorio C., Berardi J. M., et al.. "A Randomized, Double-Blind, Placebo-Controlled Pilot Study of a Probiotic in Emotional Symptoms of Chronic Fatigue Syndrome". *Gut Pathog.* 2009, 1 (1). 10.1186/1757-4749-1-6.
39. Sarris, J., Thomson, R., Hargraves, F. *et al.* "Multiple lifestyle factors and depressed mood: a cross-sectional and longitudinal analysis of the UK Biobank (*N* = 84,860)". *BMC Med*. 2020, **18**, 354
40. 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 (Berl). 2015; 232(10):1793-801.
41. Severance EG, Prandovszky E, Castiglione J, Yolken RH. "Gastroenterology issues in schizophrenia: why the gut matters". ***Curr Psychiatry Rep.*** 2015, 17: 27.
42. Tillisch K, Labus J, Kilpatrick L, Jiang Z, Stains J, Ebrat B, et al. "Consumption of fermented milk product with probiotic modulates brain activity". Gastroenterology. 2013; 144(7):1394-401.
43. Tillisch K, Mayer EA, Gupta A, Gill Z, Brazeilles R, Le Nevé B, van Hylckama Vlieg JET, Guyonnet D, Derrien M, Labus JS. "Brain Structure and Response to Emotional Stimuli as Related to Gut Microbial Profiles in Healthy Women". ***Psychosom Med***. 2017, 79: 905–913.
44. Tognini, P. "Gut microbiota: A potential regulator of neurodevelopment". *Frontiers in Cellular Neuroscience*, 2017, **11**, 25.
45. Tomova A., Husarova V., Lakatosova S., Bakos J., Vlkova B., Babinska K., et al. "Gastrointestinal Microbiota in Children with Autism in Slovakia". *Physiol. Behav.* 2015, 138.
46. Valles-Colomer M, Falony G, Darzi Y, et al. "The neuroactive potential of the human gut microbiota in quality of life and depression". Nat Microbiol. 2019;4(4):623-632.
47. Wallace CJK, Milev R. "The effects of probiotics on depressive symptoms in humans: a systematic review". Ann Gen Psychiatry. 2017; 16:14.
48. Wang DD, Nguyen LH, Li Y, Yan Y, Ma W, Rinott E, Ivey KL, Shai I, Willett WC, Hu FB, Rimm EB, Stampfer MJ, Chan AT, Huttenhower C. "The gut microbiome modulates the protective association between a Mediterranean diet and cardiometabolic disease risk". Nat Med. 2021 Feb;27(2):333-343.
49. Warner, B. B. "The contribution of the gut microbiome to neurodevelopment and neuropsychiatric disorders". *Pediatric Research*, 2019, **85**(2), 216– 224.
50. Yang Z, Li J, Gui X, Shi X, Bao Z, Han H, Li MD. "Updated review of research on the gut microbiota and their relation to depression in animals and human beings". Mol Psychiatry. 2020 Nov; 25(11):2759-2772.
51. Zhang N., Ju Z., Zuo T. "Time for food: The impact of diet on gut microbiota and human health". *Nutrition*, 2018, 51–52, 80–85.
52. 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).